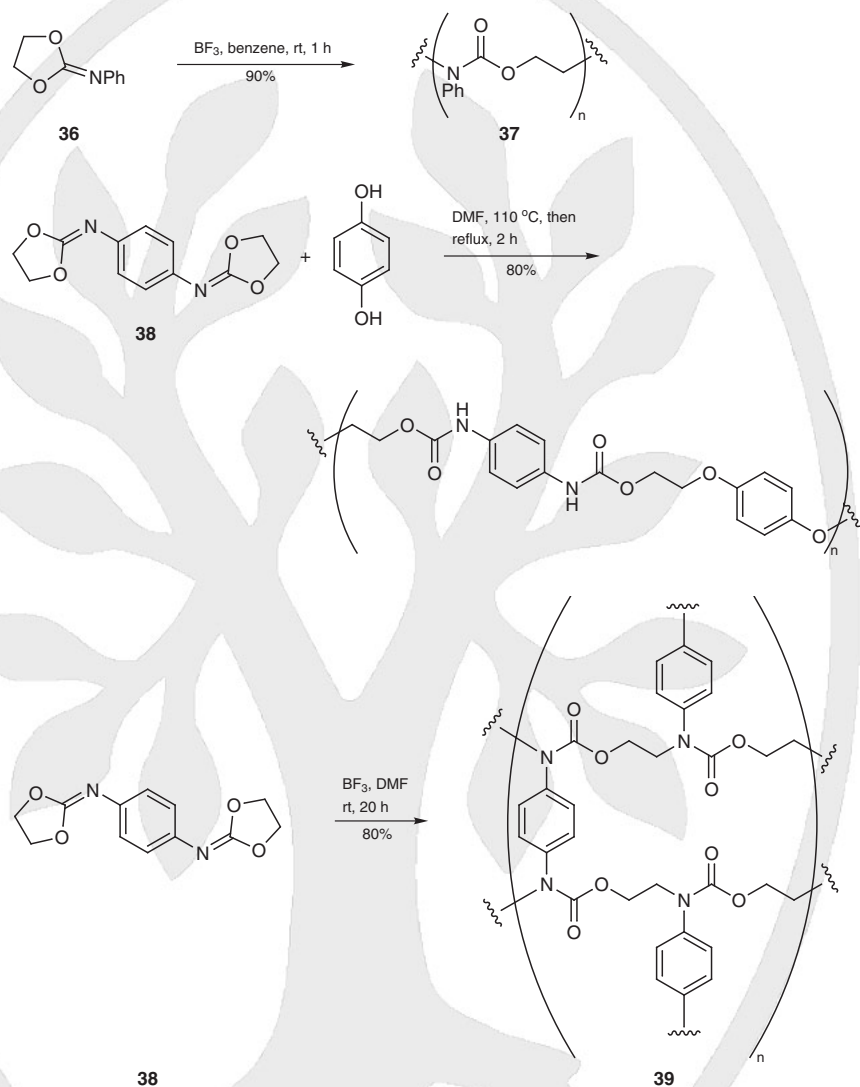


of boron trifluoride.^[38] Ring-opening polymerization of *N,N'*-di-1,3-dioxolan-2-ylidenebenzene-1,4-diamine (**38**) in the presence of boron trifluoride produces a cross-linked polyurethane **39**.^[38]

Scheme 15 Polymerization of Iminocarbonates^[38]



Polyurethane 37:^[38]

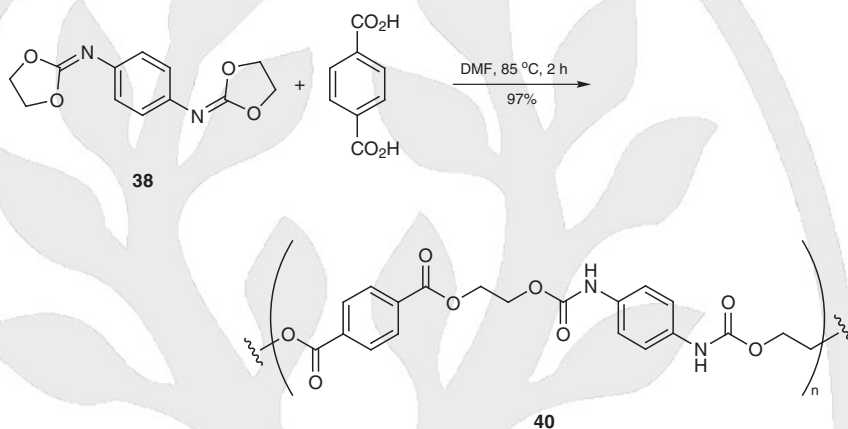
To a soln of *N*-1,3-dioxolan-2-ylideneaniline (**36**; 1.0 g, 6.1 mmol) in dry benzene (5 mL) (**CAUTION: carcinogen**) was added BF_3 (0.01–0.07% based on **36**). After 1 h, the benzene was removed and the residue was dissolved in CHCl_3 . The soln was filtered and poured into an excess of acetone to precipitate the polymer; yield: 0.9 g (90%); mp 171–173 °C.

18.7.1.1.7

**Method 7:
From Iminocarbonates and Acids**

Bis(iminocarbonates), which can be thought of as acetals of isocyanates, react with a variety of acids to produce compounds with alternating urethane and ester linkages.^[39] The reaction of *N,N'*-di-1,3-dioxolan-2-ylidenebenzene-1,4-diamine (**38**) with terephthalic acid (benzene-1,4-dicarboxylic acid) produces the corresponding polyurethane **40** (Scheme 16).^[39] This method is very similar to that described in Section 18.7.1.1.6.

Scheme 16 Condensation of an Iminocarbonate with a Diacid^[39]


Polyurethane 40; Typical Procedure:^[39]

A mixture of *N,N'*-di-1,3-dioxolan-2-ylidenebenzene-1,4-diamine (**38**; 0.6 g, 2.4 mmol) and terephthalic acid (0.4 g, 2.4 mmol) in DMF (15 mL) was heated and stirred at 85 °C for 2 h and then filtered. The clear soln was vigorously stirred into H₂O to precipitate the polymer, which separated as a white solid. The polymer was collected by filtration and washed several times by stirring with H₂O and finally dried overnight in vacuo; yield: 1.01 g (97%); mp 236 °C.

18.7.2

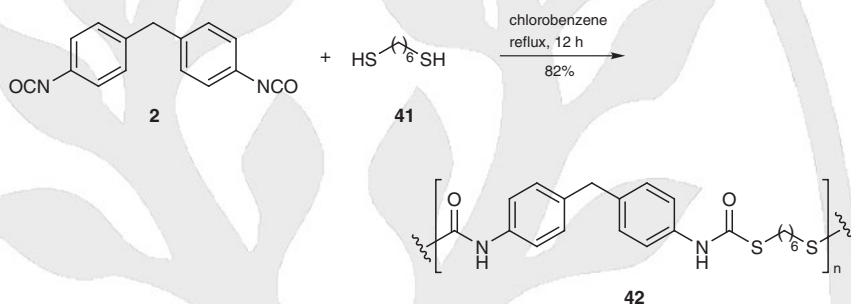
**Product Subclass 2:
Polythiocarbamates**

Polythiocarbamates are the analogues of polycarbamates in which the ethereal oxygen has been replaced by sulfur. These polymers can be manufactured by the addition of thiols to isocyanates or the condensation of chlorothioformates with amines. The advantages of these reactions are that they can be run neat at moderate temperatures and give no byproducts. The drawback in the former reaction is in the use of isocyanates, which, as mentioned in the general introduction, are toxic and potent allergenics. In addition, the use of thiols in the laboratory is unpleasant because of their disagreeable odor and difficulties in handling as a result of autoxidation. The resulting polymers are highly insoluble and tend to decompose in light, in hot solvents, and in aqueous bases. Their melting points are somewhat higher than those of their oxygen analogues, but they are less thermally stable. Because of these drawbacks, no industrial applications of these polymers have been found.

18.7.2.1 Synthesis of Product Subclass 2

18.7.2.1.1 Method 1:
Addition of Thiols to Isocyanates

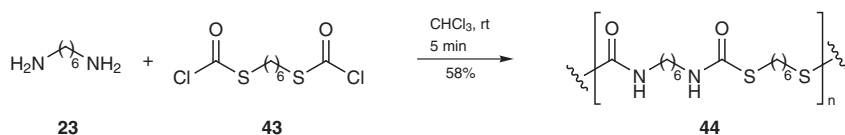
The polymerization of dithiols (e.g., **41**) with diisocyanates (e.g., **2**) can be effected in solution through the use of tertiary amine catalysts (Scheme 17).^[11,40,41] This is similar to the method used in the solution polymerization of diisocyanates with diols (see Section 18.7.1.1.1). The dithiol–diisocyanate method requires a controlled balance of pure reactants, must be carried out in a system free of moisture and oxygen, and requires a reaction time of about 12 hours. This method produces higher yields of lower-molecular-weight polymers **42** than does the bis(chlorothioformate) method.^[41]

Scheme 17 Addition of Dithiol Addition to a Diisocyanate^[41]**Polythiocarbamate 42; Typical Procedure:**^[41]

A soln of 1,1'-methylenebis(4-isocyanatobenzene) (**2**; 6.25 g, 25 mmol) in chlorobenzene (100 mL) was added dropwise to a stirred soln of hexane-1,6-dithiol (**41**; 3.75 g, 25 mmol) and Pr_3N (0.03 g) in chlorobenzene (200 mL) at reflux under a stream of N_2 . The diisocyanate **2** was added over 3 h and the reaction was continued for a further 9 h. Anhyd MeOH (50 mL) was then added to the cool mixture, which was left to stand overnight. The powdery polymer was collected by filtration, washed with MeOH, dissolved in hot DMF (100 mL), filtered, and reprecipitated by dropwise addition of the soln to rapidly stirred MeOH (750 mL). The reprecipitation process was repeated and the product obtained was dried under vacuum to afford a fine white powder; yield: 8.26 g (82%).

18.7.2.1.2 Method 2:
From Bis(chlorothioformates) and Diamines

The polycondensation of bis(chlorothioformates) (e.g., **43**) and diamines (e.g., **23**) to give polythiocarbamates (e.g., **44**) (Scheme 18) can be effected by the interfacial technique,^[41] and is similar to the preparation of polycarbamates from bis(chloroformates) and diamines (see Section 18.7.1.1.2.1). The lower yields associated with this method can be attributed in part to the loss of low-molecular-weight polymer on reprecipitation. Unlike the diisocyanate–dithiol method, this method does not require any of the precautions previously mentioned (see Section 18.7.2) and the reaction is complete within a few minutes.^[41]

Scheme 18 Addition of a Bis(chlorothioformate) to a Diamine^[41]

Polythiocarbamate 44; Typical Procedure:^[41]

A soln of *S,S'*-hexane-1,6-diyl bis(chlorothioformate) (**43**; 4.86 g, 20 mmol) in CHCl_3 (150 mL) was added quickly to a soln of distilled hexane-1,6-diamine (**23**; 2.32 g, 20 mmol) and Na_2CO_3 (4.21 g, 40 mmol) in H_2O (150 mL) with violent agitation. A reaction took place instantaneously and was allowed to continue for 5 min. The suspended polymer was collected by filtration, washed with CHCl_3 and H_2O , and then dried. The polymer was dissolved in DMF (200 mL), filtered, and reprecipitated by cooling. The mixture was then diluted with MeOH and filtered. Following a second reprecipitation, the polymer product was dried under a vacuum at 50 °C; yield: 3.7 g (58%); mp 194–196 °C.

References

- [1] Woods, G., *The ICI Polyurethanes Book*, Wiley: Chichester, UK, (1987); p 30.
- [2] Ulrich, H., *Chemistry and Technology of Isocyanates*, Wiley: Chichester, UK, (1996); p 469.
- [3] Sandler, S. R.; Karo, W., *Polymer Synthesis*, 2nd ed.; Academic: San Diego, (1992); Vol. 1, p 233.
- [4] Hepburn, C., *Polyurethane Elastomers*, Applied Science: London, UK, (1982).
- [5] Woods, G., *Flexible Polyurethane Foams: Chemistry and Technology*, Applied Science: London, UK, (1982).
- [6] Buist, J. M., Ed., *Developments in Polyurethanes*, Applied Science: London, UK, (1978).
- [7] Lyman, D. J., *J. Polym. Sci.*, (1960) **45**, 49.
- [8] Beachell, H. C.; Peterson, J. C., *J. Polym. Sci., Part A-1*, (1969) **7**, 2021.
- [9] Marvel, C. S.; Johnson, J. H., *J. Am. Chem. Soc.*, (1950) **72**, 1674.
- [10] Dyer, E.; Bartels, G. W., Jr., *J. Am. Chem. Soc.*, (1954) **76**, 591.
- [11] Hanford, W. E.; Holmes, D. F., US 2 284 896, (1942); *Chem. Abstr.*, (1942) **36**, 6706.
- [12] Woods, G., *The ICI Polyurethanes Book*, Wiley: Chichester, UK, (1987); pp 42–45.
- [13] Reegen, S. L.; Frisch, K. C., *J. Polym. Sci., Part A-1*, (1970) **8**, 2883.
- [14] Abbate, F. W.; Ulrich, H., *J. Appl. Polym. Sci.*, (1969) **13**, 1929.
- [15] Wicks, Z. W., Jr., *Prog. Org. Coat.*, (1975) **3**, 73.
- [16] Frisch, K. C., *Adv. Urethane Sci. Technol.*, (1973) **2**, 1; *Chem. Abstr.*, (1975) **82**, 17 130.
- [17] Dieter, J. A.; Frisch, K. C.; Wolgemuth, L. G., *J. Paint Technol.*, (1975) **47**, 65; *Chem. Abstr.*, (1975) **83**, 133 479.
- [18] Müller, H. P.; Wagner, K.; Müller, R., US 4 044 171, (1977); *Chem. Abstr.*, (1977) **84**, 91 789.
- [19] Querat, E.; Tighzert, L.; Pascault, J. P.; Dušek, K., *Angew. Makromol. Chem.*, (1996) **242**, 1.
- [20] Lee, S.-D.; Sanda, F.; Endo, T., *J. Polym. Sci., Part A: Polym. Chem.*, (1997) **35**, 1333.
- [21] Kinstle, J. F.; Sepulveda, L. E., *J. Polym. Sci., Polym. Lett. Ed.*, (1977) **15**, 467.
- [22] Kumar, A.; Ramakrishnan, S., *J. Chem. Soc., Chem. Commun.*, (1993), 1453.
- [23] Versteegen, R. M.; Sijbesma, R. T.; Meijer, E. W., *Angew. Chem.*, (1999) **111**, 3095; *Angew. Chem. Int. Ed. Engl.*, (1999) **38**, 2917.
- [24] Whelan, J. M., Jr.; Hill, M.; Cotter, R. J., US 3 072 613, (1963); *Chem. Abstr.*, (1963) **58**, 14 148.
- [25] Wittbecker, E. L.; Morgan, P. W., *J. Polym. Sci.*, (1959) **40**, 289.
- [26] Schaeffgen, J. R.; Koontz, F. H., *J. Polym. Sci.*, (1959) **40**, 377.
- [27] Wittbecker, E. L.; Katz, M., *J. Polym. Sci.*, (1959) **40**, 367.
- [28] Hollander, J.; Trischler, F. D.; Gosnell, R. B., *J. Polym. Sci., Part A-1*, (1967) **5**, 2757.
- [29] Kwolek, S. L.; Morgan, P. W., *J. Polym. Sci., Part A: Gen. Pap.*, (1964) **2**, 2693.
- [30] Tousignant, W. F.; Pledger, H., Jr., US 2 894 935, (1959); *Chem. Abstr.*, (1960) **54**, 16 025.
- [31] Spindler, R.; Frechet, J. M. J., *Macromolecules*, (1993) **26**, 4809.
- [32] Kothandaraman, H.; Sultan Nasar, A., *Polymer*, (1993) **34**, 610.
- [33] Nasar, A. S.; Subramani, S.; Radhakrishnan, G., *J. Polym. Sci., Part A: Polym. Chem.*, (1999) **37**, 1815.
- [34] Dyer, E.; Wright, G. C., *J. Am. Chem. Soc.*, (1959) **81**, 2138.
- [35] Miyake, Y.; Ozaki, S.; Hirata, Y., *J. Polym. Sci., Part A-1*, (1969) **7**, 899.
- [36] Lundberg, R. D.; Montgomery, D. R., US 3 523 924, (1970); *Chem. Abstr.*, (1970) **73**, 111 037.
- [37] Soga, K.; Hosoda, S.; Ikeda, S., *Makromol. Chem.*, (1974) **175**, 3309.
- [38] Mukaiyama, T.; Fujisawa, T.; Nohira, H.; Hyugaji, T., *J. Org. Chem.*, (1962) **27**, 3337.
- [39] Mukaiyama, T.; Fujisawa, T.; Hyugaji, T., *Bull. Chem. Soc. Jpn.*, (1962) **35**, 687.
- [40] Catlin, W. E., US 2 284 637, (1942); *Chem. Abstr.*, (1942) **36**, 6707.
- [41] Dyer, E.; Osborne, W., *J. Polym. Sci.*, (1960) **47**, 361.

Product Class 8: Acyclic and Cyclic Ureas

G. Sartori and R. Maggi

General Introduction

Previously published information regarding this product class can be found in *Houben-Weyl*, Vol. E 4. Reviews published on this topic in 1999 and 2000 focus only on specific aspects such as industrial application^[1] or environmentally friendly synthetic approaches.^[2]

In this section, the most important contributions reported in the last fifteen years are considered; each selected synthetic method is briefly discussed and examples of the more useful synthetic approaches are provided. When available, the number of examples described and the yield range are reported.

The simplest and most direct synthesis of substituted ureas is represented by a process that essentially involves two steps: (1) reaction of a selected amine with a reagent containing the carbonyl group to form an intermediate that possesses a leaving group linked to the carbonyl group; and (2) further reaction of this compound with the same amine or with a different amine to form a symmetrical or unsymmetrical substituted urea. The more interesting unsymmetrically 1,3-disubstituted ureas are prepared by using carbonyl-containing reagents that already contain an amino framework such as carbamates and isocyanates. In most cases carbamates and isocyanates are reactive intermediates that are not isolated, but are trapped in situ with amines to produce directly the desired unsymmetrical ureas. These approaches are viable synthetic strategies that are readily applicable to amines also bearing multifunctional groups that will constitute part of the final urea backbone; it follows that, frequently, the major difficulties in urea preparation are those found in the synthesis of these starting reagents. Special advantages such as the use of eco-efficient experimental conditions, the high level of atom economy, and the multicomponent reaction approach will be particularly emphasized as well as solid-phase combinatorial synthesis that allows easy and fast preparation of urea libraries. Finally, for many procedures discussed, it must be emphasized that the experimental conditions can be arranged on the basis of more environmentally friendly approaches, for example, by replacing problematic solvents such as benzene with toluene or xylenes.

Ureas have found use in a wide variety of areas ranging from antioxidants in gasoline, corrosion inhibitors, and valuable starting materials for the synthesis of drugs and agroprotectives; they are also utilized in the polymer industry and in more specialized areas such as supramolecular chemistry and molecular recognition.

Product Subclass 1: Unfunctionalized Ureas

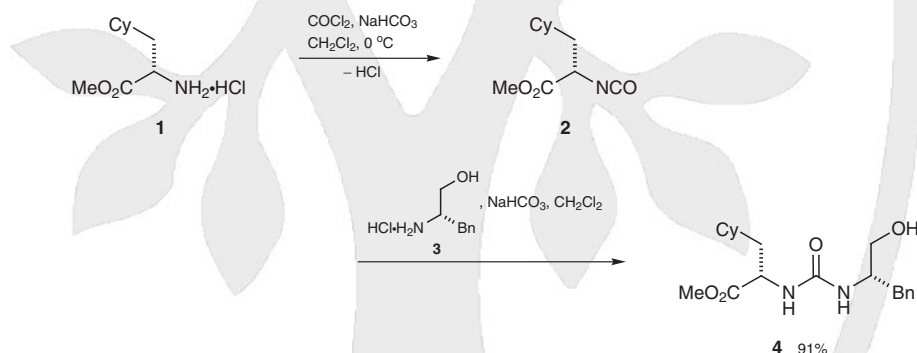
In this section procedures are described for the preparation of ureas where the ureidic nitrogens are linked only to hydrogens or carbon atoms; if functional groups are present, they are located in the ω -position.

18.8.1.1 Synthesis of Product Subclass 1

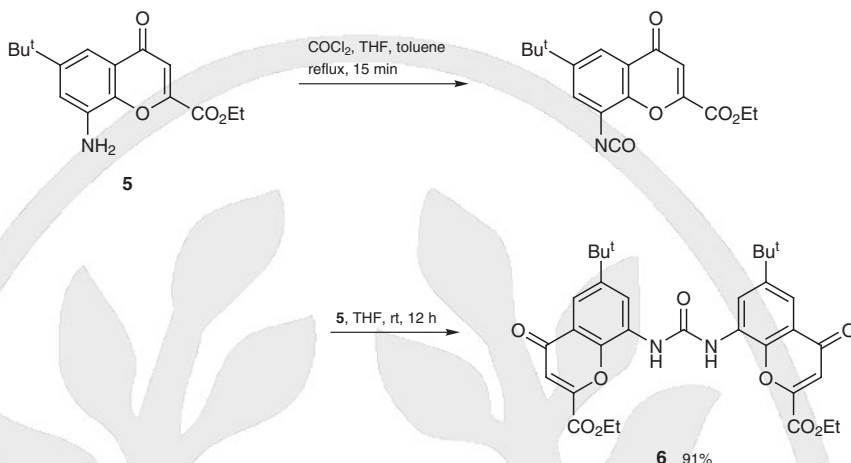
18.8.1.1.1 Method 1:
From Phosgene

Phosgene is the simplest and historically it was the earliest used reagent for urea synthesis. Despite its intrinsic high reactivity and low cost, the use of this compound has gradually been abandoned. The production and use of phosgene has many toxicological and environmental concerns that are connected with the manipulation and storage of large amounts of chlorine, the production of large quantities of waste consisting of aqueous solutions contaminated by chlorine byproducts, and the high environmental risk in storage, transportation, and use of a reagent characterized by high toxicity and volatility. As a consequence, it might be expected that the use of phosgene would be limited, as a precautionary measure, to laboratory scale preparation of special ureas, however, the quantity of phosgene that is produced and used worldwide is about 2 million tons per year.

Unsymmetrical peptidyl ureas, which are highly active as pepsine inhibitors, are synthesized by using various amino acid or amino alcohol hydrochlorides and phosgene. Thus urea **4** is prepared in 91% yield according to the synthetic sequence shown in Scheme 1 which consists of a two-step, one-flask process involving first production of the isocyanate **2** from amino acid methyl ester **1** and phosgene followed by in situ condensation with (*S*)-2-amino-3-phenylpropanol (**3**); a total of 15 examples are reported for this synthesis with a yield range of 51–95%.^[3]

Scheme 1 Synthesis of an Unsymmetrical Peptidyl Urea^[3]

Similarly 1,3-bis(1-benzopyran-8-yl)urea **6** is synthesized in 91% yield from ethyl 8-amino-6-*tert*-butyl-4-oxo-4*H*-1-benzopyran-2-carboxylate (**5**) upon reaction with phosgene (Scheme 2). Both ester groups of 1,3-bis(1-benzopyran-8-yl)urea **6** can be readily transformed into amides by aminolysis with 2-ethylhexylamine to afford the corresponding biscarboxamide, a receptor of carboxylates.^[4] A macrocyclic chiral receptor for lactic and mandelic acids is synthesized by using similar methodology.^[5]

Scheme 2 Synthesis of a 1,3-Bis(1-benzopyran-8-yl)urea^[4]

A similar approach can be successfully utilized for the preparation of cyclic ureas from diamines and phosgene in the presence of a dehydrochlorinating agent. For example, symmetrically and unsymmetrically substituted 1,2-diamines react with phosgene in the presence of a base such as sodium hydroxide^[6] or triethylamine^[7] to give the corresponding imidazolidin-2-ones, which are utilized as dipolar aprotic solvents and intermediates for pesticides and pharmaceuticals.

1,3-Bis[6-*tert*-butyl-2-(ethoxycarbonyl)-4-oxo-4*H*-1-benzopyran-8-yl]urea (**6**):^[4]

CAUTION: Phosgene is a severe respiratory irritant and very toxic by inhalation.

A soln of ethyl 8-amino-6-*tert*-butyl-4-oxo-4*H*-1-benzopyran-2-carboxylate (**5**; 0.1 g, 0.35 mmol) in THF (20 mL) was slowly added to 20% COCl_2 /toluene (3.2 mmol) and then refluxed for 15 min. Evaporation of the solvent gave a white solid. A soln of ethyl 8-amino-6-*tert*-butyl-4-oxo-4*H*-1-benzopyran-2-carboxylate (**5**; 0.1 g, 0.35 mmol) in THF (10 mL) was then added. The reaction was kept at rt for 12 h. The solvent was removed by evaporation under reduced pressure and the residue was washed with 2 M HCl and extracted with EtOAc. The organic layer was dried and evaporated to give a yellow solid that was then purified by crystallization (EtOAc) affording the product; yield: 0.19 g (91%); mp 192–193 °C.

18.8.1.1.2

Method 2: From Ureas and Thioureas

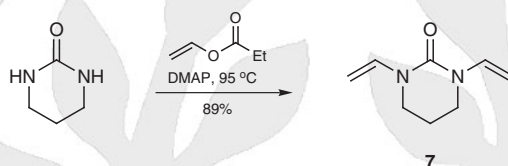
Urea itself and monosubstituted or 1,3-disubstituted ureas can be conveniently utilized as versatile and environmentally safe building blocks for the synthesis of more complex compounds containing the ureido moiety by various reactions including, at one or both amino groups, displacement, N-alkylation, imine–enamine formation, and cyclocondensation. The main drawback of these methodologies is the formation of organic and inorganic salts due to the conventional workup.

Thioureas can be also utilized as starting reagents for urea production by direct transformation of the C=S bond into C=O.

18.8.1.1.2.1

**Variation 1:
From Cyclic Ureas by N-Alkylation**

The simplest method for the preparation of N-substituted cyclic ureas is by the N-alkylation of cyclic ureas containing at least one NH group with various alkylating reagents. For example, tetrahydropyrimidin-2(1H)-one reacts with vinyl propanoate in the presence of 4-(dimethylamino)pyridine at 95 °C affording the corresponding 1,3-divinyl derivative **7** in 89% yield (Scheme 3).^[8]

Scheme 3 N-Alkylation of a Cyclic Urea^[8]

18.8.1.1.2.2

**Variation 2:
From N-(ω-Functionalized) Ureas**

Various N-(ω-functionalized) ureas can be utilized for the preparation of substituted imidazolidinones and pyrimidinones. In particular allyl- or but-3-enylureas are useful precursors of the corresponding five- or six-membered cyclic ureas. The reaction involves intramolecular N-alkylation by the double bond performed in the presence of a transition-metal catalyst, such as palladium(II) chloride, e.g. the formation of **8** (Scheme 4),^[9] N-bromosuccinimide,^[10] or iodine.^[11] Examples are given in Table 1.

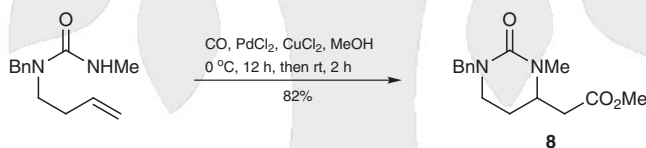
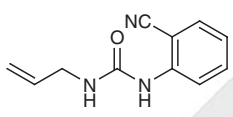
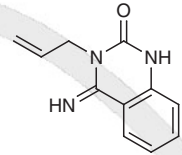
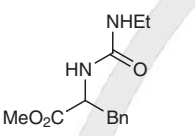
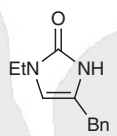
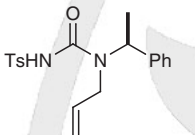
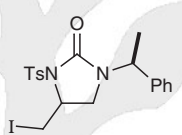
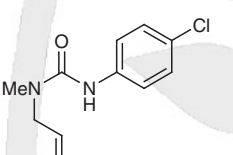
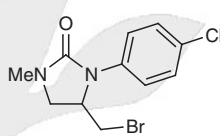
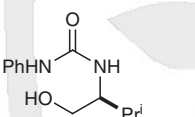
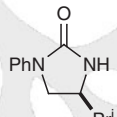
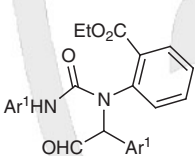
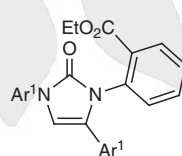
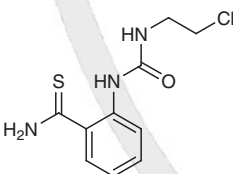
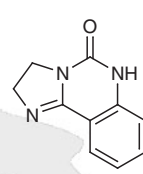
Scheme 4 Intramolecular N-Alkylation of an N-But-3-enylurea with Carbon Monoxide and Palladium(II) Chloride^[9]

Table 1 Imidazolidinone and Pyrimidinone Synthesis from *N*-(ω -Functionalized) Ureas^[10–16]

Starting Urea ^a	Reagent	Catalyst	Conditions	Product Urea ^a	Yield (%)	Ref
	–	catalase	EtOH, 37 °C, 6 h		95	[15]
	DIBAL-H	HCl	toluene/CH ₂ Cl ₂ (1:1), –78 °C, 30 min		93	[13]
	I ₂	NaHCO ₃	THF, 1 h		92 ^b	[11]
	NBS	–	CCl ₄ , 23 °C		68	[10]
	TsCl	<i>t</i> -BuOK	THF, 0 °C, 10 min		61	[16]
	O ₃	TFA	CH ₂ Cl ₂ , –78 °C, 2 min then 25 °C, 15 min		59	[14]
	–	NaOH	100 °C, 2 min		52	[12]

^a Ar¹ = 4-Tol.^b 1:1 diastereomeric ratio.

Other synthetic strategies involve the use of ureas carrying C≡N, C=O, or C=S groups that after single or double ring closure afford the corresponding substituted imidazolidinones and pyrimidinones. These reactions are promoted by basic^[12,17] or acid^[13,14] catalysts or by enzymes.^[15]

2-Hydroxyureas^[16] can also produce imidazolidinones and dihydroquinazolinones, respectively, in basic or uncatalyzed reactions.

Methyl (1-Benzyl-3-methyl-2-oxohexahydropyrimidin-4-yl)acetate (8); Typical Procedure:^[9]

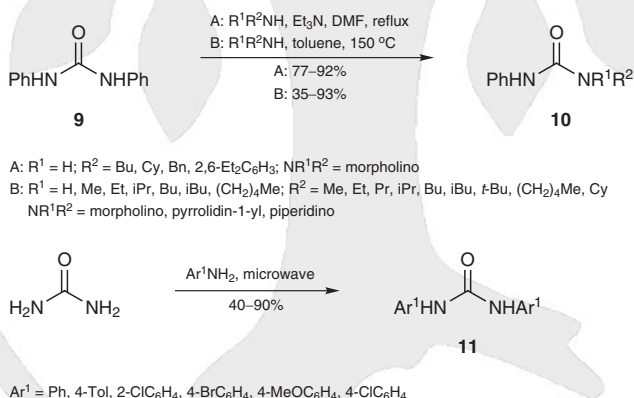
CAUTION: Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

A 10-mL, two-necked round-bottomed flask, containing a magnetic stirring bar, PdCl₂ (17.6 mg, 0.1 mmol), and CuCl₂ (400 mg, 3 mmol), was fitted with a serum cap and reflux condenser equipped at the top with a three-way stopcock connected to a balloon filled with CO. The apparatus was purged with CO by repeating pumping/filling several times via a three-way stopcock. 1-Benzyl-1-but-3-enyl-3-methylurea (204 mg, 0.94 mmol) dissolved in MeOH (5 mL) was introduced to the flask via syringe, and the mixture was stirred at 0 °C for 12 h and then at rt for 2 h. After evaporation of the solvent to dryness, EtOAc was added and the mixture was filtered with suction through a Celite pad on a medium fritted funnel. The filter cake was washed several times with EtOAc and the filtrate was washed with sat. NaHCO₃. After drying (MgSO₄), the solvent was evaporated, and the residue was purified by column chromatography (silica gel, EtOAc) affording the product; yield: 213 mg (82%).

18.8.1.1.2.3

**Variation 3:
Transamidation of Ureas**

1,3-Diphenylurea (**9**) undergoes selective triethylamine-catalyzed replacement of one aromatic amine with a primary amine or morpholine in dimethylformamide affording 1-alkyl-3-phenylureas **10** (Scheme 5). The reaction does not proceed with sterically hindered secondary amines and aromatic amines bearing electron-withdrawing groups.^[18] By carrying out the reaction in a sealed autoclave, not only primary but also secondary aliphatic amines react very well with 1,3-diphenylurea (**9**) in toluene without a catalyst giving 1,1-dialkyl-3-phenylureas **10** (Scheme 5).^[19]

Scheme 5 Reaction of Ureas with Various Aliphatic Amines^[18–20]

Symmetrically disubstituted 1,3-diarylureas **11** are similarly prepared under environmentally benign conditions by reaction of urea with aromatic amines under microwave irradiation without solvent via displacement of two molecules of ammonia (Scheme 5).^[20]

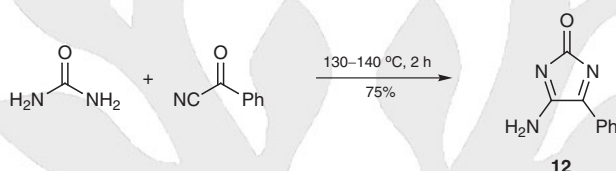
1,3-Bis(4-methoxyphenyl)urea (11, Ar¹ = 4-MeOC₆H₄); Typical Procedure:^[20]

4-Methoxyaniline (0.25 g, 2.0 mmol) was mixed thoroughly with urea (0.06 g, 1.0 mmol) in a 5-mL beaker. Then the beaker was placed in a conventional microwave oven and heated until the mixture became liquid (4 min). H₂O (10 mL) was added and the mixture was filtered to remove the unreacted urea. The recovered material was recrystallized (EtOH/H₂O) to give the product; yield: 0.23 g (85%); mp 236–238 °C.

18.8.1.1.2.4

Variation 4:
By Reaction with Bifunctional Compounds

Simple, 1-alkyl- and 1,3-dialkylureas react with 1,2- or 1,3-difunctionalized compounds affording the corresponding five- or six-membered ring ureas via double nucleophilic substitution. The bifunctional starting material can be represented by symmetrical reagents such as diols,^[21] bis(trimethylsilyl)-protected diols,^[22] alkylene carbonates,^[23] 1,2- or 1,3-dicarbonyl compounds^[24–27] and 1,2-diamines^[28] or by α -hydroxy ketones,^[29] benzoyl cyanides (e.g., formation of **12**, Scheme 6),^[30] and β,β -dialkoxy cyanides.^[31] Examples are given in Table 2. The synthesis of steroids bearing heterocycles fused on ring D has pharmaceutical interest, thus heterosteroids have been synthesized in which the C₁₆–C₁₇ bond of the steroid is fused to a pyrimidine ring. Thus, treatment of 3 β -acetoxy-17-oxoandro-5-ene with various aromatic aldehydes gives the corresponding C16 arylidene derivatives which, on base-catalyzed condensation with urea affords the 3 β -acetoxy-6'-aryl-3',6'-dihydroandro-5-eno[17,16-*d*]pyrimidin-2'(1'*H*)-one.^[32]

Scheme 6 Formation of 4-Amino-5-phenyl-2*H*-imidazol-2-one^[30]

Table 2 Formation of Five- or Six-Membered Ring Ureas via Double Nucleophilic Substitution^[21,23,26,27,29,31,32]

R ¹	R ²	X–Y	Catalyst	Conditions	Product	Yield (%)	Ref
Me	H		TMSCl	DMF, 20 °C, 12 h		99	[27]
Me	Me		–	230 °C, 5 h		99	[23]
Me	Me		RuCl ₂ (PPh) ₃	THF, 180 °C, 5 h		79	[21]
H	H		NaOH	EtOH, reflux, 15 h		77	[32]

Table 2 (cont.)

R ¹	R ²	X–Y	Catalyst	Conditions	Product	Yield (%)	Ref
H	H		NaOMe	xylene, reflux, 3 h		74	[31]
H	H		–	ethylene glycol, 180 °C, 1 h		70	[29]
H	H		HCO ₂ H	130–135 °C, 1.5 h		63	[26]

4-Amino-5-phenyl-2H-imidazol-2-one (12); Typical Procedure:^[30]

A mixture of urea (1.20 g, 20 mmol) and benzoyl cyanide (2.62 g, 20 mmol) was heated on an oil bath at 130–140 °C for 2 h. The solid obtained on cooling was recrystallized (EtOH) to give the product; yield: 2.60 g (75%); mp 204–206 °C.

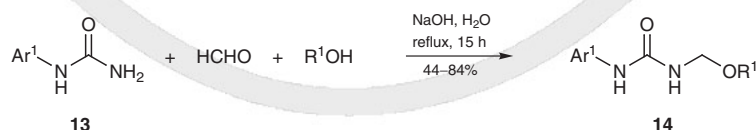
18.8.1.1.2.5

**Variation 5:
Reductive N-Alkylation of Ureas**

N-Alkylation of urea or N-monosubstituted ureas with aldehydes affords N-alkylideneureas that are readily converted into 1,3-disubstituted unsymmetrical ureas by reduction with sodium borohydride. The production of the intermediate N-alkylideneurea is catalyzed by the Lewis acid titanium(IV) isopropoxide. The reaction is efficiently performed with aromatic aldehydes whereas aldehydes containing α -hydrogens undergo side reactions. A total of ten examples are reported with a yield range of 39–94%.^[33]

In the presence of chlorotrimethylsilane as a dehydrating agent in a one-pot process, the N-monoalkylation of urea occurs efficiently and can be performed by using a large excess of urea (20:1).^[34]

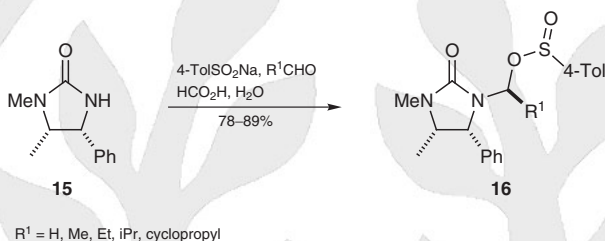
1-(Alkoxyethyl)-3-arylureas **14** are formed by three-component condensation of an arylurea **13** with formaldehyde and an alcohol in the presence of sodium hydroxide (Scheme 7). The reaction probably involves the formation of an iminium ion intermediate.^[35]

Scheme 7 Three-Component Synthesis of 1-(Alkoxyethyl)-3-arylureas^[35]

Ar¹ = Ph, 4-ClC₆H₄, 4-OC₆H₄; R¹ = Me, Et

Similarly cyclic ureas **16** are synthesized in a one-pot, three-component preparation from aldehydes, sodium 4-toluenesulfinate, and cyclic ureas **15** (Engbert's method) (Scheme 8); the reaction, which affords analytically pure products after simple filtration of the crude mixture, can be performed under acidic conditions (formic acid) at room temperature for a very short reaction time (15 min). It is interesting to note that when chiral imidazolidin-2-ones are employed in the sulfonylalkylation reaction, a single diastereomeric sulfone is produced.^[36]

Scheme 8 Diastereoselective Three-Component Urea Synthesis^[36]



Reductive 1,3-dialkylation of cyclic ureas such as imidazolidin-2-one with isobutyraldehyde in the presence of formic acid at 110 °C for 30 hours gives the corresponding 1,3-diisobutylimidazolidin-2-one in 83% yield.^[37]

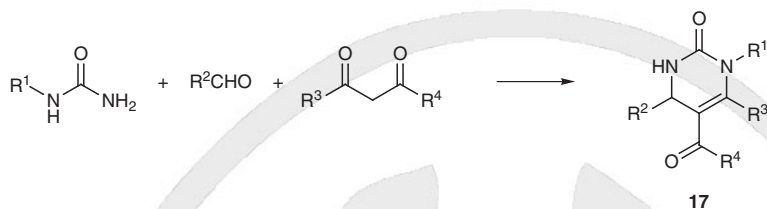
(4R,5S)-1,5-Dimethyl-4-phenyl-3-[(1S)-1-(4-tolylsulfinyloxy)ethyl]imidazolidin-2-one (16, $R^1 = \text{Me}$); Typical Procedure:^[36]

Freshly distilled MeCHO (1.10 g, 25.0 mmol) in MeOH (0.5 mL) was added to a soln of (4R,5S)-1,5-dimethyl-4-phenylimidazolidin-2-one (**15**; 0.96 g, 5.0 mmol) and sodium 4-toluenesulfinate dihydrate (1.17 g, 5.5 mmol) in H_2O (5 mL). The pH was adjusted to ca. 2 with 88% HCO_2H (20 mL), and the mixture was stirred at rt for 15 min. The resulting white precipitate was filtered and washed sequentially with H_2O and petroleum ether, giving the product as white solid; yield: 1.58 g (85%); mp 115.5–116.5 °C.

18.8.1.1.2.6

Variation 6:
By Three-Component Reaction with Aldehydes and
 β -Dicarbonyl Compounds (Biginelli Reaction)

The Biginelli condensation is the most practical method for the preparation of dihydropyrimidines. In general the reaction is carried out by simply heating a mixture of the three easily accessible and inexpensive reagents (an aldehyde, a β -dicarbonyl compound, and a urea) with a protic or Lewis acid as the catalyst. The product **17** of this one-pot, three-component synthesis precipitates on cooling of the reaction mixture; the most relevant results of practical application are summarized in Scheme 9. Thus a domino multi-component process occurs without isolation of any intermediate, reducing time, saving money, energy, and raw materials, with both economic and environmental benefit.^[38,39] A further advantage of this methodology is represented by the high atom economy^[40] as only two water molecules are eliminated during the process.

Scheme 9 The Formation of Dihydropyrimidin-2(1*H*)-ones by the Biginelli Condensation^[41–50]

R ^{1a}	R ²	R ³	R ⁴	Catalyst	Conditions	Yield (%)	Ref
H	3-O ₂ NC ₆ H ₄	OH	CO ₂ H	TFA	ClCH ₂ CH ₂ Cl, reflux, 12 h	99	[45]
H	2-thienyl	Me	OEt	AcOH, microwave	2 min	97	[44]
H	Ph	Me	OEt	FeCl ₃ •6H ₂ O, HCl	EtOH, reflux, 4 h	94	[41]
H	2-pyridyl	Me	Me	InCl ₃	THF, 65–70 °C, 6 h	93	[42]
H	(CH ₂) ₄ Me	Me	OEt	1-butyl-3-methylimidazolium tetrafluoroborate	100 °C, 30 min	93	[49]
H	Cy	Me	OEt	BiCl ₃	MeCN, reflux, 5 h	92	[46]
H	2-furyl	Me	OEt	LiClO ₄	MeCN, reflux, 5 h	85	[43]
H	CH=CHPh	Me	OEt	montmorillonite KSF	130 °C, 48 h	70	[48]
H	2-F ₃ CC ₆ H ₄	Me	OCH ₂ (P) ^b	HCl	dioxane, 70 °C, 48 h	70	[50]
H		Me	OEt	CuCl, BF ₃ •OEt ₂ , AcOH	65 °C, 24 h	63 ^c	[47]

^a These examples show urea as the substrate but examples are available with R¹ = alkyl and phenyl.

^b (P) = polymer (Wang resin).

^c 3:1 diastereomeric ratio.

The multifunctionalized dihydropyrimidine scaffold is a heterocyclic system of remarkable pharmacological importance and a tremendous increase in interest in this topic has occurred since 1999 as shown by the growing number of publications and patents on this subject. The best results are obtained with aromatic aldehydes,^[41–45,51–54] whereas only few cases are reported for aliphatic aldehydes.^[46,47,55,56] More environmentally friendly methodologies for performing the Biginelli reaction have been developed. These include the use of natural clays,^[48] ionic liquids,^[49] and resin-bound Lewis acids^[57] as catalysts that are easily removed from the reaction mixture and can be reused. The reaction can also be performed in the solid phase by using polymer-bound reagents such as the urea^[58] or the β-dicarbonyl compound.^[50]

Advances in the Biginelli synthesis have been discussed in a review.^[59]

Ethyl 6-Methyl-2-oxo-4-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate
(17, R¹ = H; R² = CH=CHPh; R³ = Me; R⁴ = OEt); Typical Procedure:^[48]

To a flask equipped with magnetic stirrer and condenser were added (*E*)-cinnamaldehyde (1.3 g, 10 mmol), urea (0.9 g, 15 mmol), ethyl acetoacetate (1.3 g, 10 mmol), and montmorillonite KSF (0.5 g). The mixture was heated at 130 °C under stirring for 48 h. Hot MeOH

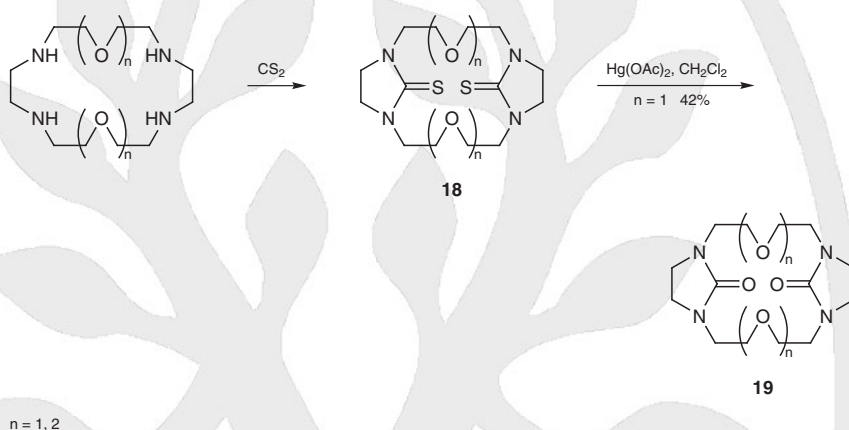
(100 mL) was added and the mixture was filtered to remove the catalyst. The product crystallized overnight and was recovered by filtration; yield: 2.0 g (70%); mp 232–235 °C.

18.8.1.1.2.7

Variation 7: Transformation of Thioureas

A short method for the synthesis of ureas is the transformation of the thiourea group C=S to the urea group C=O. In particular, macrocyclic ureas **19** are obtained after treatment of the corresponding macrocyclic thioureas **18**, prepared from carbon disulfide and 1,4-diaza compounds, with mercury(II) acetate in dichloromethane (Scheme 10).^[60]

Scheme 10 Synthesis of Macrocyclic Ureas^[60]



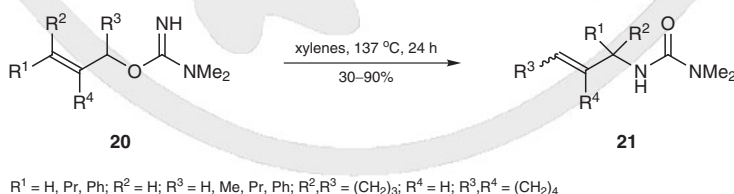
18.8.1.1.3

Method 3: From Isoureas by Isomerization

Isoureas, alternatively called pseudoureas, are related to ureas in terms of structure, stability, and reactivity.^[61] The overall synthetic utility of isoureas relies on their conversion into different classes of organic compounds such as esters, ethers, sulfides, and ureas.

The synthesis of ureas from isoureas is based on a thermal [3,3]-sigmatropic rearrangement of allyl and propargyl substituents on the isourea oxygen. *O*-Allylisoureas **20** are simply prepared by reaction of an allyl alcohol with dimethylcyanamide (1:1 molar ratio) in the presence of sodium hydride (0.1 molar equivalents) at room temperature. Thermal rearrangement of **20** in refluxing xylenes results in the transposition of oxygen and nitrogen functionalities with the production of ureas **21** (Scheme 11).^[62]

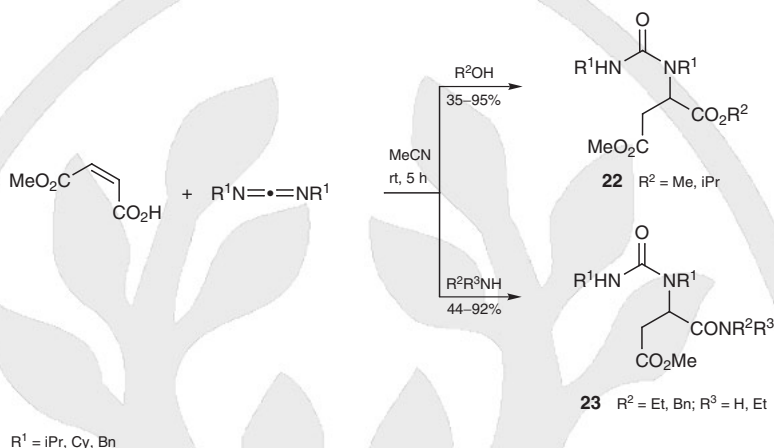
Scheme 11 Thermal Rearrangement of Isoureas into Ureas^[62]



Ureidosuccinic acid derivatives **22** are efficiently prepared by a three-component reaction between maleic acid monomethyl ester, carbodiimides, and alcohols in acetonitrile at room temperature for 5 hours (Scheme 12). Addition of primary or secondary amines in

place of the alcohol affords the corresponding amido ester derivatives **23** via an *O*-acylisourea intermediate.^[63]

Scheme 12 Ureidosuccinic Acid Derivatives from Maleic Acid Monomethyl Esters, a Carbodiimide, and Alcohols or Amines^[63]



2-Ureido-1,3-dienes are produced from 3-ethynylisoureas, readily prepared from the corresponding alcohols and diisopropylcarbodiimide in the presence of copper(I) chloride. The 3-ethynylisoureas are converted into the corresponding oxazolidines by treatment with silver trifluoromethanesulfonate. Reaction of oxazolidines with 1 equivalent of acetic acid in boiling benzene affords 2-ureido-1,3-dienes; four examples are reported but the yield is unspecified.^[64]

Methyl 3-[(Benzylamino)carbonyl]-3-(1,3-dicyclohexylureido)propanoate (23, $R^1 = \text{Cy}$; $R^2 = \text{Bn}$; $R^3 = \text{H}$); Typical Procedure:^[63]

To a soln of dicyclohexylcarbodiimide (0.3 g, 1.49 mmol) and BnNH_2 (1.8 mL, 1.64 mmol) in MeCN (1.2 mL) was added dropwise a soln of maleic acid monomethyl ester (0.19 g, 1.49 mmol) in MeCN (8.3 mL). The mixture was stirred at rt for 5 h and then the soln was concentrated under reduced pressure. EtOAc was added to the residue and the soln was successively washed with 1 M HCl and NaHCO_3 . The organic layer was dried (MgSO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc 23:2) affording the product; yield: 0.61 g (92%); mp 133–135°C.

18.8.1.1.4

**Method 4:
From Isocyanates**

Isocyanates are useful intermediates in organic synthesis^[65] especially in the preparation of substituted ureas. The most common method for the preparation of these compounds comprises the reaction of phosgene with aliphatic and aromatic amines.^[66] This method has been modified by using various substitute reagents for the highly toxic phosgene^[67] and also by using an *in situ* method with conversion into the desired ureas via a cascade process. The easy production of isocyanates, even from multifunctional precursors, makes this methodology one of the most frequently utilized synthetic routes for urea synthesis. It is important to underline that only a few isocyanates are commercially available and the preparation of isocyanates in the laboratory has obvious environmental problems.

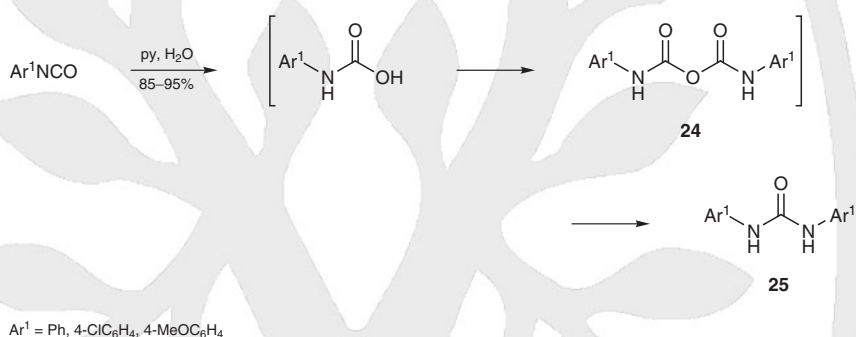
18.8.1.1.4.1

**Variation 1:
By Reaction with Amines or Imines**

The direct reaction of commercially available isocyanates with amines is the simplest route for the large-scale preparation of substituted ureas. Thus 3-methyl-1,1-diphenylurea is prepared in 95% yield by reaction of methyl isocyanate and diphenylamine in toluene at 100°C for 8 hours in the presence of a small amount of dibutyl phosphate.^[68] The same approach can be utilized for the synthesis of more sophisticated ureas for protein chemistry and biology.^[69]

As expected, symmetrical ureas **25** are selectively prepared by partial hydrolysis of aryl isocyanates with pyridine/water mixture. The process is notably of use where the parent amine is not readily accessible and it is also compatible with isocyanates generated in situ from carboxylic acid azides via the Curtius rearrangement. There is evidence for an amine-free mechanistic pathway probably involving a carbamic anhydride **24** (Scheme 13).^[70]

Scheme 13 Conversion of Aryl Isocyanates into Symmetrical 1,3-Diarylureas^[70]



A complete one-flask process for the production of ureas bearing methacrylate frameworks is represented by the reaction of isolable isocyanates with the amine derived from partial hydrolysis of the isocyanate itself. These isocyanates are produced by the condensation of sodium cyanate with chloroalkyl methacrylate under phase-transfer catalytic conditions.^[71]

Bromo-Wang resin reacts with various amines affording amino resins that then react with a variety of isocyanates giving traceless ureas (ureas prepared through traceless linkers) after cleavage from the resin by treatment with trifluoroacetic acid.^[72]

Ultrapur ureas are prepared by reaction of aliphatic amines with an excess of isocyanate, and subsequent treatment with aminomethyl polystyrene resin that acts as a scavenger for the unreacted isocyanate.^[73]

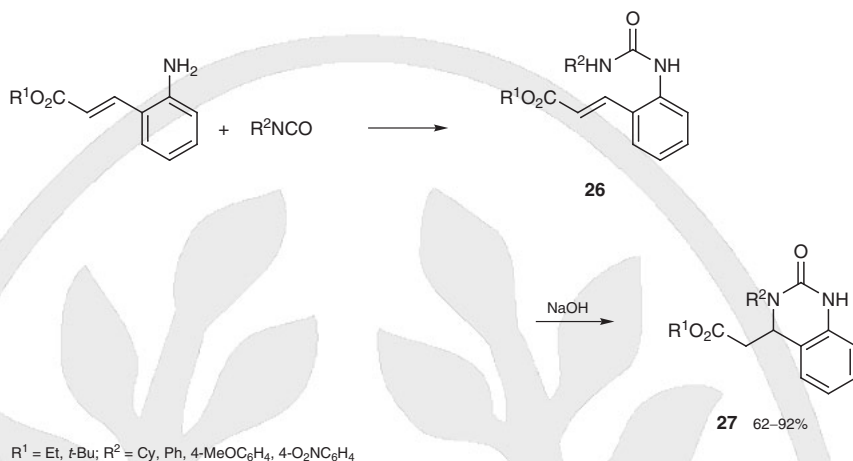
Macrocycles bearing urea moieties are synthesized in good yields simply by reacting cyclams or their partially protected derivatives with alkyl isocyanates, a total of six examples are reported with a yield range of 30–98% yield.^[74] Following the same synthetic strategy, two examples of the synthesis of bismacrocycles bridged by urea moieties are available, these are obtained by reacting the starting amines with diisocyanates in 67–69% yield.^[74] Their complexes with metal ions such as zinc(II) or copper(II) show especially strong affinity for DNA.

Cyclic ureas are produced by a similar reaction when the starting amine or imine contains an additional group in the 2- or 3-position able to undergo ring closure by intramolecular reaction with linear ureas produced by the initial addition of the imino group to the isocyanate. Some examples are reported in Table 3.^[75–78]

Table 3 The Formation of Cyclic Ureas^[75–78]

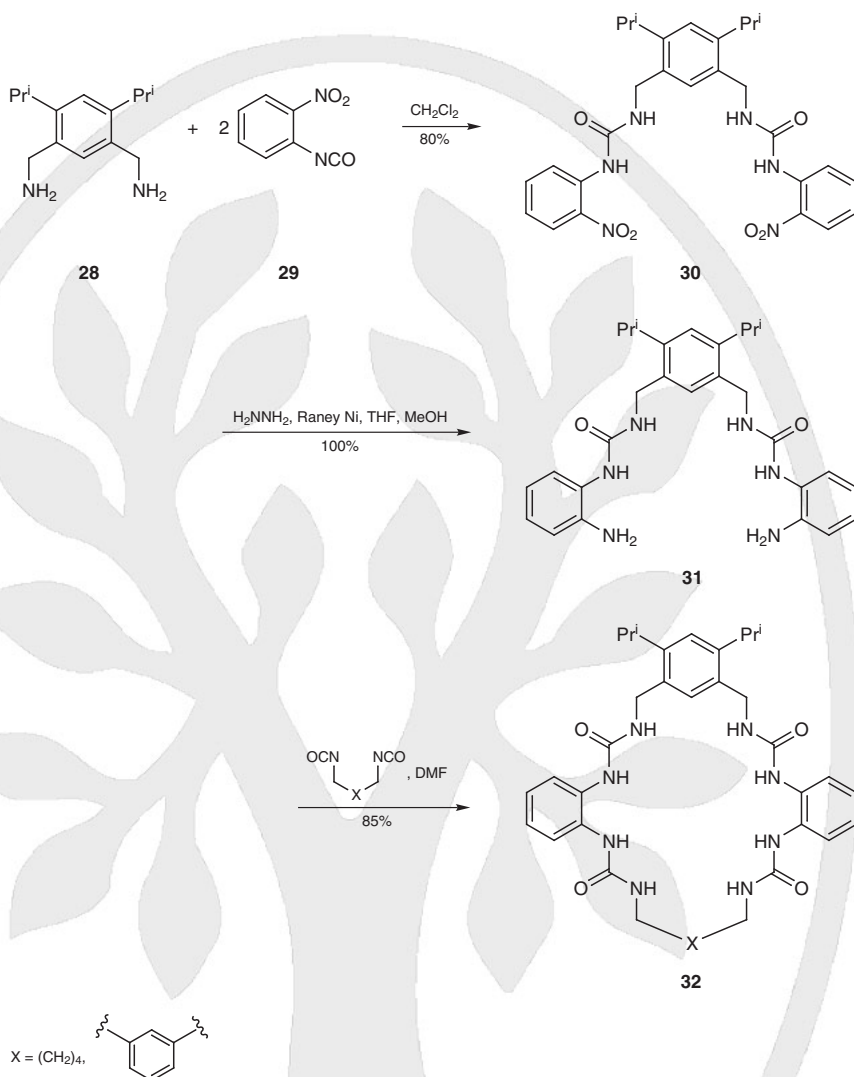
Entry	FG–NH ₂	R ¹ NCO	Catalyst, Conditions	Product	Yield (%)	Ref
1		PhNCO	microwave, DMA, 6+5 min		82	[77]
2			benzene, 25 °C, 4–5 h		81	[78]
3		PhNCO	1. Et ₂ O, rt, 8 h 2. NaOH, THF, rt, 10 min		75	[76]
4		PhNCO, (EtO) ₂ CO	K ₂ CO ₃ , heat		51	[75]

For example, 1-phenyl-3-vinylimidazolidin-2-one (Table 3, entry 4) is prepared in 51% yield on reaction of phenyl isocyanate with diethanolamine in the presence of diethyl carbonate and potassium carbonate by removing the ethanol formed during the reaction.^[75] More interestingly dihydroquinazolinone derivatives **27** (Scheme 14 and Table 3, entry 3), an important class of heterocyclic compounds with pharmaceutical application, are synthesized by the intramolecular hetero-Michael addition of a phenylurea to an *ortho*-substituted α,β -unsaturated ester **26** in the presence of sodium hydroxide. The yield is strictly dependent on the substituent on the isocyanate (Scheme 14).^[76]

Scheme 14 The Formation of Dihydroquinazolinones^[76]

Arylcarbodiimides bearing an α,β -unsaturated ester moiety in the *ortho* position (derived from the aza-Wittig reaction of an iminophosphorane with an isocyanate) afford the same class of products **27** after cyclization promoted by tetrabutylammonium fluoride in tetrahydrofuran, a total of eight examples are reported with a yield range of 40–88%.^[79] High purity 1,3-dihydro-2*H*-benzimidazol-2-ones are prepared in very short reaction times under microwave irradiation by treatment of 1,2-diaminoarenes with phenyl isocyanate in dimethylacetamide/diethylene glycol (9:91) as solvent, three examples are reported in 88–94% yield, an example is shown in Table 3, entry 1; see also *Science of Synthesis*, Vol. 12 [Five-Membered Hetarenes with Two Nitrogen or Phosphorus Atoms (Section 12.4.1.1.1.1)].^[77] The preparation of dihydrobenzoxadiazepin-4(3*H*)-ones in 52–81% yield (six examples) is performed by an uncatalyzed ring closure of 1-aryloxy-1,1-disubstituted methyl isocyanates with 2-aminophenols, for an example see Table 3, entry 2; the disadvantage of this method is the use of benzene as the solvent.^[78]

Special macrocyclic ureas **32** are prepared by a three-step process involving first a reaction between 1,3-bis(aminomethyl)arene **28** and 2-nitrophenyl isocyanate **29**, a reduction of the nitro group in the product **30** to give the amine **31** and final reaction with a diisocyanate (Scheme 15). The so obtained tetrakisureas **32**, in which four hydrogen bond donating urea moieties are present in a preorganized fashion, exhibit strong binding of the phosphate anion with at least 100-fold selection for the phosphate anion over chloride.^[80]

Scheme 15 Preparation of Macrocyclic Ureas^[80]

Ethyl (2-Oxo-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (27, R¹ = Et; R² = Ph);

Typical Procedure:^[76]

To a soln of ethyl 2-aminocinnamate (191 mg, 1.0 mmol) in Et₂O (5 mL) was added PhNCO (119 mg, 1.0 mmol). The mixture was stirred at rt for 8 h, the precipitate was then filtered and washed with Et₂O to give the pure urea product ethyl 2-(3-phenylureido)cinnamate (**26**, R¹ = Et; R² = Ph); yield: 254 mg (82%). This urea derivative (31 mg, 0.1 mmol) was then dissolved in THF (1 mL), followed by the addition of 1 M NaOH (0.1 mL). The mixture was allowed to stir at rt for 10 min to complete the reaction. This was diluted with H₂O and extracted with EtOAc. The organic phase was dried (MgSO₄), filtered, and concentrated under reduced pressure to afford the product as white solid; yield: 28 mg (91%); mp 139–140 °C.

18.8.1.1.4.2

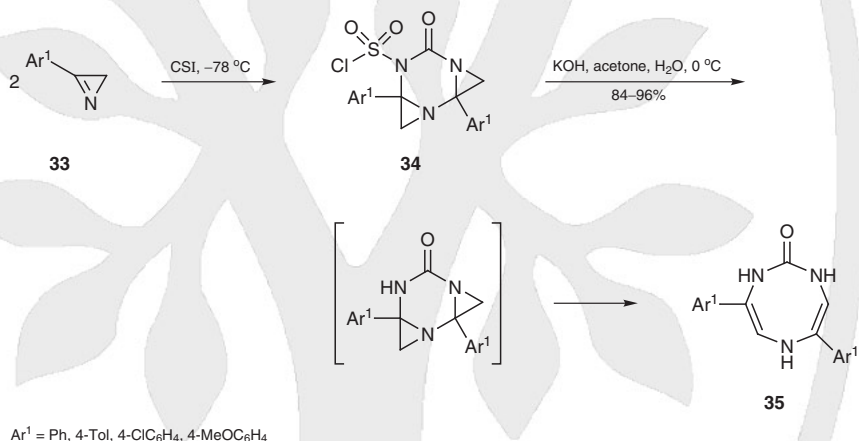
**Variation 2:
By Reaction with Azirines and Aziridines**

Aziridines react with isocyanates in the presence of palladium-based catalysts to afford imidazolidin-2-ones via a [3+2]-cycloaddition process. The reaction is characterized by a high level of regioselectivity, leading to the formation of a single regioisomer.^[81,82] Following this procedure, two chiral imidazolidin-2-ones have been prepared in 80–86% yield starting from enantiomerically pure disubstituted aziridines.^[82]

Azirines can also be employed for the preparation of substituted imidazol-2-ones in similar reactions when trimethylsilyl isocyanate is used as the starting reagent; the presence of a proton source, namely methanol, is required. The intermediate in the process is a zwitterionic form derived by rearrangement of the cycloaddition product that is solvolyzed by methanol; three examples are reported with a yield range of 30–76%.^[83]

An elegant synthesis of eight-membered ring ureas **35** is performed by a three-component reaction between two azirine molecules **33** and chlorosulfonyl isocyanate (CSI) (Scheme 16). The process requires the presence of aqueous potassium hydroxide for the hydrolysis of the [2+2+2]-cycloaddition products **34**.^[84]

Scheme 16 Synthesis of Eight-Membered Ring Ureas^[84]


4,7-Diphenyl-3,6-dihydro-1,3,6-triazocin-2(1H)-one (35, Ar¹ = Ph); Typical Procedure:^[84]

3-Phenyl-2*H*-azirine (**33**, Ar¹ = Ph; 0.468 g, 4 mmol) was treated with CSI (0.36 mL, 4 mmol). Chromatography (silica gel) afforded the cycloadduct product **34** (Ar¹ = Ph); yield: 0.25 g (33%); mp 95 °C. This **34** (Ar¹ = Ph; 0.15 g, 0.4 mmol) was dissolved in acetone/H₂O (9:1, 20 mL) and cooled to 0 °C. 5% aq KOH was added slowly until the soln became neutral. It was then diluted with H₂O (10 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The combined extracts were dried (Na₂SO₄) and evaporated under reduced pressure. The residue was flash chromatographed (Et₂O/acetone 1:1) and recrystallized (CH₂Cl₂/petroleum ether 1:1); yield: 0.1 g (90%); mp 125 °C.

18.8.1.1.4.3

**Variations 3:
Miscellaneous Reactions**

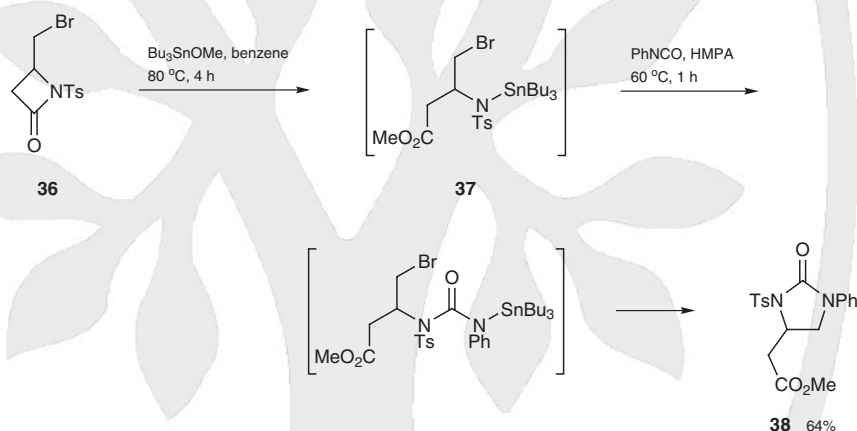
Various compounds are utilized in the reaction with both organic and inorganic isocyanates for the preparation of pyrimidinones, pyrimidinediones, imidazolidinones, and quinazolinones and are included in this section.

2-Vinyl-4,5-dihydrooxazoles, readily prepared from β -amino alcohols and α,β -unsaturated acid chlorides, can act as azadienes in a cycloaddition reaction with isocyanates to give the corresponding dihydropyrimidinone derivatives with complete diastereocontrol; five examples are reported with a yield range of 59–82% yield.^[85]

Diacylketene *N,S*-acetals refluxed in toluene for 2.5 hours under argon with phenyl isocyanates without addition of catalyst afford functionalized pyrimidin-2(1*H*)-ones; five examples are reported with a yield range of 78–88%.^[86] By carrying out the same reaction with 2,2-diacylethene-1,1-diamines, double addition with isocyanates is observed; subsequent double dehydration affords 4,6-dihydropyrimido[4,5-*d*]pyrimidine-2,7(1*H*,3*H*)-diones in 28–71% yield.^[86]

4-(Bromomethyl)-1-tosylazetidin-2-one (**36**) undergoes ring opening by reaction with tributyltin methoxide in benzene giving a tin–amide intermediate **37** that in turn can be trapped with phenyl isocyanate to produce the corresponding imidazolidin-2-one **38**. The reaction needs the presence of hexamethylphosphoric triamide, which coordinates the tin in the tin–amide intermediate **37** thus favoring its nucleophilicity toward the phenyl isocyanate (Scheme 17).^[87] The use of two suspect human carcinogen substances such as benzene and hexamethylphosphoric triamide makes this method applicable only with special care.

Scheme 17 Synthesis of Imidazolidin-2-ones from Azetidin-2-ones^[87]



Cyclic carbamates and carbonates react with one or two molecules of isocyanate in the presence of aluminum trichloride or ethylenebis(triphenylphosphine)platinum(0) respectively, affording substituted imidazolidin-2-ones.^[88,89]

Inorganic isocyanates are also employed for the production of cyclic ureas. In particular potassium isocyanate reacts, as expected, with 2-aminopropanal dimethyl acetal in acidic water affording the ureido acetal intermediate, which undergoes ring closure to a 1,3-dihydroimidazol-2-one after treatment with hydrogen chloride in ethanol.^[90] Similarly aromatic *o*-amino ketones react with potassium isocyanate in glacial acetic acid directly affording the corresponding quinazolin-2(1*H*)-ones.^[91]

Methyl (2-Oxo-1-phenyl-3-tosylimidazolidin-4-yl)acetate (**38**).^[87]

CAUTION: Hexamethylphosphoric triamide is a possible human carcinogen and an eye and skin irritant.

Bu_3SnOMe (1.85 g, 5.7 mmol) was added to 4-(bromomethyl)-1-tosylazetidin-2-one (**36**; 1.94 g, 6.0 mmol) in benzene (5 mL) (**CAUTION:** carcinogen) under N_2 . This soln was stirred at 80°C for 4 h then, after cooling to rt, PhNCO (0.60 g, 5 mmol) and HMPA (0.90 g,

5 mmol) were added. After heating at 60 °C for 1 h, the mixture was chromatographed (silica gel) affording a white solid that after recrystallization (benzene/hexane) gave the product as white needles; yield: 1.24 g (64%); mp 148–149 °C.

18.8.1.1.5

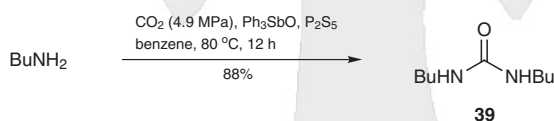
Method 5: From Carbon Dioxide

The use of carbon dioxide in industrial applications represents an important goal since minimization of carbon dioxide emission can be achieved by direct fixation into the target compound.^[92] Despite the fact that activation and use of carbon dioxide in chemical reactions is not an easy process, several important applications have been developed such as the production of carbamates which are utilized *per se* and as intermediates to fine chemicals including unsymmetrical ureas.

It is well known that carbon dioxide readily undergoes addition to amines to give the corresponding carbamic acids even at room temperature and ambient pressure. The formation of ureas from carbamic acids requires high reaction temperatures, ~200 °C, and pressures higher than 10 MPa because the conversion of carbamic acids into isocyanates, the active intermediates, occurs only under such conditions.^[93] Moreover the synthesis of ureas from amines and carbon dioxide involves elimination of water. Although the use of various dehydrating agents such as carbodiimides^[94] and diorgano phosphites^[95] converts this method into a direct condensation, the methodology is of little practical interest since it involves the use of expensive and problematic reagents in stoichiometric amounts.

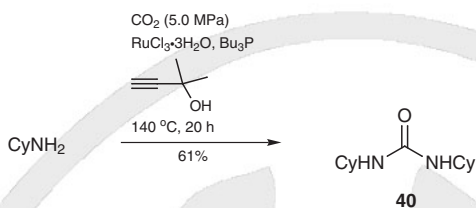
Triphenylstibine oxide catalyzes the carbonylation of diamines $\text{H}_2\text{N}(\text{CH}_2)_n\text{NHR}^1$ ($n = 2, 3$; $\text{R}^1 = \text{Me}, \text{CH}_2\text{CH}_2\text{OH}, \text{CH}_2\text{CHMeOH}$) with carbon dioxide in the presence of 3-Å molecular sieves, giving the corresponding cyclic ureas in 83–98% yield.^[96] The modified catalyst triphenylstibine oxide/phosphorus pentasulfide (utilized in the molar ratio amine/ $\text{Ph}_3\text{SbO}/\text{P}_2\text{S}_5$ 40:1:2) is highly effective for the carbonylation of both amines and diamines giving linear and cyclic ureas at 80–150 °C for 12 hours with carbon dioxide (4.9 MPa).^[97] An example is shown in Scheme 18 for the formation of 1,3-dibutylurea (**39**).^[97]

Scheme 18 The Formation of 1,3-Dibutylurea from Butylamine and Carbon Dioxide with Triphenylstibine Oxide/Phosphorus Pentasulfide as the Catalyst^[97]



In a more sophisticated way propargyl alcohols are utilized in stoichiometric amounts as water scavengers. The reaction of aliphatic and aromatic primary amines with carbon dioxide is performed at 120–140 °C in the presence of ruthenium(III) chloride trihydrate/tributylphosphine mixture (molar ratio amine/ruthenium 100:1) and an excess of propargyl alcohol derivative (generally 2-methylbut-3-yn-2-ol) affording 1,3-disubstituted symmetrical ureas in 41–68% yield, e.g. the formation of 1,3-dicyclohexylurea (**40**) (Scheme 19).^[98] However, both the triphenylstibine oxide and propargyl alcohol based processes can only be exploited on a laboratory scale due to the use of toxic and/or expensive reagents.

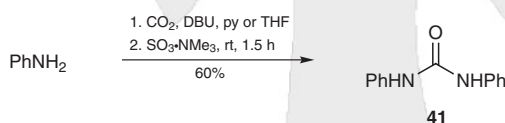
Scheme 19 The Formation of 1,3-Dicyclohexylurea from Cyclohexylamine and Carbon Dioxide with Ruthenium(III) Chloride Trihydrate as the Catalyst^[98]



More conveniently, carbamate esters are synthesized by reaction of amines with carbon dioxide and alkyl halides in the presence of a base.^[99] Use of sterically hindered guanidine bases gives best results (80–99% yield with virtually 100% selectivity). Amino acids and diamines are efficiently converted into the corresponding carbamates that can be utilized as intermediates in the synthesis of ureas. However, the use of stoichiometric amounts of base represents a serious limitation for the large-scale application of this process. A further disadvantage of this methodology is the alkylation of the amine, which affords unwanted byproducts. This side reaction can be avoided by performing the alkylation of alkylammonium alkylcarbamates readily obtained from primary amines and carbon dioxide in the presence of the crown ether 18-crown-6, which can be recovered quantitatively at the end of the reaction.^[100] An advantage that increases the industrial interest of this methodology is the possibility of reducing the production of chloride waste. In fact, different alkylating agents instead of alkyl chlorides can also be employed. The entire process occurs with yields close to 100%.^[92]

A method involving the use of carbon dioxide at ambient pressure is performed by introducing carbon dioxide into a solution of aniline and 1 equivalent of 1,8-diazabicyclo[5.4.0]undec-7-ene in pyridine or tetrahydrofuran until the exothermic reaction subsides. Addition of sulfur trioxide–trimethylamine complex as a commercially available solid, stirring at room temperature for 1.5 hours and quenching with water gives 1,3-diphenylurea (**41**) in 60% yield (Scheme 20).^[101]

Scheme 20 The Formation of 1,3-Diphenylurea from Aniline and Carbon Dioxide at Ambient Pressure^[101]



The carbon dioxide based method can be successfully utilized for the preparation of more complex compounds, such as various urea-linked sugar podando-coronand derivatives obtained by coupling of cyclams with β-cyclodextrin (β-CD) units through a urea linkage. A total of 11 examples are reported with a yield range of 14–89%.^[102] By a similar method the fully substituted narrow rim bithiazolyl-β-cyclodextrin is prepared in 29% yield.^[103]

1,3-Dibutylurea (39); Typical Procedure:^[97]

In a stainless steel reactor BuNH₂ (2.9 g, 40 mmol), Ph₃SbO (370 mg, 1.0 mmol), P₂S₅ (890 mg, 2.0 mmol), and benzene (20 mL) (**CAUTION: carcinogen**) were charged and then CO₂ was introduced under a pressure of 4.9 MPa at rt. The reactor was heated at 80 °C for 12 h. After cooling the mixture was treated with hot benzene (3 × 20 mL) and filtered to remove an insoluble residue containing the catalyst and phosphoric acid derivatives. The collected benzene soln was then evaporated to dryness. Crystallization (ligroin) afforded the pure product as colorless crystals; yield: 2.99 g (88%); mp 73 °C.

18.8.1.1.6

**Method 6:
From Carbon Monoxide**

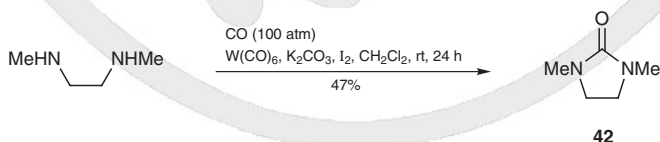
Carbon monoxide is an important reagent for the functionalization of organic compounds and is used in a wide variety of industrial and laboratory scale processes. In particular the reductive carbonylation of organic nitro compounds and the oxidative carbonylation of amines are useful phosgene-free methods for the industrial and laboratory scale synthesis of carbamates, ureas, and isocyanates, characterized by high atom economy value.^[1] The sole problem is the requirement for variable amounts of a transition-metal catalyst which raises the cost of the process because this results in special handling during waste disposal and the need for complete recovery of the catalyst when biologically active compounds are prepared. On the other hand, notably the direct conversion of aromatic nitro compounds into 1,3-diarylureas avoids the storage and manipulation of aromatic amines.

Symmetrical 1,1,3,3-tetrasubstituted ureas are synthesized in variable yield (45–69%) by carbonylation of lithium amides, prepared from the amine and butyllithium, with carbon monoxide at atmospheric pressure under mild conditions. Ureas are formed in tetrahydrofuran solution by in situ oxidation with oxygen of a hypothetical dilithium intermediate. The advantages of this method are the short reaction time and the use of oxygen as oxidant; three examples are reported with a yield range of 38–62%.^[104]

Direct carbonylation of primary amines to symmetrical 1,3-disubstituted ureas with a nitridotungsten(IV) carbonyl complex is performed in good yield (56–100%). The reaction is carried out at room temperature under nitrogen followed by oxidation with air at ambient pressure. Unfortunately the process requires a stoichiometric amount of the carbonyl complex and ureas are only obtained with primary amines since secondary ones afford formamides.^[105] In a similar improved method the reaction can be performed in high yields by using catalytic amounts of hexacarbonyltungsten. Studies of functional groups compatibility using a series of substituted benzylamines demonstrate broad tolerance of functionality during the carbonylation reaction. For many substrates, yields of ureas are higher when a two-phase dichloromethane/water system is used; a total of 19 examples are reported with a yield range of 14–85%. An example is shown in Table 4, entry 2.^[106]

The reaction of 1,ω-diamines with carbon monoxide affords cyclic ureas in moderate yield via catalytic oxidative carbonylation promoted by hexacarbonyltungsten in the presence of iodine. High dilution conditions must be used in order to avoid the formation of undesirable oligomers. This methodology is the first transition-metal-catalyzed synthetic method applicable to both primary and secondary amines. In addition, mainly due to the mild reaction conditions (rt) the procedure can tolerate a wide range of functionalities, such as halides, esters, alkenes, and nitriles. A total of 12 examples are reported with a yield range of 10–51%; a typical example is given for the formation of 1,3-dimethylimidazolidin-2-one (**42**) in Scheme 21.^[107]

Scheme 21 The Formation of 1,3-Dimethylimidazolidin-2-one from *N,N'*-Dimethylethylenediamine and Carbon Monoxide with Hexacarbonyltungsten as the Catalyst^[107]

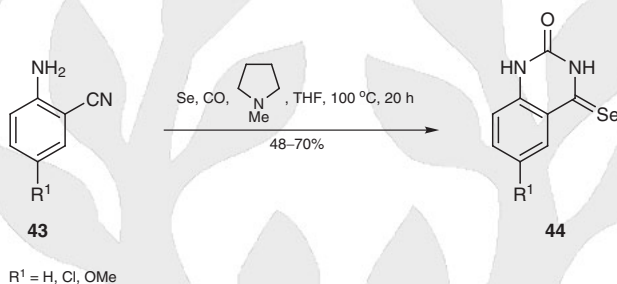


1,2-Phenylenediamine and similar aromatic compounds as well as aromatic amines bearing an amino or an alkylamino substituent in the *ortho* position can be converted into cyclic ureas by reaction with carbon monoxide in the presence of selenium and 1-methylpyrrolidine. The aliphatic amino groups, which are more nucleophilic than the aromatic

ones, react faster with selenium and carbon monoxide affording the selenocarbamate intermediates that successively undergo intramolecular cyclization by the attack of the aromatic amino group affording the five-, six-, and seven-membered ring ureas in 81–99% yield.^[108,109] Acyclic ureas were not detected in any case examined.

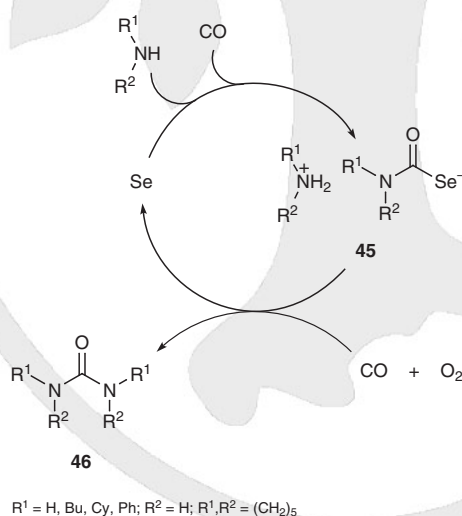
Analogously by using 2-aminobenzonitriles **43**, the same cyclization process is accomplished with carbon monoxide, selenium, and 1-methylpyrrolidine. In this case the selenium is incorporated into the final product and 4-selenoxo-3,4-dihydroquinazolin-2(1H)-ones **44** are isolated (Scheme 22).^[110]

Scheme 22 Synthesis of 4-Selenoxo-3,4-dihydroquinazolin-2(1H)-ones^[110]

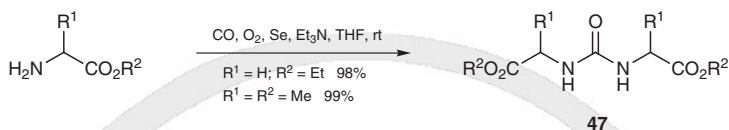


Selenium reacts with carbon monoxide and amines under mild conditions (15 °C, 1 atm) to give ammonium selenocarbamates **45** that are converted into the corresponding ureas **46** by aminolysis upon oxidation with molecular oxygen, which converts the unwanted hydrogen selenide into selenium regenerating the catalyst (Scheme 23). Under controlled conditions the reaction proceeds with a catalytic amount of selenium and its turnover number reaches ca. 1×10^4 . The reaction is strongly accelerated at elevated temperatures and pressure conditions [120 °C, O₂ (4 atm)].^[111]

Scheme 23 Selenium-Catalyzed Synthesis of 1,3-Disubstituted Ureas^[111]



The process can be successfully applied to the preparation of urea derivatives from amino acid esters. A total of ten examples are reported with a yield range of 97–99% yield, examples are shown for the formation of **47** in Scheme 24.^[112]

Scheme 24 The Formation of Urea Derivatives from Alanine and Glycine Esters^[112]

47

This approach is applicable to the synthesis of unsymmetrical phenylureas through the selenium-catalyzed reductive carbonylation of nitrobenzene in the presence of aliphatic secondary amines as coreagents. The reaction is characterized by good yields and selectivities (40–80%). By contrast, when primary amines are used as coreagents, a mixture of all three possible ureas is obtained in 20–80% yield.^[113]

It should be noted that even if elemental selenium and stable metallic selenides are relatively nontoxic, the reactive selenides, the volatile and soluble selenium compounds are highly toxic and must be handled with care.

From the approaches discussed it appears that the synthesis of ureas, with particular regard to the production of fine chemicals and pharmaceuticals, is mainly achieved through carbonylation of amines with generation of large amounts of inorganic salts that represent the main components of industrial waste. Consequently, the development of salt-free technologies by industrial and academic research groups is necessary that not only involves simpler raw materials, but also permits the replacement of stoichiometric reactions with catalytic processes. The catalytic carbonylation of nitro compounds with particular interest in nitro aromatic compounds has been extensively studied with the main focus being upon the production of isocyanates that show great commercial importance in the preparation of important industrial targets including ureas.^[114]

Different catalysts can be used to promote the process including group 8–10 metal compounds (generally Pd, Ru, and Rh) combined with a Lewis acid cocatalyst (generally FeCl_3 , MoCl_5 , V_2O_5 , Fe_2O_3) or Brønsted acid (e.g., 2,4,6-trimethylbenzoic acid). The methodology is particularly utilized with the aim of producing 4,4'-methylenedi(phenyl isocyanates) and phenylene diisocyanates, which are of commercial importance in the manufacture of polyurethanes. Concerning the synthesis of mono-isocyanates, because of their instability under the reaction conditions, the process is better utilized in the production of phenylcarbamates by trapping isocyanates with alcohols. Furthermore isocyanates can be converted in situ into ureas by reaction with amines either added to the reaction mixture or produced in situ by reduction of the nitro compound.^[1]

Some *para*-substituted symmetric 1,3-diarylureas can be synthesized in satisfactory yields by reductive carbonylation of aromatic nitro compounds with carbon monoxide in the presence of dodecacarbonyltriruthenium catalyst in a special solvent such as (*Z*)-cyclooctene (substrate/catalyst 25:1). Variable amounts of the aromatic amine and secondary amine derived by insertion of a nitrene intermediate at the allylic position of cyclooctene are also produced. Five examples are reported with a yield range of 24–88%.^[115]

Symmetrical 1,3-disubstituted ureas are obtained in fairly low yields (45–55%, three examples) by oxidative carbonylation of aliphatic amines with carbon monoxide/oxygen mixtures in the presence of different nickel complexes (substrate/catalyst 25:1) (see Table 4, entry 4).^[116] Similarly, moderate yields of symmetrical ureas are also obtained by performing the reaction in the presence of tricarbonyl(η -methylcyclopentadienyl)manganese complex irradiated with UV light. Eight examples are reported with a yield range of 10–49%, see also Table 4, entry 5.^[117]

1,3-Diphenylurea is synthesized in almost quantitative yield from nitrobenzene, aniline, and carbon monoxide in the presence of a palladium(II) complex with triphenylphosphine (0.2 mol% with respect to aniline) dissolved in a nonpolar solvent such as toluene or xylene at 120 °C. The carbamoyl complex $[\text{PhNCO}(\text{Pd})]$ or nitrene complex $[\text{PhN}(\text{Pd})]$ can be formed depending on whether nitrobenzene or aniline react with the catalyst.

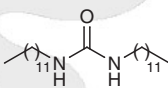
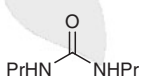
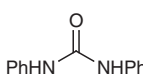
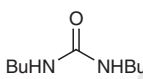
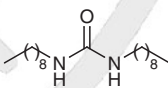
Studies with deuterated nitrobenzene suggest that the reaction involves the carbamoyl intermediate [PhNCO(Pd)] even if it is not clear how important this pathway is.^[118]

Unsymmetrical substituted ureas are likewise synthesized by reductive carbonylation of 4-substituted nitrobenzenes in the presence of an excess of an aliphatic secondary amine using palladium(II) acetate, bipyridyl, and copper 4-toluenesulfonate as cocatalyst; the best selectivity is obtained by continuously adding the aliphatic amine during the period of reaction (~10 h). Four examples are reported with a yield range of 53–99%.^[119]

Some advantages from an operational and economic point of view can be achieved by utilizing transition-metal complexes supported on heterogeneous materials that can be easily removed from the final reaction mixture and reused. The use of catalytic amount of montmorillonite-supported diacetato(bipyridyl)palladium(II) combined with di-*tert*-butyl peroxide and a little copper(II) chloride efficiently promotes the oxidative carbonylation of amines (e.g., Table 4, entry 3).^[120]

The synthesis of symmetrical 1,3-disubstituted ureas in good yields and selectivities by oxidative carbonylation of aliphatic amines is also performed in the presence of a sulfate-modified zirconia supported palladium catalyst with an initial total pressure of 4.0 MPa at 135 °C and a satisfactory turn-over frequency (TOF) value (from 190 to 718). Aromatic amines are less reactive and the reaction can be extended to the synthesis of unsymmetrical ureas with a little lower efficiency. Nine examples of symmetrical ureas are reported with a yield range of 12–99% yield (see the example given in Table 4, entry 1), while only three examples of unsymmetrical ureas are reported with a yield range of 30–88%.^[121]

Table 4 Synthesis of Ureas from Amines and Carbon Monoxide^[106,116,117,120,121]

Entry	Amine	Carbonylating Agent	Catalyst	Conditions	Product	Yield (%)	Ref
1	Me(CH ₂) ₁₁ NH ₂	CO	O ₂ , Pd, ZrO ₂ /SO ₄ ²⁻	MeCN, 135 °C, 1 h		99	[121]
2	PrNH ₂	CO	W(CO) ₆	CH ₂ Cl ₂ , H ₂ O, 90 °C, 1 h		85	[106]
3	PhNH ₂	CO	CuCl ₂ , (t-BuO) ₂ , montmorillonite/Pd(OAc) ₂ (bipy)	MeOH, HCl, rt, 10 h		89	[120]
4	BuNH ₂	CO	O ₂ , Ni(BuNH ₂) ₄ Br ₂	MeCN, 50 °C, 8 h		55	[116]
5	Me(CH ₂) ₈ NH ₂	Mn(CO) ₅ (η-MeC ₅ H ₄)	UV light	rt, 140 h		49	[117]

1,3-Dimethylimidazolidin-2-one (42); Typical Procedure:^[107]

CAUTION: Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

To a stirred soln of W(CO)₆ (30 mg, 0.085 mmol) in CH₂Cl₂ (90 mL) in the glass liner of a Parr high-pressure vessel were added *N,N'*-dimethylethylenediamine (1.36 mL, 12.8 mmol), K₂CO₃ (3.63 g, 26.4 mmol), and I₂ (3.02 g, 11.9 mmol). The vessel was then charged with CO (100 atm) and left to stir under pressure at rt for 24 h. The pressure was

released, and the yellow soln was filtered away from a white solid and concentrated. The resulting pale yellow oil was dissolved in EtOAc and column chromatographed (silica gel, EtOAc) to give the product as colorless liquid; yield: 0.68 g (47%); bp 224–226 °C.

1,3-Bis[(ethoxycarbonyl)methyl]urea (47, R¹ = H; R² = Et); Typical Procedure:^[112]

CAUTION: Carbon monoxide is extremely flammable and exposure to higher concentrations can quickly lead to a coma.

CO was passed (60 mL/min) through a vigorously stirred mixture of ethyl glycinate (1.03 g, 10 mmol), Se (0.16 g, 2 mmol), Et₃N (1 mL), and THF (40 mL) at rt until a homogeneous pale yellow soln was obtained (~1 h). Then, a mixture of CO/O₂ (20:1) was passed through the stirred soln at a rate of 10 mL·min⁻¹ for 3 h to perform the catalytic reaction, followed by O₂ alone to recover Se. Se was recovered by filtration, the filtrate evaporated and the residual solid recrystallized [benzene (**CAUTION:** carcinogen)/MeOH] to give the product as colorless solid; yield: 1.14 g (98%); mp 147–148 °C.

18.8.1.1.7

**Method 7:
From Alkyl Carbonates and Dithiocarbonates**

Alkyl carbonates are versatile chemicals mainly utilized as environmentally friendly alkylating and carboxylating reagents. The large-scale production of alkyl carbonates is performed by phosgene-free processes. Dimethyl carbonate is prepared by oxidative carbonylation of methanol and different cyclic carbonates are readily synthesized by cycloaddition of carbon dioxide with epoxides. One of the most important routes to carbamates and consequently to isocyanates, two fundamental reagents for large-scale production of ureas, is based on the methoxycarbonylation of amines with dimethyl carbonate.^[122] These processes are theoretically possible without using a catalyst, but are too slow to be useful preparative methods. The discovery of new and efficient catalysts able to promote the process consequently represents the goal of research in this field. Since these reagents contain two identical leaving groups, the success of their use in the synthesis of unsymmetrical 1,3-disubstituted ureas is dependent on the rate of the second step being much slower than that of the first, so that the formation of symmetrical ureas is minimized.

18.8.1.1.7.1

**Variation 1:
Reaction of Amines with Dimethyl Carbonate, Diethyl Carbonate,
and Bis(4-nitrophenyl) Carbonate**

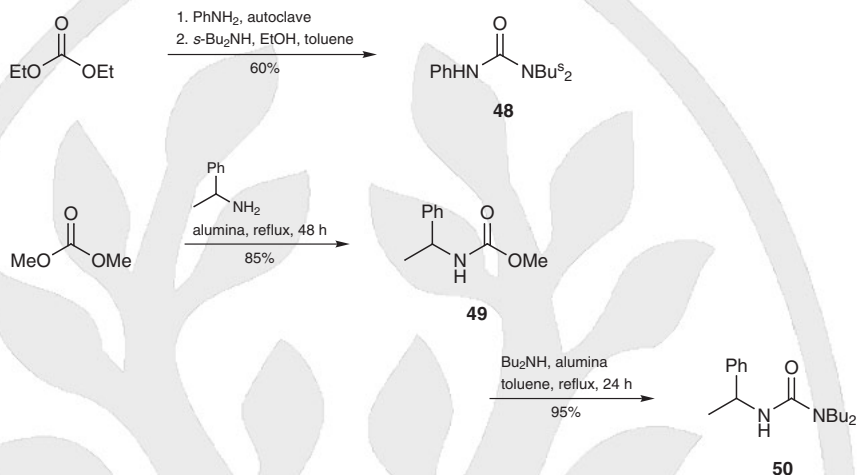
Diethyl carbonate can be efficiently utilized to produce ethyl carbamates by controlled reaction with amines, furthermore the resulting carbamates can be transformed into symmetrical or unsymmetrical ureas after further reaction with amines.

For example, diethyl carbonate is utilized as a solvent/reagent in the reaction with aniline. The first step requires a small excess of diethyl carbonate with respect to the aniline to achieve the maximum selectivity in favor of the formation of ethyl phenylcarbamate; the reaction is carried out in an autoclave. Then, after distillation of the excess diethyl carbonate and some ethanol, toluene and di-*sec*-butylamine are added. 1,1-Di-*sec*-butyl-3-phenylurea (**48**) is isolated in 60% yield (Scheme 25).^[123]

A laboratory scale procedure for the preparation of both carbamates and unsymmetrical ureas utilizes the reaction of dimethyl carbonate with amines catalyzed by γ -alumina. Selective production of carbamates in 60–95% yield and 85–100% selectivity, e.g. formation of methyl (1-phenylethyl)carbamate (**49**) (Scheme 25)^[124] is achieved only with a large excess of dimethyl carbonate. Conversion of carbamates into unsymmetrical ureas is also performed in the presence of γ -alumina and requires a 1:1 molar ratio of the re-

agents. For example, the formation of 1,1-dibutyl-3-(1-phenylethyl)urea (**50**), though a total of four examples are reported with a yield range of 66–95%.^[124] The solid catalyst can be recovered by filtration and reused after thermal activation.

Scheme 25 Unsymmetrical Ureas from Dimethyl Carbonate or Diethyl Carbonate and Amines^[123,124]



Bis(4-nitrophenyl) carbonate, which is obtained in high yield by reaction of phosgene with sodium 4-nitrophenolate, reacts at room temperature with amines producing 4-nitrophenyl alkylcarbamates in 44–78% yield (5 examples). The reaction is complete in 1–2 hours and only traces of disubstituted ureas are observed. 4-Nitrophenyl alkylcarbamates are treated with amines to form 1,3-disubstituted ureas; seventeen examples reported with a yield range of 57–96%. This reaction is considerably slower than those previously discussed. As expected, when bis(4-nitrophenyl) carbonate is reacted with an excess of amine for 4 hours, symmetrical ureas are obtained; eight examples are reported with a yield range of 93–99% yield.^[125] The process is quite simple from an experimental point of view but unfortunately requires the problematic bis(4-nitrophenyl) carbonate reagent.

1,1-Dibutyl-3-(1-phenylethyl)urea (**50**); Typical Procedure:^[124]

1-Phenylethylamine (2.4 g, 20 mmol) and the same weight of γ -alumina were mixed in dimethyl carbonate (75 mL) and refluxed under stirring for 48 h. The mixture was filtered through Celite and methyl (1-phenylethyl)carbamate (**49**) was obtained without further purification after the evaporation of dimethyl carbonate; yield: 85%. Methyl (1-phenylethyl)carbamate (**49**; 3.0 g, 16.8 mmol), the same weight of γ -alumina and Bu₂NH (2.17 g, 16.8 mmol) were mixed in toluene (10 mL) and refluxed under stirring for 24 h. The mixture was filtered through Celite and the product was obtained without further purification after the evaporation of toluene; yield: 4.4 g (95%).

18.8.1.1.7.2

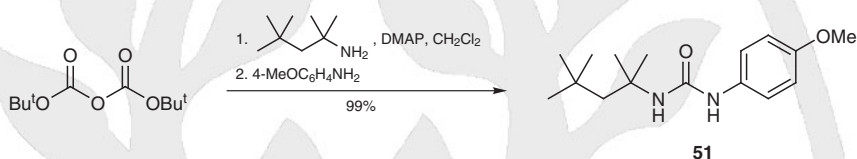
Variation 2:

Reaction of Amines with Di-*tert*-butyl Dicarbonate

Di-*tert*-butyl dicarbonate is a well-known commercially available reagent that is widely utilized as a reagent for the protection of amines as the *tert*-butoxycarbonyl group in organic synthesis. Di-*tert*-butyl dicarbonate is particularly stable under basic conditions and is inert toward many nucleophilic reagents. However, it should be emphasized that this compound is produced from phosgene and it is utilized for small-scale synthesis.

The reaction of arylamines with di-*tert*-butyl dicarbonate (molar ratio 2:1) and a catalytic amount of 4-(dimethylamino)pyridine gives symmetrical 1,3-diarylureas in 87–96% yield. The complete transformation of the isocyanate intermediate to the urea derivative is achieved by stirring the reaction mixture for 30 minutes at room temperature and subsequently for 14 hours at 40 °C. The methodology can be successfully applied to the synthesis of unsymmetrical ureas, e.g. **51** (Scheme 26). In this case the selectivity is also achieved by condensation of the sterically more hindered amine to give the isocyanate followed by nucleophilic addition of the less hindered amine; twelve examples are reported with a yield range of 81–99%.^[126] The crucial role of isocyanates as intermediates in this approach is confirmed by a detailed mechanistic study which demonstrates that carbamates are byproducts that cannot be converted into ureas.^[67]

Scheme 26 Formation of 1-(4-Methoxyphenyl)-3-(1,1,3,3-tetramethylbutyl)urea^[126]



An intramolecular version of the 4-(dimethylamino)pyridine-catalyzed reaction of amines with di-*tert*-butyl dicarbonate provides an easy access to a variety of cyclic ureas. Thus, both aliphatic and aromatic chiral 1,2-diamines are transformed into imidazolidin-2-ones and 1,3-dihydro-2*H*-benzimidazol-2-ones under very mild conditions in 81–100% (for only three examples) with complete retention of the optical activity.^[127]

N-*tert*-Butoxycarbonyl protected aromatic amines are initially converted in situ into the corresponding isocyanates by a strong base such as an alkyl lithium and subsequently converted into unsymmetrical substituted ureas by reaction with amines. The method is poorly compatible with amino acid chemistry as the chirality of the asymmetric center is altered due to the strongly basic conditions. Thirteen examples are reported with a yield range of 30–100%.^[128]

1-(4-Methoxyphenyl)-3-(1,1,3,3-tetramethylbutyl)urea (**51**); Typical Procedure:^[126]

To a soln of Boc₂O (683 mg, 3.13 mmol) in CH₂Cl₂ (10 mL) was successively added a soln of DMAP (36 mg, 0.30 mmol) in CH₂Cl₂ (3 mL) and a soln of 1,1,3,3-tetramethylbutylamine (385 mg, 2.98 mmol) in CH₂Cl₂ (5 mL). After stirring for 20 min at rt, 4-methoxyaniline (385 mg, 3.13 mmol) in CH₂Cl₂ (5 mL) was added. The mixture was stirred at rt for an additional 30 min and then at 40 °C for 14 h. Evaporation of the solvent and flash chromatography of the residue (silica gel, hexane/CH₂Cl₂/EtOAc 58:28:14) gives the product as colorless crystals; yield: 825 mg (99%); mp 123 °C.

18.8.1.1.7.3

Variation 3:

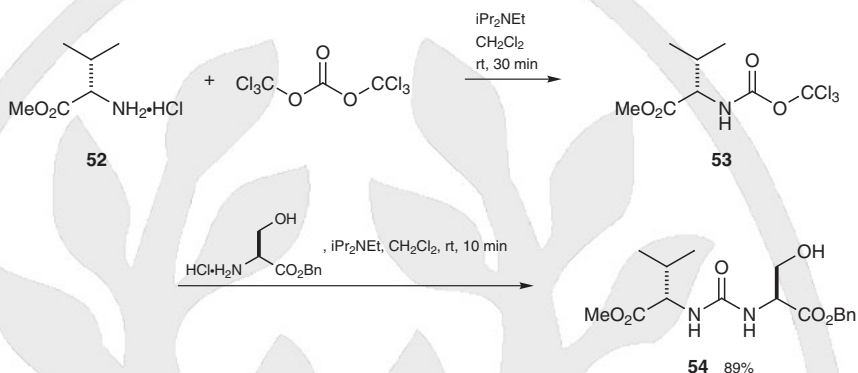
Reaction of Amines with Bis(trichloromethyl) Carbonate (Triphosgene)

Bis(trichloromethyl) carbonate (triphosgene) is a crystalline, stable solid prepared by exhaustive light-promoted chlorination of dimethyl carbonate that is easy to transport and store.^[129] However, as phosgene is a possible intermediate in many reactions of this compound, particular care must be taken during its manipulation.

Bis(trichloromethyl) carbonate is successfully utilized for the sequential synthesis of unsymmetrical ureas bearing chiral amino acid derivatives, without having to purify the intermediates. Thus, in a typical sequential, three-component reaction methyl valinate hydrochloride (**52**) is reacted with bis(trichloromethyl) carbonate in the presence of *N,N*-diisopropylethylamine affording the carbamate intermediate **53** that after addition of

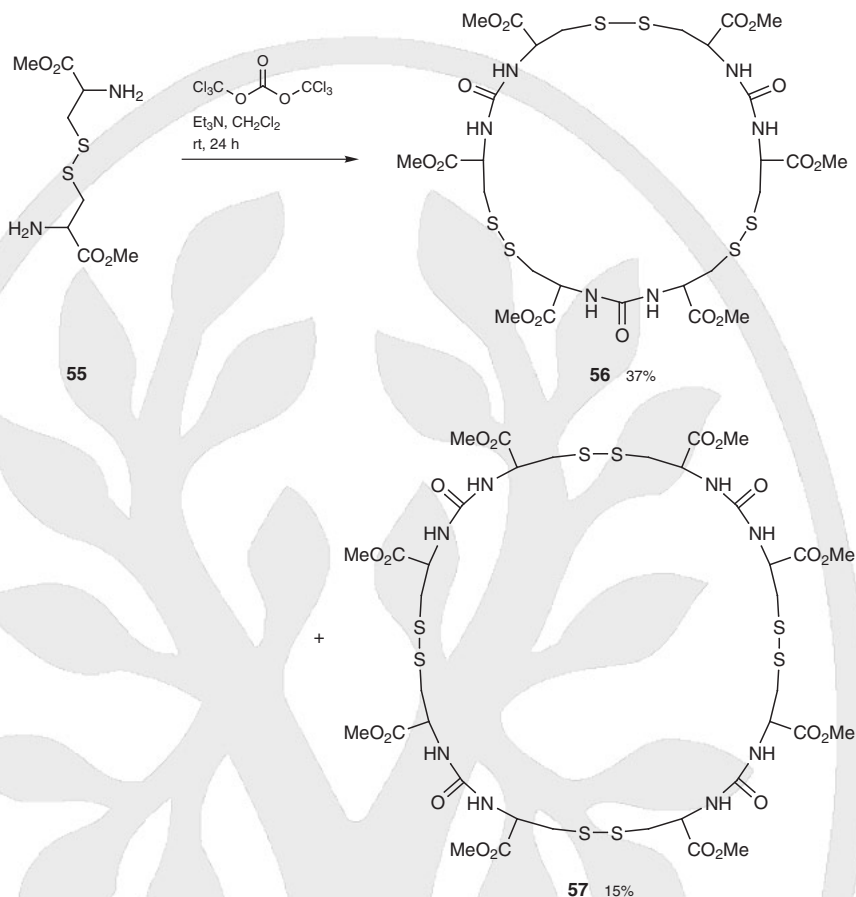
benzyl serinate hydrochloride and *N,N*-diisopropylethylamine gives product **54** (Scheme 27). The reaction is successfully applied to various amines containing multiple functionalities such as unprotected primary and secondary alcohols; seven examples are reported with a yield range of 88–91%.^[130]

Scheme 27 Bis(trichloromethyl) Carbonate Based Synthesis of a Peptidyl Urea^[130]



An important application of this strategy is the use of *O*-trimethylsilyl protected amino acid hydrogen chlorides to produce half-acid/half-ester urea dipeptides in 45–49% yield, starting materials for a variety of pharmacologically active compounds. Addition of the selected *O*-trimethylsilyl-protected amino acid hydrochloride to a solution of bis(trichloromethyl) carbonate in chloroform and in the presence of *N,N*-diisopropylethylamine results in the formation of an isocyanate intermediate that is converted in situ into the urea dipeptide upon reaction with a second amino acid methyl ester in methanol. A total of eight examples are reported with 45–85% yield.^[131]

Cystine-based symmetrical macrocyclic oligoureases are prepared from L-cystine dimethyl ester (**55**) and bis(trichloromethyl) carbonate. The reaction is carried out under high dilution conditions and affords two products, a trimeric macrocycle **56** (27-membered) and a tetrameric macrocycle **57** (36-membered), in 37 and 15% yield, respectively (Scheme 28).^[132] The multiple hydrogen-bonding sites distributed symmetrically all over the ring make these macrocycles especially suited for molecular recognition. In particular the triurea supramolecular structure is able to complex with spherical (halide) and trigonal planar (nitrate) anions, whereas the tetraurea architecture can trap the tetragonal planar squarate dianions.

Scheme 28 Synthesis of Cystine-Based Cyclic Oligoureas^[132]

Macrocyclic ureas incorporating one, two, or three icosahedral carboranes (chemical building blocks of high boron content) can be prepared by using diamines and dicarbamoyl chlorides deriving from the same diamines and bis(trichloromethyl) carbonate, three examples are reported with a yield range of 41–60%.^[133]

Methyl 2-[3-[1-(Benzyloxycarbonyl)-2-hydroxyethyl]ureido]-3-methylbutanoate (54);

Typical Procedure:^[130]

CAUTION: Handle and manipulate triphosgene in a well-ventilated hood.

A mixture of methyl valinate hydrochloride (**52**; 167.5 mg, 1 mmol) and $i\text{Pr}_2\text{NEt}$ (378 μL , 2.2 mmol) in CH_2Cl_2 (3.5 mL) was slowly added to a stirred soln of $(\text{Cl}_3\text{CO})_2\text{CO}$ (110 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) over a period of 30 min using a syringe pump. After a further 5 min of stirring, a soln of benzyl serinate hydrochloride (231.5 mg, 1 mmol) and $i\text{Pr}_2\text{NEt}$ (378 μL , 2.2 mmol) in CH_2Cl_2 (2 mL) was added in one portion. The mixture was stirred for 10 min at rt, evaporated to dryness, diluted with EtOAc, washed with 10% aq KHSO_4 , 5% aq NaHCO_3 , and brine, dried (MgSO_4), and evaporated to give the pure product; yield: 314 mg (89%); mp 145–147 °C.

18.8.1.1.7.4

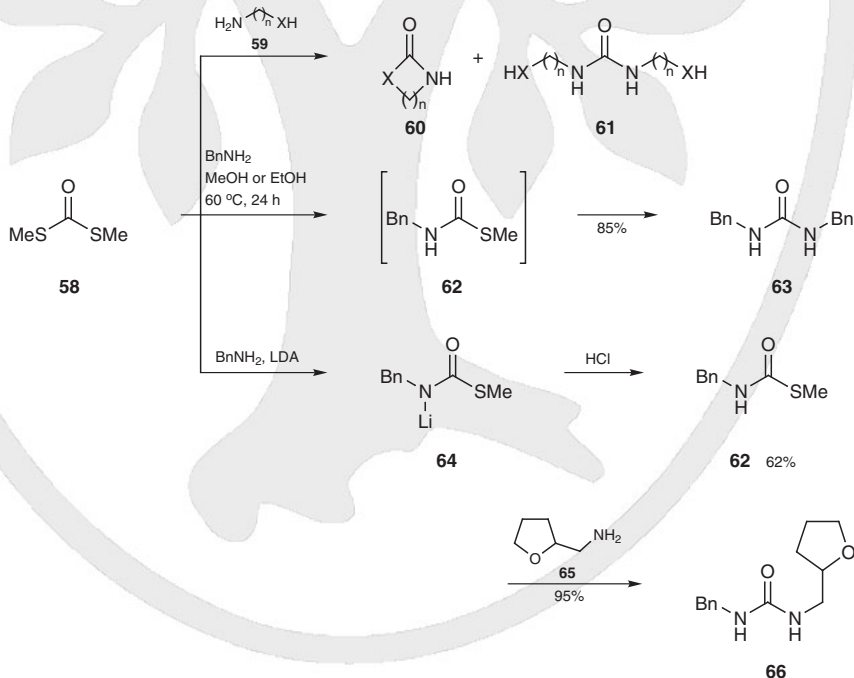
Variation 4:

Reaction of Amines with Dithiocarbonates

S,S-Dimethyl dithiocarbonate (**58**) is a mild and safely handled reagent structurally similar to phosgene that is useful in the synthesis of ureas. *S,S*-Dimethyl dithiocarbonate (**58**) is prepared from methanol, carbon disulfide, and dimethyl sulfate by a two-step sequence.^[134] Although dimethyl sulfate is a suspected human carcinogen, it is relatively nonvolatile and can be handled safely with care in the laboratory.

A representative example of this type of synthesis is shown in Scheme 29, *S,S*-dimethyl dithiocarbonate (**58**) reacts with aliphatic amines **59** bearing a hydroxy (XH = OH) or an amino substituent (XH = NH₂) at the β- or γ-position; in dilute solution it provides predominantly cyclic ureas or carbamates **60** (40–80% yield). By increasing the concentration of the starting reagent with respect to *S,S*-dimethyl dithiocarbonate, the symmetrical ureas **61** are obtained in high yield (75–100%) without need for protection and deprotection procedures. If reagent **58** is reacted with 2 equivalents of benzylamine at 60 °C for 24 hours in methanol or ethanol, symmetrical 1,3-dibenzylurea (**63**) is obtained in 85% yield. Results of mechanistic studies confirm that the second reaction stage is faster than the formation of *S*-methyl benzylthiocarbamate (**62**). By carrying out the reaction under basic conditions (LDA), the intermediate **62** is deprotonated immediately after being formed giving the corresponding lithium salt **64** in quantitative yield, which is relatively stable toward nucleophilic substitution at room temperature and will not react further to give 1,3-dibenzylurea. Treatment of **64** with aqueous hydrogen chloride affords thiocarbamate **62** that can react further with different aliphatic amines such as tetrahydrofurfurylamine (**65**) furnishing unsymmetrical ureas such as **66**.^[135]

Scheme 29 Reactivity of *S,S*-Dimethyl Dithiocarbonate with Amines^[135]



Dithiocarbonates are also utilized for the synthesis of cyclic ureas. Thus, 1,2-phenylenediamine affords 1,3-dihydro-2*H*-benzimidazol-2-one in 87% yield after reaction with *S,S*-bis(1-phenyl-1*H*-tetrazol-5-yl) dithiocarbonate via a thiocarbamate intermediate. The process does not require the presence of a catalyst.^[136]

1-Benzyl-3-(tetrahydrofurfuryl)urea (**66**):^[135]

To a soln of BnNH_2 (0.93 g, 0.87 mmol) and iPr_2NH (0.89 g, 8.8 mmol) in THF (20 mL) at -78°C under N_2 was added 1.6 M BuLi in hexane (10.9 mL, 17.5 mmol). The soln was stirred at the same temperature for 30 min, followed by addition of a soln of *S,S*-dimethyl dithiocarbonate (**58**; 1.07 g, 8.8 mmol). The soln was stirred at rt for 20 h, then was quenched by pouring it into a mixture of ice/dilute HCl. The crude solid was dissolved into EtOAc, washed with Na_2CO_3 and brine, dried (anhyd MgSO_4), concentrated under reduced pressure, and recrystallized (hexane) to provide *S*-methyl benzylthiocarbamate (**62**) as colorless crystals; yield: 0.95 g (62%); mp $76\text{--}79^\circ\text{C}$. To a stirred soln of *S*-methyl benzylthiocarbamate (**62**; 0.11 g, 0.63 mmol) in MeOH (2 mL) was added tetrahydrofurfurylamine (**65**; 0.12 g, 1.1 mmol). The mixture was heated at 60°C for 24 h and then the mixture was concentrated under reduced pressure, providing a crude solid that after recrystallization ($\text{CHCl}_3/\text{hexane}$) gave the product **66** as colorless crystals; yield: 0.14 g (95%); mp $78\text{--}80^\circ\text{C}$.

18.8.1.1.8 Method 8: From Carbamates or Thiocarbamates

Aminolysis of carbamates is an efficient and general method for the synthesis of substituted ureas with particular application to the synthesis of unsymmetrical ureas. The reaction is commonly performed under basic conditions and because the alkoxy group works as a leaving group to generate an isocyanate as the intermediate, the rate of aminolysis may depend on the ability of alkoxy to act as a leaving group. The success of this approach mainly depends on the availability of starting carbamates whose preparation is now possible through a wide variety of methods, some of which are industrial processes.

18.8.1.1.8.1 Variation 1: By Reaction with Amines

This reaction is performed by treatment of carbamates with amines under either basic or Lewis acid catalysis; some uncatalyzed processes are also reported with excellent yields. Several representative examples are reported in Table 5 and Scheme 30.

The ring opening of cyclic amides by nucleophilic reagents is a useful method for the synthesis of ω -functionalized amides; in particular, when oxazolidinones react with tetrahydroisoquinoline at 90°C in the presence of aluminum trichloride in 1,2-dichloroethane, ω -hydroxyureas are produced in good yields (see Table 5, entry 4).^[137] Trifluoroethyl carbamates, readily prepared by electrochemically induced Hofmann rearrangement of amides in the presence of trifluoroethanol, are utilized in the synthesis of unsymmetrical ureas by aminolysis with different amines; for an example see Table 5, entry 7. The reaction requires an excess of sodium hydride in tetrahydrofuran as the solvent. Interestingly, unsymmetrically protected diamines with *tert*-butoxycarbonyl and 2,2,2-trifluoroethoxycarbonyl groups, give unsymmetrical ureas in which only the amino function protected with 2,2,2-trifluoroethoxycarbonyl group is converted into a urea.^[138]

Conversion of carbamates into isocyanates is the key step in this synthetic route as it is well known that isocyanates are the actual intermediates in the process. Different carbamates including *N-tert*-butoxycarbonyl carbamates are converted into isocyanates under very mild conditions by treatment with *N,N*-diisopropylethylamine and diiodosilane, and are trapped in situ with amines affording ureas in good to excellent yields; for an example see Table 5, entry 2.^[139] Another application of this method is the efficient and easy

synthesis of *tert*-butoxycarbonyl-substituted amidino ureas by aminolysis of 1-benzyl-2,3-bis(*tert*-butoxycarbonyl)guanidines in good yields even with poorly nucleophilic amines such as aniline; for an example see Table 5, entry 5. The process is highly selective and does not require any additional base since amines act, very likely, both as a base to promote the formation of an isocyanate and as a nucleophile toward this latter intermediate.^[140]

A method for the synthesis of unsymmetrical di- and trisubstituted ureas, including urea dipeptides begins with reaction of thiocarbamates with primary or secondary amines in acetonitrile at 30–80 °C without any catalyst; for an example see Table 5, entry 6. Thiocarbamate starting reagents are prepared from primary amines or amino acid esters and carbon disulfide followed by methylation with iodomethane and then hydrolysis of the resulting dithiocarbonimidates in the presence of zinc(II) chloride and water. This method, in particular, can be applied to peptide or dipeptide ureas.^[141]

Unsymmetrical ureas are prepared by the aminolysis of phenyl carbamates with a wide variety of amines. The reaction occurs with high yields at room temperature in dimethyl sulfoxide and the only byproduct is phenol which is easily removed by washing with aqueous sodium hydroxide. An example is shown in Scheme 30 for the reaction of phenyl (4-acetylphenyl)carbamate (**67**) with dibutylamine to give 3-(4-acetylphenyl)-1,1-dibutylurea (**68**). The methodology tolerates the presence of different functional groups such as acetyl, ester, and nitrile. The process can be applied in the context of combinatorial synthesis and a concomitant use of a primary and a secondary amine results in the formation of a 1:1 mixture of both ureas confirming the potential of the method for the introduction of chemical diversity.^[142]

Scheme 30 Formation of 3-(4-Acetylphenyl)-1,1-dibutylurea from Phenyl (4-Acetylphenyl)carbamate and Dibutylamine^[142]

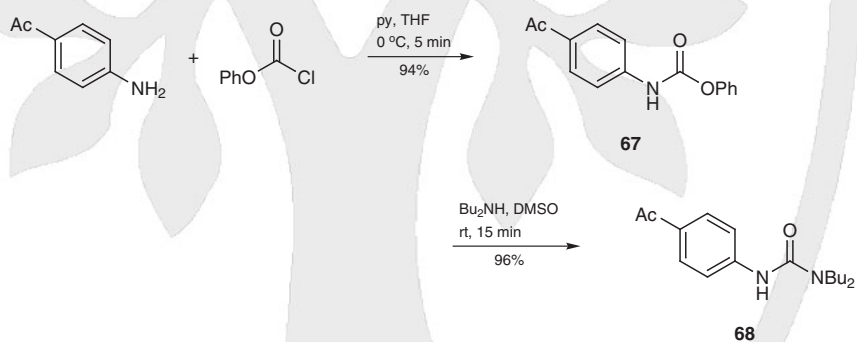


Table 5 Synthesis of Unsymmetrical Ureas from Carbamates^[137–143]

Entry	Carbamate or Thiocarbamate	Amine	Catalyst, Conditions	Product	Yield (%)	Ref
1		CyCH ₂ NH ₂	Et ₃ N, CH ₂ Cl ₂ , rt, 20 min		92	[143]
2		BnNH ₂	H ₂ SiI ₂ , iPr ₂ NEt, CH ₂ Cl ₂ , low temperature		91	[139]
3			DMSO, rt, 1.5 h		89	[142]
4			AlCl ₃ , 1,2-dichloroethane, 90°C, 16 h		88	[137]
5		Et ₂ NH	THF, reflux, 15 h		85	[140]
6			MeCN, 80°C, 12 h		81	[141]
7		allylamine	NaH, THF, rt, 5 h		42	[138]

Aminolysis of a resin-supported carbamate provides a solid-phase synthesis of unsymmetrical ureas that is becoming more frequently utilized for the production of urea-containing combinatorial libraries. Thus resin-bound benzylcarbamate, readily prepared from Merrifield resin, is utilized for the single batch preparation of a small library of ureas by treatment with primary or secondary amines with sequential release of products by a milking procedure.^[144]

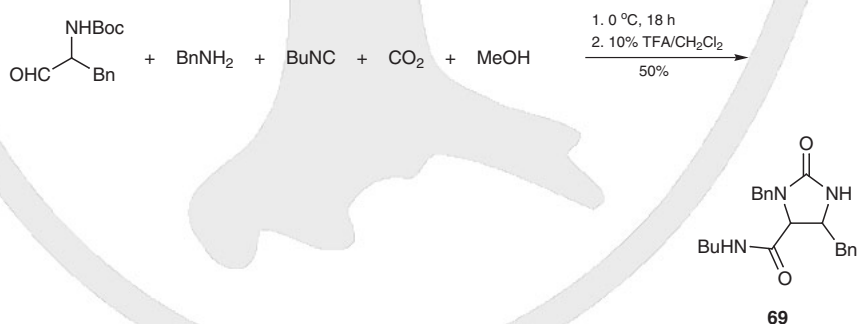
Similar results for the generation of urea-containing combinatorial libraries are achieved in the polymer-based synthesis of urea amino acids. 9-Fluorenylmethoxycarbonyl-protected amino acids on Wang resin are converted into isocyanates by treatment with chlorotrimethylsilane and triethylamine in dichloromethane. The resin-bound isocyanates are treated in situ with amines to produce, upon cleavage, the desired ureas in high HPLC purities. Seven examples are reported with yields in the range 76–92%.^[145]

Alkyl carbamates where the carbamate amino group has a substituent that bears an ω -amino function can give cyclic ureas by intramolecular displacement of the carbamate alkoxy group. It is generally accepted that aminolysis of the alkoxy group of alkyl carbamates does not proceed readily under mild conditions, hence the transformation of the amine into its magnesium salt, by treatment with ethylmagnesium bromide, facilitates the reaction providing the corresponding five- and six-membered cyclic ureas in nearly quantitative yields. Three examples are reported with high yields of 95–98%.^[146]

Similarly 1,3-dicarbamates, derived from 1,3-diaminopropanes, can afford tetrahydropyrimidin-2(1*H*)-ones under basic conditions (Cs_2CO_3). The necessity of a base indicates that the key step of the process is the deprotonation of one of the nitrogen atoms, which then attacks the carbonyl carbon on the other carbamate group eliminating alcohol. Depending on the reaction conditions, one or both the carbamate protecting groups may be removed in the cyclization step; however only two examples are reported with 61–96% yield.^[147]

Compounds containing both carbamate and amino functions can be elegantly prepared by a five-component Ugi reaction by mixing together methanol, carbon dioxide, aldehyde, amine, and isocyanide. Subsequent in situ treatment with 10% trifluoroacetic acid solution in dichloromethane and then with saturated sodium carbonate solution or an acid scavenger affords the cyclic ureas. An example is given in Scheme 31 for the formation of the imidazolidin-2-one **69**; a total of 12 examples are reported with yields in the range 10–83%.^[148]

Scheme 31 Ugi Five-Component Preparation of a Cyclic Urea^[148]



Water-soluble, chiral, and amphiphilic macrocyclic ureas are prepared by reacting diamines with dicarbamates derived from the same diamines after reaction with 4-nitrophenyl chloroformate. The reaction is carried out in dimethylformamide in the presence of 4-(dimethylamino)pyridine and pyridine as basic catalysts. Only three examples are reported with 28–53% yield.^[149] These macrocyclic ureas display diverse functionalities ca-

pable of taking part in different types of intermolecular interactions such as hydrogen bonds, charge–charge, van der Waals, and hydrophobic interaction.

3-(4-Acetylphenyl)-1,1-dibutylurea (68); Typical Procedure:^[142]

A dry, 500-mL flask equipped with an N₂ inlet adapter, a rubber septum, and a magnetic stirring bar, was charged with 4-aminoacetophenone (13.5 g, 0.1 mol) in anhyd THF (200 mL) and cooled to 0°C. Pyridine (10.1 mL, 0.125 mol) and phenyl chloroformate (12.9 mL, 0.103 mol) were added to the mixture. The resulting suspension was stirred at 0°C for 5 min and allowed to warm to rt for 1 h. EtOAc (600 mL) was added and the suspension was washed successively with 1 M HCl (100 mL), H₂O (100 mL), sat. NaHCO₃ (200 mL), and brine (100 mL), dried (MgSO₄), and concentrated under reduced pressure; the crude product was triturated (hot Et₂O/hexane) to furnish phenyl (4-acetylphenyl)carbamate (**67**) as an ivory solid; yield: 23.9 g (94%); mp 167–169°C. This product **67** (6.38 g, 25 mmol) in DMSO (50 mL) was placed into a dry, 100-mL flask equipped with an N₂ inlet adapter, a rubber septum, and a magnetic stirring bar. Then Bu₂NH (4.42 mL, 26.25 mmol) was slowly added to the mixture. The resulting soln was stirred at rt for 15 min, after which time EtOAc (250 mL) was added to the mixture. The latter was washed successively with H₂O (2 × 50 mL), 1 M HCl (100 mL), H₂O (100 mL), 1 M NaOH (100 mL), and brine (100 mL), dried (MgSO₄), and concentrated under reduced pressure to give a crude solid, which was triturated (Et₂O/hexane) to give the product **68** as a white solid; yield: 6.98 g (96%); mp 90–92°C.

18.8.1.1.8.2

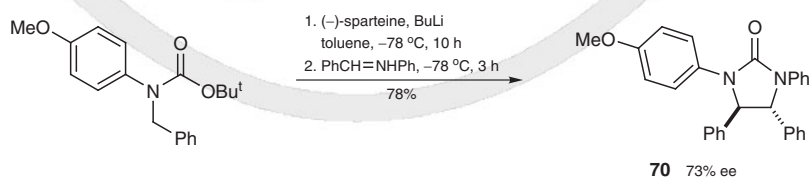
Variation 2: By Reaction with Imines

Various cyclic ureas can be prepared by a synthetic strategy that requires the presence on the same starting material of both imine and carbamate functional groups; the imine can be formed by reaction between an amine and a carbonyl compound. The difunctionalized reagent undergoes intramolecular condensation reaction. Depending on the starting reagents, the process can be performed in the presence of sodium dithionite/sodium hydroxide (13 examples reported; 50–89% yield),^[150] 4-toluenesulfonic acid,^[151] or without additional reagents (23 examples reported; 40–80% yield).^[152]

Benzylcarbamates undergo hydrogen abstraction by a strong base and the corresponding carbanion subsequently undergo addition to the C=N group of imines affording an amine intermediate that cyclizes with the carbamate moiety producing cyclic ureas via alcohol displacement. The reaction can be carried out with sodium hydride^[153] or with *sec*-butyllithium (seven examples reported; 45–92% yield).^[154]

An asymmetric deprotonation results when using butyllithium in the presence of (–)-sparteine; chiral imidazolidin-2-ones are synthesized in good yield and enantiomeric excess. An example is shown in Scheme 32 for the formation of (4*R*,5*R*)-1-(4-methoxyphenyl)-3,4,5-triphenylimidazolidin-2-one (**70**).^[155]

Scheme 32 Formation of (4*R*,5*R*)-1-(4-Methoxyphenyl)-3,4,5-triphenylimidazolidin-2-one by Asymmetric Deprotonation of *tert*-Butyl Benzyl(4-methoxyphenyl)carbamate^[155]



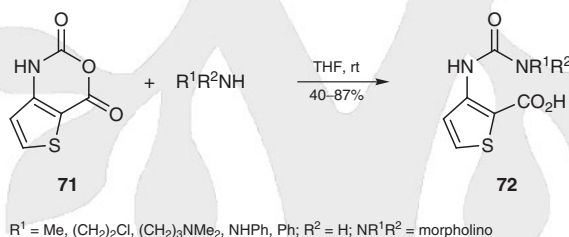
(4R,5R)-1-(4-Methoxyphenyl)-3,4,5-triphenylimidazolidin-2-one (70); Typical Procedure:^[155]

To a soln of (–)-sparteine (0.19 g, 0.8 mmol) in toluene (8 mL) at -78°C was added 1.6 M BuLi in hexanes (0.48 mL, 0.8 mmol). The mixture was stirred at -78°C for 30 min and then a soln of *tert*-butyl benzyl(4-methoxyphenyl)carbamate (200 mg, 0.64 mmol) in toluene (3 mL) was transferred to the above soln at -78°C . The resulting mixture was stirred at -78°C for 10 h, and then benzyldeneaniline (139 mg, 0.8 mmol) in toluene (4 mL) was added after precooling. After stirring at -78°C for 3 h, the mixture was allowed to slowly warm to rt. Then H_2O was added, and the aqueous layer was extracted with Et_2O . The combined organic phases were extracted with sat. NH_4Cl and dried (anhyd MgSO_4). After filtration the crude product was concentrated in vacuo and purified by chromatography; yield: 209 mg (78%); 73% ee; mp $157\text{--}160^{\circ}\text{C}$.

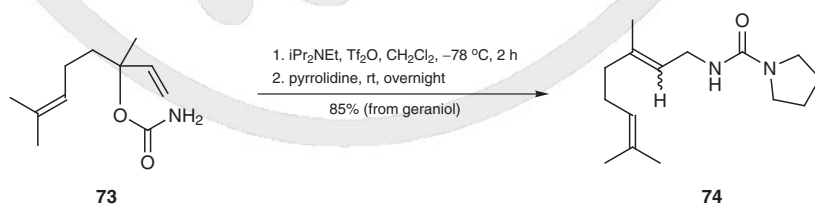
18.8.1.1.8.3

**Variations 3:
Miscellaneous Reactions**

Thiophene analogues of isatoic anhydride {2*H*-thieno[3,2-*d*][1,3]oxazine-2,4(1*H*)-dione (**71**) and the corresponding [2,3-*d*]-isomer} react with amines affording ureido-substituted thiophenecarboxylic acids, e.g. **72**, in satisfactory to good yields without the formation of *o*-aminocarboxamides (Scheme 33). It appears that under these mild conditions (room temperature) the most reactive site of both anhydrides is the carbonyl group of the carbamate function and not of the ester.^[156] The use of phosgene for the preparation of such anhydrides represents a serious drawback for this synthetic approach.

Scheme 33 Synthesis of 3-Ureidothiophene-2-carboxylic Acids^[156]

An interesting approach to *N*-(3,7-dimethylocta-2,6-dienyl)pyrrolidine-1-carboxamide (**74**) requires as a starting material the carbamate **73** produced from geraniol and trichloroacetyl isocyanate followed by hydrolysis with potassium carbonate. Dehydration of **73** gives the corresponding linear allylic cyanate, which immediately rearranges to the isocyanate via [3,3]-sigmatropic rearrangement (Scheme 34). Trapping of the isocyanate with pyrrolidine gives the final urea **74** in 85% yield with respect to the starting geraniol. Six examples of this type are reported with a yield range of 38–90%.^[157]

Scheme 34 Preparation of *N*-(3,7-Dimethylocta-2,6-dienyl)pyrrolidine-1-carboxamide^[157]

A fairly simple method for the production of symmetrical 1,3-diarylureas is based on the thermolysis of phenylcarbamates; fourteen examples are reported in 42–97% yield.^[158] A systematic study on the reaction mechanism reveals that the cleavage of the NH–CO bond is strongly affected by the nature and the position of the substituent on the aromatic ring.

***N*-(3,7-Dimethylocta-2,6-dienyl)pyrrolidine-1-carboxamide (74); Typical Procedure:**^[157]

To a stirred soln of 1,5-dimethyl-1-vinylhex-4-enyl carbamate (**73**; 743 mg, 3.76 mmol) and *i*Pr₂NEt (2.8 mL, 16.1 mmol) in CH₂Cl₂ (30 mL) cooled to –78 °C, Tf₂O was added dropwise. The mixture was stirred at –78 °C for 2 h, and then pyrrolidine (1.3 mL, 15.6 mmol) was added, and the stirring continued for a further 10 min; the mixture was allowed to react at rt overnight. The mixture was poured into H₂O, the aqueous layer was acidified with 6 M HCl, and then extracted with CH₂Cl₂. The combined organic layer was dried (Na₂SO₄) and evaporated to provide the residue, which was purified by chromatography (silica gel) to afford the product; yield: 849 mg (85% from geraniol).

18.8.1.1.9

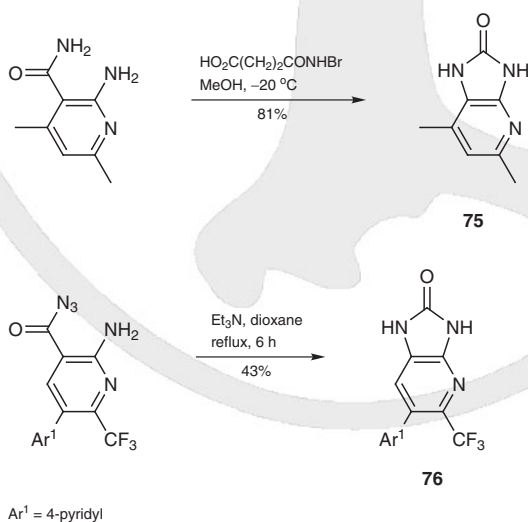
**Method 9:
From *o*-Aminoarene-carboxylic Acid Derivatives**

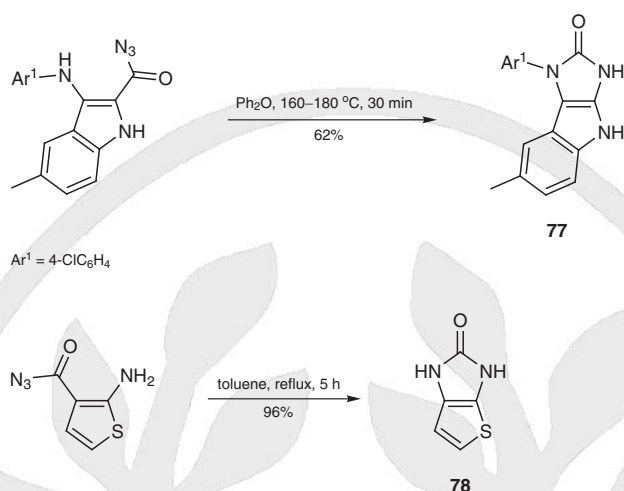
o-Aminoarene-carboxylic acid derivatives or the corresponding cyclic anhydrides are converted into cyclic ureas via Hofmann or Curtius rearrangement.

For example, substituted 2-aminopyridine-3-carboxamides undergo cyclization after Hofmann rearrangement in the presence of *N*-bromosuccinic acid monoamide (prepared from *N*-bromosuccinimide and potassium hydroxide) affording, for example, 5,7-dimethyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**75**) in 81% yield (Scheme 35).^[159]

Similarly, *o*-aminoarene-carboxylic acid azides (prepared from the corresponding carboxylic acids and diphenyl phosphorazidate)^[160] undergo thermal Curtius rearrangement affording the imidazolone ring in 43–80% yield.^[160,161] Examples are shown in Scheme 35 for the formation of **76**^[160] and **77**.^[161] The same rearrangement occurs after treatment of 2*H*-thieno[2,3-*d*]- or 2*H*-thieno[3,2-*d*][1,3]oxazine-2,4(1*H*)-diones with sodium azide, e.g. formation of **78**; a total of six examples are reported with a yield range of 21–96%.^[162]

Scheme 35 Synthesis of Substituted Pyrrolidinones from *o*-Aminoarene-carboxylic Acid Derivatives^[159–162]





1,3-Dihydro-2H-thieno[2,3-d]imidazol-2-one (78); Typical Procedure:^[162]

CAUTION: Sodium azide can explode on heating and is highly toxic. Contact of metal azides with acids liberates the highly toxic and explosive hydrazoic acid.

NaN₃ (3.9 g, 60 mmol) in minimum H₂O was added to a soln of 2H-thieno[2,3-d][1,3]-oxazine-2,4(1H)-dione (5 g, 30 mmol) in acetone (100 mL). After 1 h at rt the solvent was removed under reduced pressure and the residue was treated with H₂O (50 mL). The precipitate was filtered, washed with Et₂O (10 mL) and dried to give 2-aminothiophene-3-carbonyl azide; yield: 4.2 g (85%). This product (2.0 g, 12 mmol) was dissolved in toluene (10 mL) and refluxed for 5 h. Crystallization on cooling furnished the product; yield: 1.5 g (96%); mp 256 °C.

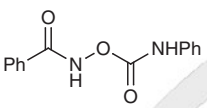
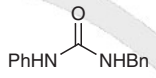
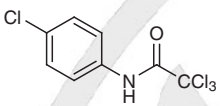
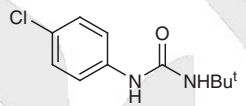
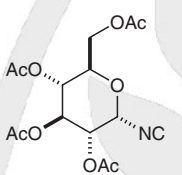
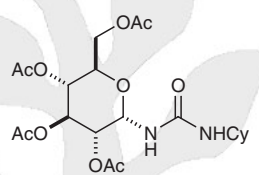
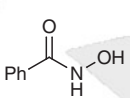
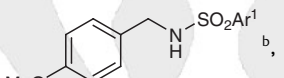
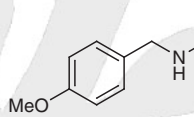
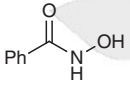
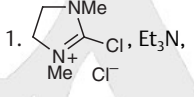
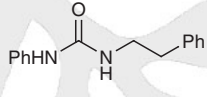
18.8.1.1.10

Methods 10: Miscellaneous Reactions

This section collects and exemplifies methods for the synthesis of ureas that are of synthetic interest, however they have not as yet been studied and developed.

According to the three-component synthetic strategy, labile isocyanates prepared by the combination of different reagents can be trapped in situ with amines affording unsymmetrical ureas thus avoiding the need to isolate and purify any intermediate. Some important methods are reported in Table 6. A simple and viable method for the synthesis of ureas including some important herbicides, is based on the reaction of readily accessible trichloroacetamides with 1,8-diazabicyclo[5.4.0]undec-7-ene and primary aliphatic amines, for an example see Table 6, entry 2.^[163] Remarkably, the preparation of α- and β-D-glucopyranosylureas has been developed.^[164] Oxidation of glucopyranosyl isocyanides provides the corresponding isocyanates which can be trapped in situ with amines to afford glucopyranosylureas in good yields, for an example see Table 6, entry 3.

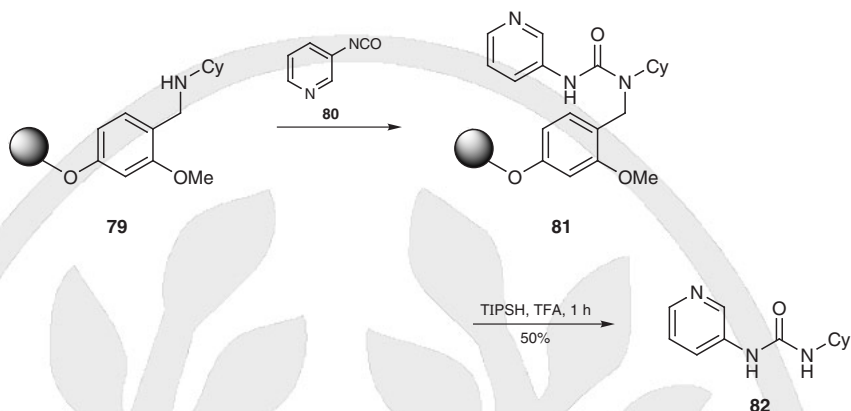
Table 6 Synthesis of Unsymmetrical Ureas by in Situ Trapping of Isocyanates with Amines^[163–167]

Entry	Isocyanate Generation	Amine, Conditions	Product	Yield (%)	Ref
1		BnNH ₂ ^a , CH ₂ Cl ₂ , reflux, 30 min		96	[165]
2		DBU, <i>t</i> -BuNH ₂ , DMSO, 80 °C, 4 h		92	[163]
3		1. pyridine 1-oxide, I ₂ , MeCN, rt, 25 min 2. CyNH ₂ , rt, 25 min		91	[164]
4		 Cs ₂ CO ₃ , DMF, rt, 4 h		79	[166]
5		1.  , Et ₃ N, CH ₂ Cl ₂ , rt, 30 min 2. Ph(CH ₂) ₂ NH ₂ , rt 19 min		78	[167]

^a In this case, the amine was used as a base for isocyanate formation and as the amine for urea formation.

^b Ar¹ = 2,4-(O₂N)₂C₆H₃.

An efficient method for trapping isocyanates, generated in situ from the Curtius rearrangement, with amine-bound resins has been described. Thus a commercially available carboxylic acid is treated with diphenyl phosphorazidate followed by thermal Curtius rearrangement giving an isocyanate (e.g., **80**), which is trapped with cyclohexylamine derivatized ArgoGel MB-CHO resin **79** affording a supported urea (e.g., **81**); cleavage from the resin gives a 1,3-disubstituted urea (e.g., **82**) in excellent purity (Scheme 36). Eight examples are reported with a yield range of 50–81% and with 90–95% purity.^[168]

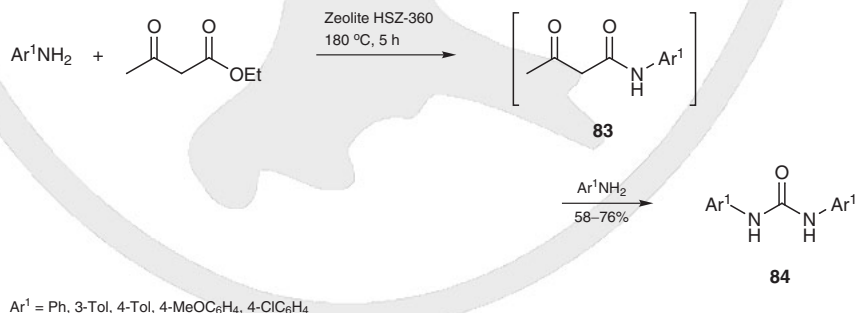
Scheme 36 Solid-Phase Preparation of a Highly Pure Unsymmetrical Urea^[168]

Dichlorotris(triphenylphosphine)ruthenium-catalyzed reaction of formamides with aromatic amines results in the production of ureas in high yield accompanied by evolution of hydrogen. The method, which can even be applied to large-scale production, utilizes formamides as the carbonyl source and can be efficiently applied to the preparation of symmetrical ureas. Five examples are reported in 85–93% yield.^[169] The process cannot be selectively applied to the preparation of unsymmetrical 1,3-diarylureas.

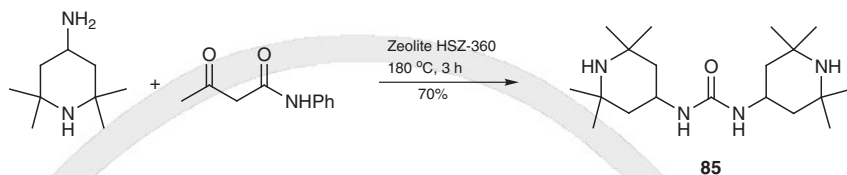
A similar dehydrogenative method is used in the synthesis of unsymmetrical 1-alkyl-3-arylureas in high yield and selectivity by exploiting the different nucleophilicity of the reagents. Six examples are reported with a wide yield range of 10–90%.^[170]

Unsymmetrical diaryl-substituted ureas are produced on reaction of aromatic amines and formamides with different substitution patterns on the aromatic ring in the presence of a small quantity of dodecacarbonyltriruthenium at atmospheric pressure.^[171]

Ethyl and methyl acetoacetates can be utilized as the carbonyl source in the preparation of symmetrically substituted ureas by reaction with amines catalyzed by solid acids represented by Y-zeolite (five examples; 58–76% yield)^[172] or molybdenum(0)/zirconia (Mo/ZrO₂) (nine examples; 57–75% yield).^[173] Both processes occur under solvent-free conditions and catalysts can be recovered and reused with similar efficiency after washing and activation. The formation of urea **84** is attributed to the initial production of the acetoacetanilide **83** and its subsequent reaction with a second molecule of amine (Scheme 37).^[172]

Scheme 37 Zeolite-Promoted Synthesis of Symmetrical 1,3-Diarylureas^[172]

By using acetoacetanilide as the carbonyl source and an excess of an aliphatic amine under solvent-free conditions in the presence of the same Y-zeolite, symmetrically substituted 1,3-dialkylureas, e.g. **85** (Scheme 38), are prepared in high yields and excellent selectivities. Nine examples are reported with a yield range of 65–95%.^[174]

Scheme 38 Zeolite-Promoted Synthesis of Symmetrical 1,3-Dialkylureas^[174]

Different special carbonylating reagents can be utilized for the preparation of ureas, particularly those that are unsymmetrically substituted. The commercially available and easily handled crystalline solid 1,1'-carbonyldiimidazole is utilized as starting reagent for the general synthesis of unsymmetrical tetrasubstituted ureas. The intermediate 1-carbamoyl-1*H*-imidazole is first obtained by reaction of 1,1'-carbonyldiimidazole with a secondary amine and is successively converted into the more reactive and resonance-stabilized imidazolium salt by *N*-alkylation of the imidazole moiety with iodomethane. Addition of a different secondary amine furnishes unsymmetrical 1,1,3,3-tetrasubstituted ureas in high yield. Fourteen examples are reported with a yield range of 72–99%.^[175] Imidazolium salts are produced quantitatively and do not require additional purification for the final conversion into the ureas. Although the salts are hygroscopic, they can be stored for several weeks without detectable decomposition.

The carbonyldiimidazole-based approach can also be successfully applied to the synthesis of more sophisticated unsymmetrical urea dipeptides that are building blocks for the preparation of inhibitors of HIV protease. These compounds are simply obtained by mixing in sequence 1,1'-carbonyldiimidazole with the selected amino acid ester hydrochloride salt in the presence of 4-methylmorpholine followed by the second amino acid methyl ester, and avoiding the use of strong bases such as butyllithium or lithium diisopropylamide that can racemize the stereogenic centers.^[176]

Similarly, 1,1'-carbonyldi(benzotriazole) can be utilized in the synthesis of unsymmetrical 1,1,3,3-tetrasubstituted ureas by one-pot reaction with an amine to produce the 1-carbamoyl-1*H*-benzotriazole intermediate that reacts under more forceful conditions with a second different amine giving the final urea in satisfactory to good yields. Twelve examples are reported in 25–85% yield.^[177] The reaction conditions and the yields of the 1-carbamoyl-1*H*-benzotriazole intermediate are significantly affected by the steric hindrance of the substituents of the amines utilized. The procedure succeeds at room temperature in tetrahydrofuran for 48 hours in 40–71% yield for cyclic, aliphatic, and aromatic amines, whereas harsher conditions are required and lower yields obtained from congested secondary amines. Unfortunately 1,1'-carbonyldi(benzotriazole) is not commercially available and must be synthesized directly from 1*H*-benzotriazole and phosgene. This drawback makes the above approach less attractive and means that it can be utilized only for laboratory-scale preparation.

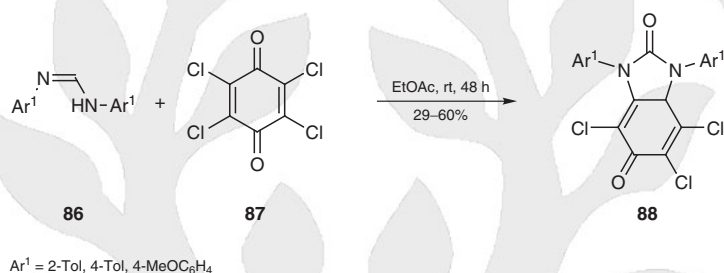
Various 1,2-diamino derivatives are transformed into the corresponding cyclic ureas by reaction with different carbonylating reagents such as methyl acetoacetate in the presence of potassium hydroxide^[178] or 1,1'-carbonyldi(triazole).^[179] Similarly 2-nitroanilines reacted with sulfur/ammonium formate/potassium carbonate mixture to afford, after reductive carbonylation, the corresponding 1,3-dihydro-2*H*-benzimidazol-2-ones. Only four examples are reported with a yield range of 27–94%.^[180]

Quite complex molecules such as benzothiazepinobenzimidazole 6,6-dioxides (12 examples reported; 91–99% yield)^[181] and guanines (6 examples reported; 67–91% yield)^[182] can undergo ring-opening processes after hydrolysis affording substituted imidazol-2-ones. The thermodynamic stability of the product determines the regioselectivity of the ring opening.^[182]

An efficient route to the pyrimidine ring is represented by the inverse electron demand [4+2]-cycloaddition reaction carried out between 1,3-diazabutadienes and enamines. The process is characterized by a high level of diastereoselectivity.^[183]

A special method for the formation of functionalized 1*H*-benzimidazole-2,5(3*H*,7*aH*)-diones **88** involves chloranil (**87**) and *N,N'*-diarylformimidamides **86** which undergo a double C–N forming reaction (Scheme 39).^[184] The process requires the replacement of a chlorine atom of chloranil and subsequent formation of an intermediate that undergoes a hydration/dehydration sequence and oxidation/reduction processes affording functionalized 1*H*-benzimidazole-2,5(3*H*,7*aH*)-diones **88**.

Scheme 39 Synthesis of Functionalized Benzimidazolones from Diarylformimidamides^[184]



Finally, enantiopure tetrahydropyrimidin-2(1*H*)-ones are synthesized in 61–87% yield by chemoselective reduction of dihydropyrimidine-2,4(1*H*,3*H*)-diones.^[185] The process uses borane–tetrahydrofuran complex as the reducing agent at room temperature; if lithium aluminum hydride or diisobutylaluminum hydride are used as the reducing agent the major products are the 4-hydroxytetrahydropyrimidin-2(1*H*)-ones.

1,3-Bis(2,2,6,6-tetramethylpiperidin-4-yl)urea (**85**); Typical Procedure:^[174]

To a mixture of 4-amino-2,2,6,6-tetramethylpiperidine (3.13 g, 20 mmol) and zeolite HSZ-360 (0.5 g) at 180 °C was added portionwise acetoacetanilide (0.9 g, 5 mmol) under vigorous magnetic stirring. After 3 h at this temperature, the mixture was cooled to rt, hot MeOH (50 mL) was added and the catalyst was removed by filtration and washed with hot MeOH (50 mL). After cooling to rt, the product 1,3-bis(2,2,6,6-tetramethylpiperidin-4-yl)urea was precipitated by adding distilled H₂O (150 mL) and isolated by Büchner filtration; recrystallization (MeOH) furnished the product as a white solid; yield: 1.18 g (70%); mp 225–228 °C.

18.8.2 Product Subclass 2: *N*-Haloureas

18.8.2.1 Synthesis of Product Subclass 2

Cyclic 1,3-dichlorourea **90** is obtained by perchlorination of glycoluril (**89**) in quantitative yield in an aqueous solution of potassium bromate and hydrogen chloride at room temperature (Scheme 40).^[186]

was filtered, and the white solid was washed with H₂O. The resulting wet solid was suspended in hexanes (800 mL), refiltered, and collected (2 ×) to remove excess phenyl chloroformate. The resulting solid was dissolved in Et₂O (800 mL), washed with brine, dried (MgSO₄), and concentrated to afford phenyl (phenoxycarbonyloxy)carbamate (**91**; 200 g) as a white solid. This material was dissolved in Et₂O (450 mL) with heating, and hexanes (500 mL) were added with continued heating until some cloudiness developed. Seed crystals were added, and the product began to crystallize (precipitate). As solid formed, more hexanes (total volume of 1.8 L) were added and the flask allowed to stand overnight at rt. The mixture was then cooled to 5 °C and the white solid collected, washed with hexanes, and dried to afford white crystalline phenyl (phenoxycarbonyloxy)carbamate (**91**); yield: 175 g (75%).

Phenyl Benzyl(phenoxycarbonyloxy)carbamate (92, R¹ = Bn); Typical Procedure:^[187]

At 0 °C to a stirred THF (40 mL) soln of BnOH (1.08 g, 10.0 mmol), phenyl (phenoxycarbonyloxy)carbamate (**91**; 3.0 g, 11.0 mmol), and Ph₃P (3.14 g, 12.0 mmol) was slowly added dropwise a THF (10 mL) soln of diisopropyl azodicarboxylate (2.43 g, 12.0 mmol). After the addition the mixture was concentrated. Purification by flash column chromatography (silica gel, Et₂O/hexanes 1:3) gave the product as a white solid; yield: 3.35 g (92%).

1-Benzyl-1-hydroxyurea (93, R¹ = Bn); Typical Procedure:^[187]

In a screw-top vessel with a Teflon O-ring was placed the phenyl benzyl(phenoxycarbonyloxy)carbamate (**92**, R¹ = Bn; 0.67 g, 1.85 mmol) and *t*-BuOH (3 mL). Liq NH₃ (2 mL) was condensed using a cold finger (dry ice/acetone) into the cooled (−78 °C) reaction vessel. The vessel was sealed, the ice bath was removed, and the mixture was allowed to stir at rt for 2 h. The mixture was then placed in the refrigerator overnight. The vessel was then recooled to −78 °C and opened. The ice bath was removed, the mixture was allowed to come to rt, and the NH₃ was allowed to evaporate. The mixture was diluted with hexanes and evaporated to dryness. The residue was purified by flash column chromatography (silica gel, MeOH/CH₂Cl₂ 1:19) to give the product as white solid; yield: 0.24 g (78%); mp 142–144 °C.

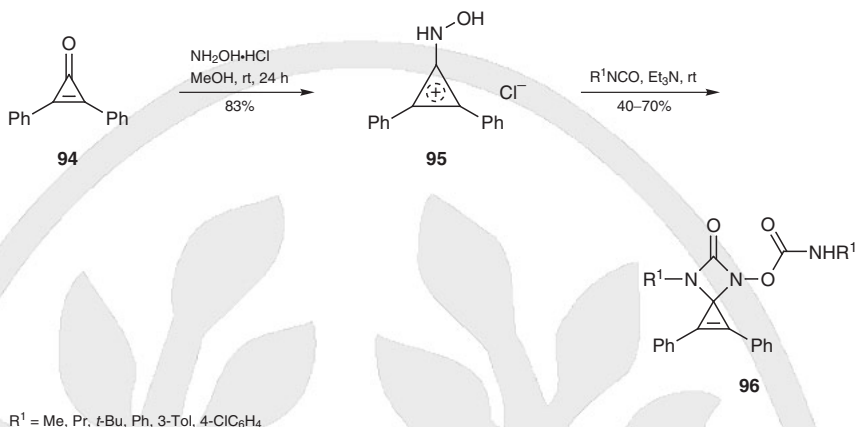
18.8.3.1.2

Method 2:

From Isocyanates and Hydroxylamine Derivatives

A multistep approach to the preparation of 1-hydroxy-1,3-dihydro-2*H*-imidazol-2-one derivatives starts from 2,2-diethoxyethyl isocyanate, obtained from 3,3-diethoxyethyl propionate by reaction with hydrazine followed by Curtius rearrangement of the resulting azide.^[188] The addition of hydroxylamine or alkoxyamines to 2,2-diethoxyethyl isocyanate yields 1-hydroxy- or 1-alkoxy-3-(2,2-diethoxyethyl)urea. On acid treatment the alkoxyureas, but not the hydroxyureas, are cyclized to 1-alkoxy-1,3-dihydro-2*H*-imidazol-2-ones. Ten examples are reported with a yield range of 40–95% yield.^[189] Following a similar method, 1-(butoxyamino)-2,2-diethoxyethane is treated with cyanic acid giving 1-butoxy-1-(2,2-diethoxyethyl)urea.^[190]

The chemistry of microcyclic aromatic compounds can be used in the synthesis of special cyclic ureas bearing an N–O bond. Thus, 1-(hydroxyamino)-2,3-diphenylcyclopropenium chloride **95** is prepared in 83% yield from 2,3-diphenylcyclopropen-1-one (**94**) and hydroxylamine hydrochloride. The salt **95** reacts with isocyanates in the presence of triethylamine to yield the 1:2-addition product **96** (Scheme 42). The reaction occurs in good yields with both aliphatic and aromatic isocyanates.^[191]

Scheme 42 Synthesis of Diazaspirohexenones^[191]

4-Methyl-6-(((methylamino)carbonyl)oxy)-1,2-diphenyl-4,6-diazaspiro[2.3]hex-1-en-5-one (96, $R^1 = \text{Me}$); Typical Procedure:^[191]

A soln of 2,3-diphenylcyclopropen-1-one (**94**; 4.13 g, 20 mmol) and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (4.17 g, 60 mmol) in MeOH (25 mL) was allowed to stand at rt for 24 h. The precipitate salt 1-(hydroxyamino)-2,3-diphenylcyclopropenium chloride (**95**) was isolated by filtration; yield: 4.3 g (83%); mp 198–202°C. This salt (3.9 g, 15 mmol) was mixed with MeNCO (1.71 g, 30 mmol) in the presence of Et_3N affording the product; yield: 3.5 g (70%); mp 135–137°C.

18.8.4

Product Subclass 4:***N*-Sulfanyl-, *N*-Sulfonyl-, *N*-Acyl-*N'*-sulfonyl-, and *N,N'*-Disulfonylureas**

Sulfanyl- and sulfonylureas are important building blocks for the preparation of agrochemicals and are products of outstanding pharmacological significance, for example in the treatment of diabetes.

18.8.4.1

Synthesis of Product Subclass 4

18.8.4.1.1

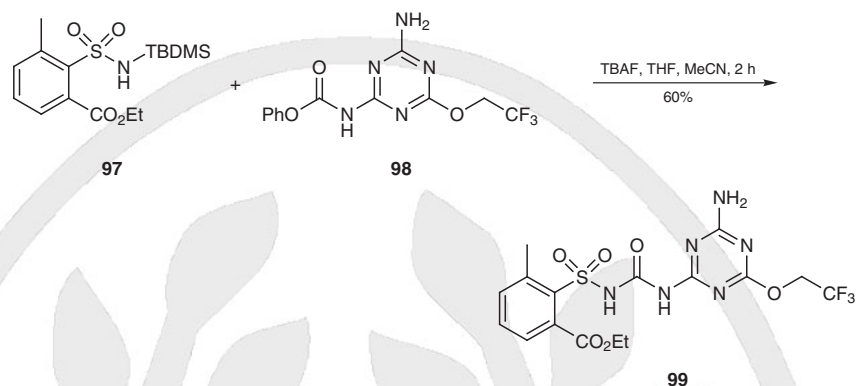
Method 1:**From Carbamates**

N-Sulfonylamides can, in principle, react with carbamates affording *N*-sulfonylureas via displacement of a convenient alcoholic group. The reaction may be performed by two approaches either directly from *N*-sulfonylaminates^[192] or from the more nucleophilic anion produced by reaction with strong bases.^[193]

The first approach is obviously simpler, since it occurs without additional reagents; the second approach requires activation of the sulfonylamide group through proton abstraction with sodium methoxide. No mention is given of the possibility of performing this reaction without base.

Activation of the *N*-sulfonylamide can also be achieved via *N*-silylation. The *N*-silyl derivative **97** reacts with carbamate **98** in the presence of tetrabutylammonium fluoride in tetrahydrofuran affording the *N*-sulfonylurea **99** in 60% yield (Scheme 43).^[194]

Scheme 43 Carbamate-Based Synthesis of an *N*-Sulfonylurea^[194]



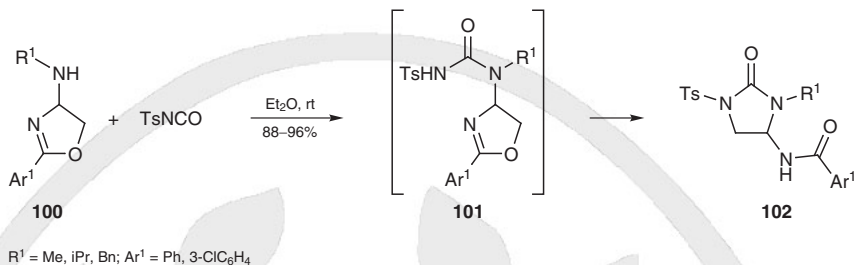
Method 2: From Isocyanates

One of the most widely used methods for the preparation of sulfonylureas is the nucleophilic addition of amines to sulfonyl isocyanates, hence a convenient and efficient synthesis of sulfonyl isocyanates is the goal of many research groups. Arylsulfonyl isocyanates are currently synthesized by phosgenation of 1-(arylsulfonyl)-3-butylureas.^[195] New and more convenient phosgene-free routes to *N*-sulfonylureas via sulfonyl isocyanates or *N*-sulfonylamines can be utilized.

N-Carbonylation of metal N-chlorosulfonamidates is a useful phosgene-free method for the synthesis of sulfonyl isocyanates. Reaction of potassium N-chloro-2-chlorobenzenesulfonamidate with carbon monoxide in the presence of a little palladium(II) chloride in dichloromethane/acetonitrile solution affords the corresponding sulfonyl isocyanate. The crude product can be directly converted into 1-(2-chlorophenyl)-3-(2-chlorophenylsulfonyl)urea by addition of 2-chloroaniline in 76% yield. A total of five examples of this type are reported in 72–80% yield.^[196]

Selenimides (selenilimines), prepared from diphenyl selenide and N-chloroarenesulfonamides,^[197] can also be utilized for the production of sulfonyl isocyanates via palladium(II)-complex catalyzed carbonylation. These catalytic N-carbonylation reactions are described as two-step oxidative carbonylations in which the oxidation of the amino group and the carbonylation of the intermediate imine are carried out as isolated steps.

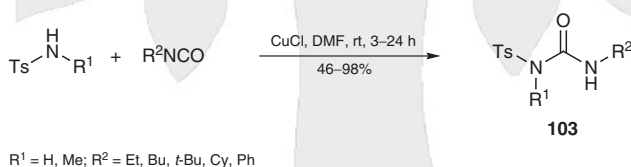
Commercially available sulfonyl isocyanates are utilized as starting reagents for the preparation of 4-(acylamino)-1-tosylimidazolidin-2-ones. The reaction of 4-(alkylamino)-2-aryl-4,5-dihydrooxazoles **100** with tosyl isocyanate is remarkably fast with almost instantaneous formation of a solid material, the imidazolidinone **102** in near quantitative yield (Scheme 44). The production of **102** is explained on the basis of the relatively highly acidic center present in the initially formed ureido intermediates **101**, which is autoactivated for nucleophilic attack at the 5-position; ring opening of the dihydrooxazole system in **101** with simultaneous ring closure leads readily to the corresponding imidazolidinones **102**.^[198]

Scheme 44 Sulfonylimidazolidinones from Sulfonyl Isocyanates^[198]

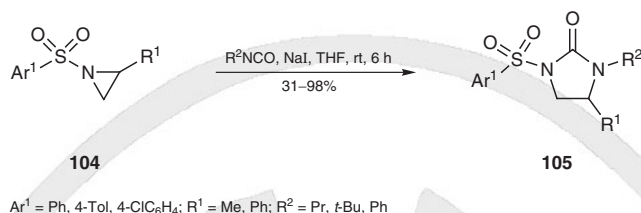
Chlorosulfonyl isocyanate is utilized as an electrophile in a three-component reaction with 4,6-dimethylpyrimidin-2-amine and ethyl 3-(methylamino)but-2-enoate for the production of (2-aminovinylsulfonyl)ureas. The entire process involves selective nucleophilic addition to the isocyanate group by 4,6-dimethylpyrimidin-2-amine and nucleophilic substitution on the chlorosulfonyl group.^[199]

All the methods discussed *vide supra* utilize sulfonyl isocyanate building blocks, of course the sulfonyl group can be linked to an amine counterpart in the synthesis of *N*-sulfonylureas. This approach is of particular interest due to the ease of preparation of the sulfonamides, which represent fundamental starting reagents in this method.

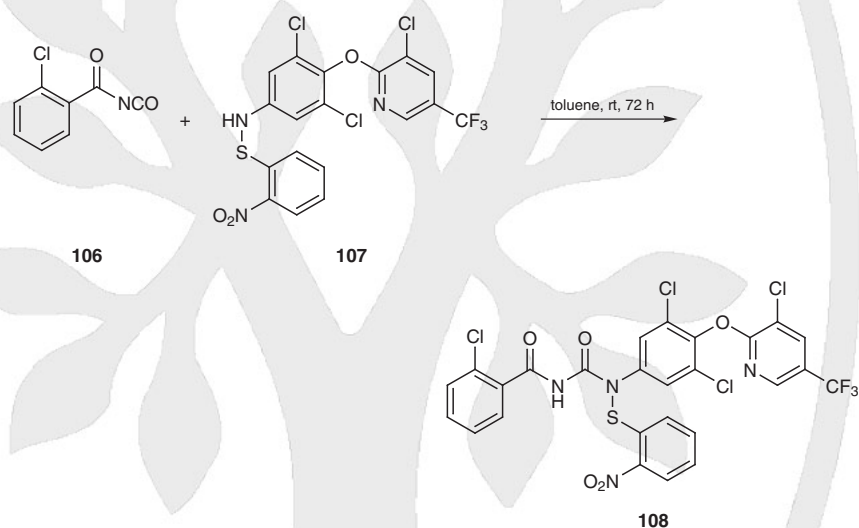
Improved experimental conditions for the synthesis of *N*-sulfonylureas from sulfonamides and isocyanates avoiding the use of highly alkaline medium, which can promote formation of various byproducts, is based on the use of copper(I) chloride which shows a remarkable catalytic effect for this process. Thus variously substituted *N*-sulfonylureas **103** are prepared in good to excellent yield (46–98%) by an extremely simple and mild process; the final highly pure products precipitate by treatment of the mixture with ice water (Scheme 45).^[200]

Scheme 45 Synthesis of *N*-Tosylurea from a 4-Toluenesulfonamide and an Isocyanate Using a Copper(I) Chloride Catalyst^[200]

Cycloaddition of *N*-sulfonylaziridines with isocyanates is a reaction that has not been widely investigated, however, the process shows high selectivity when carried out in the presence of a catalytic amount of sodium iodide. The addition of isocyanates to an equimolar mixture of 1-(arylsulfonyl)-2-methylaziridine or 2-phenylaziridine **104** and sodium iodide in tetrahydrofuran at room temperature, and stirring the resulting mixture for 6 hours gives 3,4-disubstituted 1-(arylsulfonyl)imidazolidin-2-ones **105** (Scheme 46). A great advantage of the process is its high regioselectivity.^[201]

Scheme 46 1-(Arylsulfonyl)imidazolidin-2-ones from 1-(Arylsulfonyl)aziridines^[201]

The addition of sulfenamides to isocyanates is the most utilized strategy for the synthesis of unsymmetrical *N*-sulfanylureas. Addition of a solution of 2-chlorobenzoyl isocyanate (**106**) in toluene to a stirred solution of the sulfenamide **107** in the same solvent affords, after stirring for 3 days, the complex *N*-sulfanylurea **108** (Scheme 47).^[202] Compounds such as **108** show activity as larvicides controlling insects of the acarina order.

Scheme 47 Synthesis of an *N*-Sulfanylurea^[202]**1-Butyl-3-tosylurea (103, R¹ = H; R² = Bu); Typical Procedure:**^[200]

To a stirred soln of TsNH₂ (5.0 g, 29.2 mmol) and CuCl (0.150 g, 1.52 mmol) in DMF (20 mL) was added BuNCO (3.38 mL, 30 mmol) and stirring was continued at rt for 21 h. The mixture was then poured, slowly and with vigorous agitation, into ice water (200 mL) and the resultant mixture was acidified with concd HCl (1 mL). The solid product was isolated by suction and washed with H₂O to give the product; yield: 7.4 g (85%); mp 126.5–128 °C.

18.8.4.1.3

**Methods 3:
Miscellaneous Reactions**

A mixture of 4-(methylamino)pyridine-3-sulfonamide and 2 equivalents of urea fused at 200 °C gives 4-methyl-2*H*-pyrido[4,3-*e*]-1,2,4-thiadiazin-3(4*H*)-one 1,1-dioxide via double transamination process after treatment with aqueous sodium hydroxide and precipitation of the product at pH 5.^[203]

In addition, an interesting three-component reaction patented as an efficient and easy route to certain *N*-sulfonylureas is reported. Thus sodium cyanate and 5-ethyl-2-methylbenzenesulfonyl chloride are sequentially added to a solution of 4,5-dimethyl-2,4-

dihydro-3H-1,2,4-triazol-3-one in acetonitrile and the mixture is refluxed for 18 hours giving 4,5-dimethyl-2-[[[5-ethyl-2-methylphenylsulfonyl]amino]carbonyl]-2,4-dihydro-3H-1,2,4-triazol-3-one in 68% yield.^[204]

18.8.5 Product Subclass 5: Carbamoyl Azides

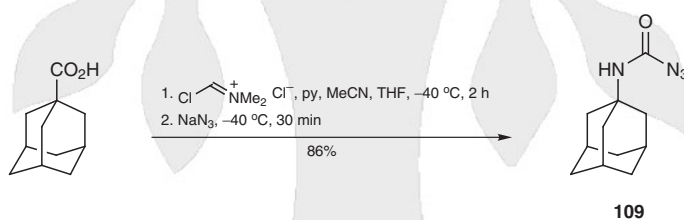
18.8.5.1 Synthesis of Product Subclass 5

Carbamoyl azides ($R^1R^2NCON_3$) were first described as a participant in the Curtius reaction, from which it is now known that they yield amino isocyanates (R^1R^2NNCO) by thermal or photochemical means. The resultant amino isocyanates rapidly undergo various reactions of general interest in organic synthesis such as, for example, solvolysis with protic solvents, and insertion reactions into aryl groups or heterocumulenes.

Carbamoyl azides are sensitive to thermal or mechanical agitation, they should, therefore, be handled with care (in small quantities using a safety shield).

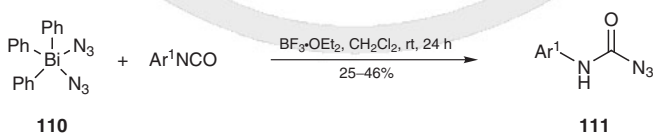
An efficient method that enables carboxylic acids or carboxylic acid chlorides to be converted directly into carbamoyl azides without the need for isolation of hazardous intermediates has been reported. For example, a solution of adamantane-1-carboxylic acid and pyridine in tetrahydrofuran is reacted with (chloromethylene)dimethylammonium chloride. The mixture is treated with sodium azide affording 1-adamantylcarbamoyl azide (**109**) in 86% yield (Scheme 48). The method avoids isolation of the isocyanate intermediate and handling hazardous hydrogen azide; seven examples of this type of reaction are reported with a yield range of 58–90%.^[205] The reaction almost certainly proceeds through sequential formation of the acid chloride and acid azide, then through rearrangement and trapping of the resultant isocyanate by excess of azide.

Scheme 48 Formation of 1-Adamantylcarbamoyl Azide^[205]



Carbamoyl azides can also be prepared by reaction of isocyanates with metal azides. The reaction of diazidotriphenylbismuth (**110**) with an aryl isocyanate in the presence of boron trifluoride results in the transfer of one azido ligand to isocyanate to give the aryl-carbamoyl azide **111** (Scheme 49). The reaction is complex and compounds **111** are obtained in relatively high yield (25–46%) only in the presence of boron trifluoride–diethyl ether complex. Alternatively, in the absence of the Lewis acid promoter, compound **111** is produced in lower yield accompanied by many other byproducts.^[206]

Scheme 49 Synthesis of Arylcarbamoyl Azides^[206]



Ar¹ = Ph, 3-Tol, 1-naphthyl

1-Adamantylcarbamoyl Azide (109); Typical Procedure:^[205]

CAUTION: Carbamoyl azides are sensitive to thermal or mechanical agitation, they should, therefore, be handled with care (in small quantities using a safety shield).

CAUTION: Sodium azide can explode on heating and is highly toxic. Contact of metal azides with acids liberates the highly toxic and explosive hydrazoic acid.

(Chloromethylene)dimethylammonium chloride, prepared by treatment of DMF (0.37 g, 5.0 mmol) with oxalyl chloride (0.76 g, 6.0 mmol) in CH_2Cl_2 followed by removal of solvent, was suspended in a mixture of MeCN (20 mL) and THF (20 mL), the suspension was cooled at -40°C and a soln of adamantane-1-carboxylic acid (0.90 g, 5.0 mmol) and pyridine (0.40 g, 5.0 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at -40°C for 2 h, before NaN_3 (1.63 g, 25.0 mmol) was added in one portion. Stirring was continued at -40°C for 30 min, then the mixture was stirred at rt overnight. H_2O was added and after extraction with Et_2O the crude product was chromatographed (silica gel) affording the product; yield: 0.95 g (86%); mp $60\text{--}63^\circ\text{C}$.

**18.8.6 Product Subclass 6:
Carbamoylazo, Carbazone, and Carbodiazone Compounds**

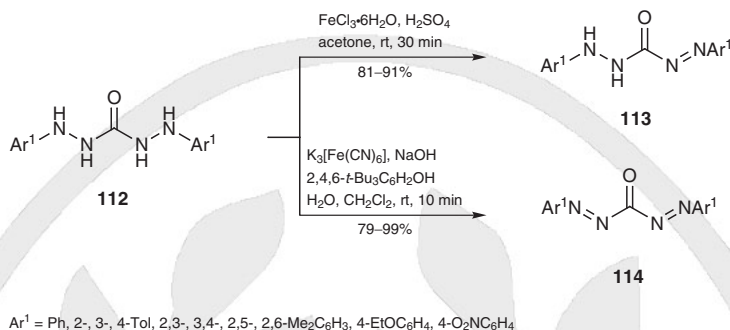
18.8.6.1 Synthesis of Product Subclass 6

1,4-Diaryl-substituted semicarbazides can be converted into the corresponding carbamoylazo derivatives (diazene-carboxamides) by the use of various oxidizing reagents.

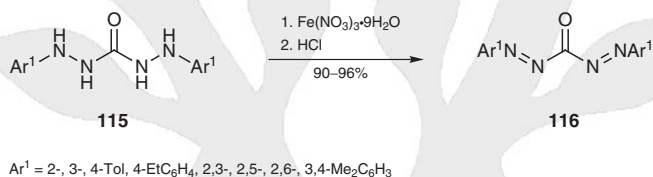
For example, using potassium chlorate/sulfuric acid/iron(II) sulfate mixture as the catalytic oxidation system, 1-(4-chlorophenyl)-4-phenylsemicarbazide is converted into the corresponding 2-(4-chlorophenyl)-N-phenyldiazene-carboxamide by gentle reflux in acetone for 2.5 minutes. Fourteen examples of this type of reaction are reported with yields in the range 91–98%.^[207] The same reaction can be performed in a two-phase system by using traces of 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yloxy free radical (10^{-2} mol% with respect the semicarbazide) in dichloromethane and shaking with saturated solution of potassium hexacyanoferrate(III) in 2 M aqueous sodium hydroxide. After 5–10 minutes the reaction is complete; ten examples are reported with yield of 91–98%.^[208]

An easier, solid-phase procedure is performed simply by mixing in a mortar iron(II) nitrate and the aromatic semicarbazide (molar ratio 2:1) at room temperature. Products are recovered by washing the mixture with acetone; eight examples are reported in 91–96% yield.^[209]

Experimental conditions for performing the highly selective mono- or bisoxidation of the N–N bonds of carbonohydrazides are available. Thus 1,5-diarylcarbazone **113** is obtained by treatment of the corresponding carbazide **112** with iron(III) chloride at room temperature. The reaction tolerates different substituents on both aromatic rings including nitro and alkyl groups (Scheme 50).^[210] The complete oxidation of both N–N bonds of carbazide **112** to carbodiazone **114** is performed by using potassium hexacyanoferrate(III) as the oxidant in a two-phase system consisting of a dichloromethane and 2 M aqueous sodium hydroxide solution.^[211]

Scheme 50 Selective Mono- and Bisoxidation of 1,5-Diarylcarbonohydrazides^[210,211]

The same process can be performed by mixing compound **115** with iron(III) nitrate nonahydrate in an agate mortar and then treating the mixture with hydrogen chloride gas in a sealed vessel to give the carbodiazone **116** (Scheme 51).^[212]

Scheme 51 Bisoxidation of 1,5-Diarylcarbonohydrazides^[212]

A clean and efficient oxidation method for converting hydrazodicarbonyl into azodicarbonyl compounds is based on the use of bromine as an oxidizing agent combined with different bases; pyridine is the best base for the reaction whereas sodium hydroxide and sodium hydrogen carbonate are less effective and less selective. This strategy does not require chromatographic methods to remove byproducts. Five examples of this approach are reported with yields of 80–93%.^[213]

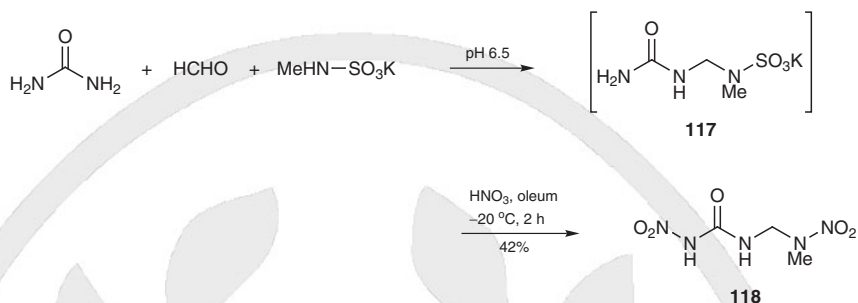
Di(2-tolyl)carbodiazone (**116**, $\text{Ar}^1 = 2\text{-Tol}$); Typical Procedure:^[212]

A mixture of 1,5-di(2-tolyl)carbonohydrazide (**115**, $\text{Ar}^1 = 2\text{-Tol}$; 0.27 g, 1.0 mmol) and $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (1.62 g, 4.0 mmol) was ground thoroughly in an agate mortar, then treated with HCl gas in a sealed vessel for 5 min at rt. The mixture was then dissolved in acetone (10 mL) and ice-cold H_2O was poured into the soln to precipitate the product. The crude was collected, washed with H_2O (3×20 mL) until the washing became neutral, and dried in vacuum to give the product; yield: 0.26 g (96%); mp 162–164 °C.

18.8.7 Product Subclass 7: *N*-Nitroureas

18.8.7.1 Synthesis of Product Subclass 7

Condensation of urea and potassium *N*-methylsulfamate with formaldehyde (33% formalin) in water at pH 6.5 results in the formation of the intermediate **117** via a three-component reaction. The mixture is concentrated in a water bath, then 98% nitric acid/20% oleum (6:5) is added at –20 °C and then stirred for 2 hours affording 1-[(methyl(nitro)amino)methyl]-3-nitrourea (**118**) (Scheme 52).^[214]

Scheme 52 Preparation of an *N*-Nitrourea^[214]

18.8.8 Product Subclass 8: Carbohydrazides

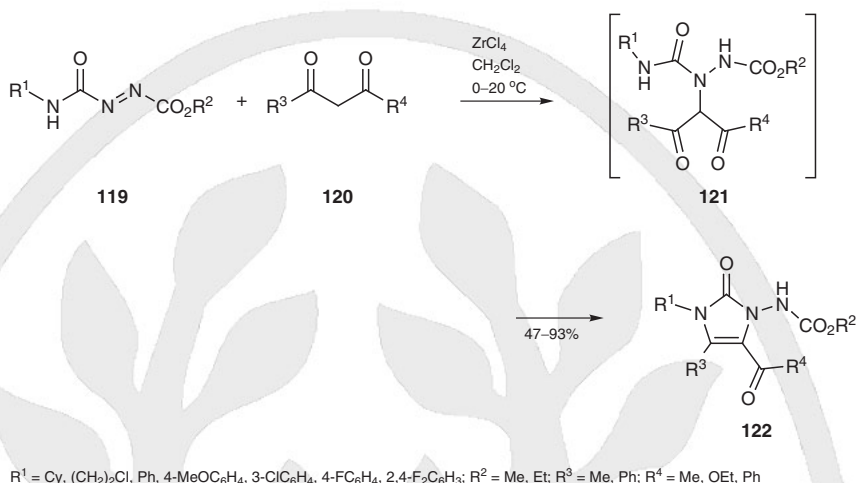
Two main synthetic approaches are utilized for the preparation of carbohydrazides. The first is based on the reduction of azo compounds, which contain an N=N bond, involving the ureidic nitrogen. More interestingly, from a synthetic point of view, this reduction can result from the Michael-type addition of nucleophilic reagents to the azo compound. The second method is the addition of *N*-amino nucleophiles to isocyanates.

18.8.8.1 Synthesis of Product Subclass 8

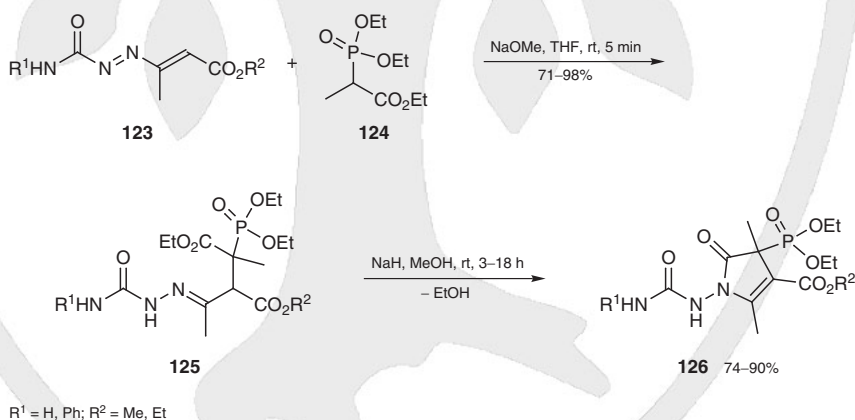
18.8.8.1.1 Method 1: From Carbamoylazo Compounds

1,1'-Azodicarbonyl compounds are synthetically useful nitrogen electrophiles. The reactivity of the N=N bond of these compounds toward a nucleophilic carbon is similar to that of the C=C and C=N analogues. These compounds are stable in the solid state and can be kept in the refrigerator for months. Most of them have solution stability for more than 24 hours.

N-Substituted 2-carbamoyldiazene-carboxylates **119**, readily available from the corresponding 1,4-disubstituted semicarbazides by *N*-bromosuccinimide treatment, can be used as a reagent for the amination of symmetrical β -dicarbonyl compounds **120** such as pentane-2,4-dione (**120**, R³=R⁴=Me) in the presence of zirconium(IV) chloride as an appropriate Lewis acid.^[215] The process selectively affords the first adduct **121** via a Michael-type addition to the ureidic nitrogen of the N=N bond. Intermediate **121** gives the corresponding 1-amino-1,3-dihydro-2*H*-imidazol-2-one **122** upon ring closure (Scheme 53). Unsymmetrical 1,3-dicarbonyl precursors such as benzoylacetone (**120**, R³=Me; R⁴=Ph), ethyl benzoylacetate (**120**, R³=Ph; R⁴=OEt), and ethyl acetoacetate (**120**, R³=Me; R⁴=OEt) react with compounds **119** following the same pathway and a single isomer is always isolated as the final product. The higher reactivity of the acetyl versus the benzoyl group of adduct **121** originating from benzoylacetone (**120**, R³=Me; R⁴=Ph) and methyl 2-(anilinocarbonyl)diazene-carboxylate (**119**, R¹=Ph; R²=Me), seems to direct the regioselective outcome of the cyclization. The formation of a single regioisomer when either acetoacetate or ethyl benzoylacetate are employed can also be explained by the difference in the reactivity of the ketonic and the ester carbonyl functionality toward the amide nitrogen of intermediate **121**.^[215]

Scheme 53 Reactivity of β -Dicarbonyl Compounds with 2-Carbamoyldiazene-carboxylates^[215]

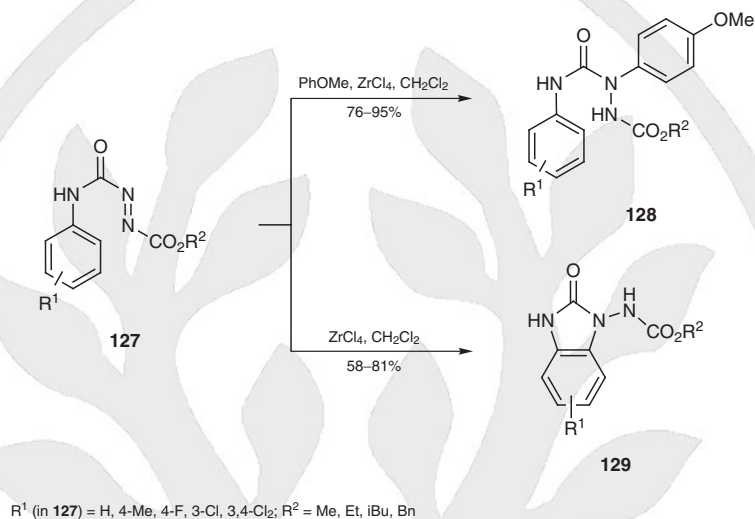
When β -phosphoryl esters containing active $-\text{CH}_2-$ or $-\text{CHR}^1-$ groups react with conjugated vinylazo compounds, 3-phosphoryl-1-ureido-1,3-dihydro-2H-pyrrrol-2-ones are produced by a high yielding procedure requiring an easy workup. In the presence of a catalytic amount of sodium methoxide, ethyl 2-(diethoxyphosphoryl)propanoate (**124**) reacts with 2-[2-(alkoxycarbonyl)vinyl]diazene-carboxyamides **123** to afford the 1-alkylidene-semicarbazide intermediate **125** which is cyclized to the 1-ureido-1,3-dihydro-2H-pyrrrol-2-ones **126** by treatment with sodium hydride in methanol (Scheme 54).^[216]

Scheme 54 Synthesis of 1-Ureido-1,3-dihydro-2H-pyrrrol-2-ones^[216]

An interesting application of diazenes, obtained by oxidation of 1,4-disubstituted semicarbazides with *N*-bromosuccinimide, in organic synthesis directly related to the method described in Scheme 54 is the electrophilic amination of arenes in the presence of a Lewis acid. Eleven examples are reported with a yield range of 76–95%.^[217] Thus, anisole is converted into 1-(alkoxycarbonyl)-4-aryl-2-(4-methoxyphenyl)semicarbazide **128** by *para*-selective electrophilic amination of alkyl 2-[(arylamino)carbonyl]diazene-carboxylate **127** (1:1 molar ratio) in the presence of zirconium(IV) chloride as the Lewis acid (Scheme 55). As expected, diazenes of type **127** undergo intramolecular reaction on treatment of a di-

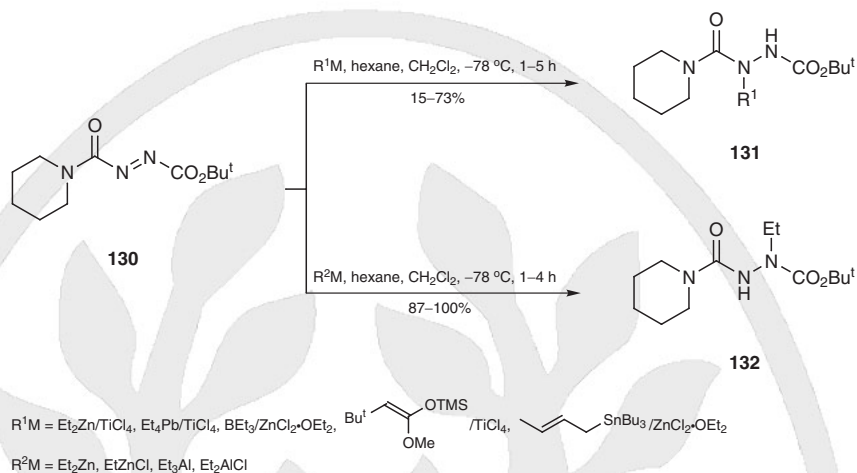
chloromethane solution with a hard Lewis acid such as zirconium(IV) chloride at room temperature to give *N*-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)carbamate **129** (Scheme 55).^[217]

Scheme 55 Lewis Acid Promoted Reactivity of Alkyl 2-[(Arylamino)carbonyl]diazencarboxylate^[217]

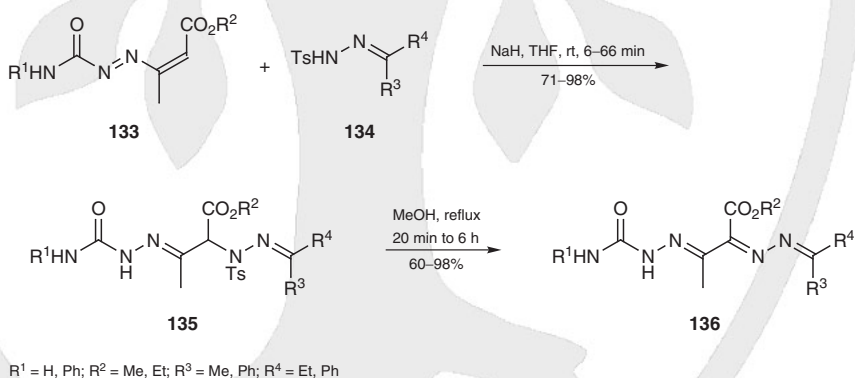


When azodicarbonyl compounds are reacted with nucleophilic reagents in the presence of a convenient chiral Lewis acid, the final product can be isolated with high enantiomeric excess. An interesting application of this approach is the addition of enol silanes of aryl ketones, acylpyrroles, and thioesters to 2,2,2-trichloroethyl 2-[(2-oxooxazolidin-3-ylamino)carbonyl]diazencarboxylate in the presence of [(*S*)-2,2'-isopropylidenebis(4-*tert*-butyl-4,5-dihydrooxazole)]copper(II) trifluoromethanesulfonate (1–10% mol) to give the chiral adducts in 90–99% ee; fifteen examples of this type are reported in 51–96% yield).^[218]

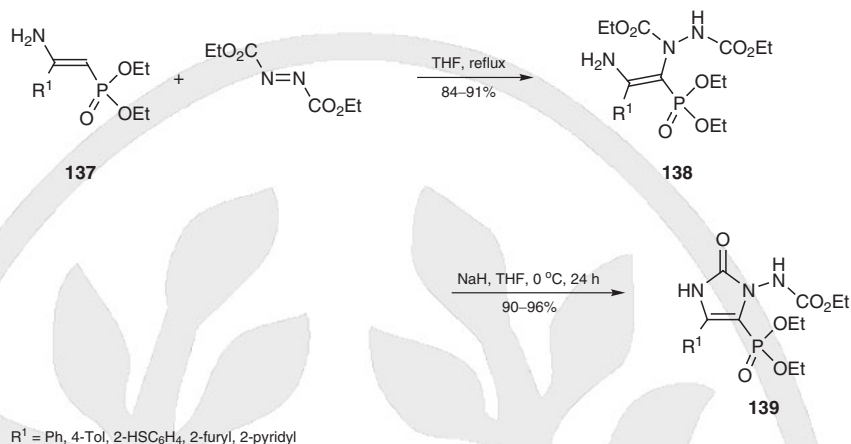
Another example of regioselective Michael-like addition to the N=N bond is the reaction of nonsymmetrical azodicarbonyl compound **130** with organometallic reagents in dichloromethane at -78°C (Scheme 56). The Lewis acid mediated reaction gives exclusively compound **131** irrespective of the reagent type (ZnEt_2 , PbEt_4 , AlEt_3 , or BEt_3) whereas the reaction of the zinc and aluminum organometallic reagents in the absence of Lewis acids produces compounds like **132** exclusively; a total of thirteen examples are reported with a yield range of 15–100% (Scheme 56).^[219]

Scheme 56 Regioselective Addition of Organometallic Reagents to Unsymmetrical 1,1'-Azodicarbonyl Compounds^[219]

α -Azinohydrazone (2,3,6,7-tetraazaalka-1,3,5-trienes) are interesting products and versatile intermediates not readily prepared owing to the presence of three conjugated $C=N$ bonds. The stable asymmetric bishydrazones **135**, smoothly produced by reaction of the corresponding 2-vinyldiazenecarboxamides **133** with the tosylhydrazones **134** in the presence of a catalytic amount of sodium hydride, undergo easy elimination of 4-toluenesulfonic acid under reflux in methanol to produce the respective α -azinohydrazone **136** (Scheme 57).^[220]

Scheme 57 Synthesis of α -Azinohydrazone^[220]

Phosphoryl-substituted 1,3-dihydro-2*H*-imidazol-2-ones **139** are prepared by addition of a solution of diethyl azodicarboxylate to (*Z*)-phosphonate **137** in tetrahydrofuran and stirring for 24 hours (Scheme 58).^[221] The key step of the complete process is heterocyclization of functionalized enamines **138**. These compounds are possibly a key intermediate for the preparation of biologically active molecules such as nucleoside antibiotics^[222] and are widely used as pharmaceuticals.

Scheme 58 Synthesis of Phosphoryl-Substituted 1,3-Dihydro-2*H*-imidazol-2-ones^[221]**Ethyl *N*-[5-Chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl]carbamate (129, $R^1 = 5\text{-Cl}$);****Typical Procedure:**^[217]

A soln of ethyl 2-[[[(3-chlorophenyl)amino]carbonyl]diazene]carboxylate (**127**, $R^1 = 3\text{-Cl}$; $R^2 = \text{Et}$; 255 mg, 1.0 mmol) in CH_2Cl_2 (7 mL) was added dropwise to a stirred suspension of ZrCl_4 (257 mg, 1.1 mmol) in CH_2Cl_2 (2 mL) at rt under argon. After 22 h the mixture was quenched with H_2O (5 mL) and neutralized with sat. NaHCO_3 . The two phases were separated and the aqueous soln was extracted with CH_2Cl_2 (5×5 mL). The combined organic extracts were then dried (Na_2SO_4) and evaporated to dryness. The residue was treated with petroleum ether/ EtOAc (17:3, 2 mL) and the solid material was filtered off to give the product; yield: 158 mg (62%); mp 214–218 °C.

18.8.8.1.2**Method 2:
From Isocyanates**

Isocyanates can be utilized as electrophiles for the preparation of carbonohydrazides by reaction with nucleophilic reagents containing an N–N bond generally prepared by N-amination of the corresponding amine.

The most frequently utilized method is the nucleophilic addition of *N*-aminoamines and similar compounds to isocyanates. Some 1-ureido-1*H*-indoles are efficiently produced by reaction of aryl isocyanates with 1*H*-indol-1-amines with pyridine as the solvent.^[223] 1*H*-Indol-1-amines are prepared by N-amination of 1*H*-indoles with *O*-(diphenylphosphoryl)hydroxylamine {see *Science of Synthesis*, Vol. 10 [Fused Five-Membered Heteroarenes with One Heteroatom (Section 10.13.1.4.3.1.3)]}.

Tropone benzoylhydrazone undergoes addition to phenyl isocyanate followed by ring closure on the heterocumulene system resulting in the production of a bicyclic imidazolone via a [8+2]-cycloaddition reaction.^[224]

A classical application of this general strategy is the addition of phenylhydrazone derivatives to phenyl isocyanates affording the corresponding semicarbazides; the reaction occurs in 4 days without any catalyst.^[225]

18.8.8.1.3**Methods 3:
Miscellaneous Reactions**

Due to their potential biological activity, *N*-aminoureas (semicarbazides and carbonohydrazides) are the target of many synthetic studies. The most common methods for urea synthesis can be, in principle, utilized for the preparation of these compounds by using

reagents containing a nucleophilic N–N bond. Experimental conditions, however, must be carefully optimized since the *N*-amino group frequently shows poor nucleophilicity. Some examples are reported in Table 7.

As expected, phosgene is utilized as the carbonylating reagent of 3-arylcarbazates and dimethylamine to produce the corresponding unsymmetrical *N*-aminoureas (Table 7, entry 4). Triethylamine is utilized as a hydrogen chloride scavenger. Carbazates are prepared in turn by reaction of arylhydrazines with the selected alkyl or aryl chloroformate.^[226]

1,1'-Carbonyldiimidazole (CDI), a safer substituent for phosgene, can be utilized in the preparation of *N*-aminoureas by using similar reagents. Thus, *tert*-butyl carbazate is treated with 1,1'-carbonyldiimidazole in dimethylformamide followed by benzyl *trans*-4-(aminomethyl)cyclohexanecarboxylate and triethylamine. The corresponding urea is obtained in 75% overall yield after hydrogenolytic debenzoylation (Table 7, entry 3).^[227]

Bis(trichloromethyl) carbonate (triphosgene), another safe substituent for phosgene in the urea synthesis, can be utilized in the ring closure of 5-(2-aminoaryl)-1*H*-pyrazoles involving double acyclic substitution, for an example see Table 7, entry 1.^[228]

Finally, the oxidative conversion of a C=S into a C=O bond is also utilized. Initial reaction of 4-chlorobenzoyl chloride with ammonium thiocyanate, followed by addition of phenoxyacetohydrazide in the presence of PEG-400 gives 4-(4-chlorobenzoyl)-1-(phenoxyacetyl)thiosemicarbazide in 90% yield. Treatment of this compound with potassium iodate in refluxing water affords the corresponding semicarbazide in 96% yield (Table 7, entry 2).^[229]

Table 7 Various Methods for the Synthesis of *N*-Aminoureas^[226–229]

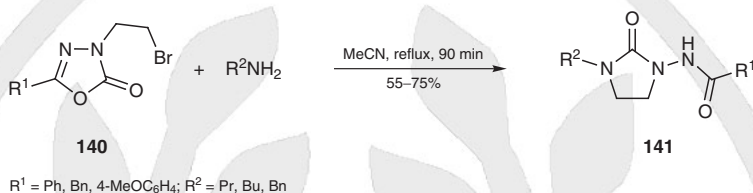
Entry	Nucleophile	Electrophile	Conditions	Product	Yield (%)	Ref
1		(Cl ₃ CO) ₂ CO	THF, Et ₃ N, rt, 30 min		98	[228]
2		–	KIO ₃ , H ₂ O, reflux, 30 min		96 ^a	[229]
3	Boc-NH ₂ +	CDI	DMF, Et ₃ N, rt, 1 h; MeOH, Pd/C, H ₂ , rt, 1 h		75	[227]
4		COCl ₂ , Me ₂ NH	EtOAc, Et ₃ N, rt, 1.5 h		42	[226]

^a Ar¹ = 4-ClC₆H₄.

Some additional special methods, based on cascade reactions, resulting in selective sequential synthetic processes are available. For example, treatment of compound **140** with primary alkyl amines in boiling acetonitrile gives 1-(acylamino)-3-alkylimidazol-

idin-2-ones **141** via intramolecular nucleophilic reaction followed by opening of the 1,3,4-oxadiazol-2-one ring (Scheme 59).^[230] With secondary amines no opening of the oxadiazolone ring occurs. The starting reagents **140** are produced in good yield by reaction of 1,2-dibromoethane in excess with the sodium salt of 5-aryl- or 5-benzyl-1,3,4-oxadiazol-2(3H)-ones.

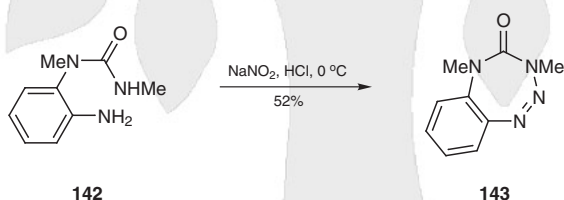
Scheme 59 Synthesis of 1-(Acylamino)-3-alkylimidazolidin-2-ones^[230]



Multifunctional compounds containing a potentially reactive group in a proximate position with respect to the ureido or carbamate functionality can be converted into fused polycyclic ureas containing an N–N bond. For example, refluxing (2-cyanocyclohex-1-enyl)urea in xylenes with phenoxyacetohydrazide in the presence of 4-toluenesulfonic acid gives 2-(phenoxyethyl)-7,8,9,10-tetrahydro[1,2,4]triazolo[1,5-c]quinazolin-5(6H)-one in 98% yield.^[231]

Another example is the diazotization of **142** (readily produced from the commercially available 2-nitrophenyl isocyanate) to give 3,5-dimethyl-3,5-dihydro-4*H*-1,2,3,5-benzotetrazepin-4-one (**143**) by cyclization of the diazonium salt intermediate (Scheme 60). Compounds such as **143** are structurally related to antineoplastic materials. The same reaction can be carried out by using 1,2,3,4-tetrahydroquinolin-8-amines and 2,3-dihydro-1,4-benzoxazin-5-amines.^[232]

Scheme 60 Preparation of 3,5-Dimethyl-3,5-dihydro-4*H*-1,2,3,5-benzotetrazepin-4-one^[232]



18.8.9

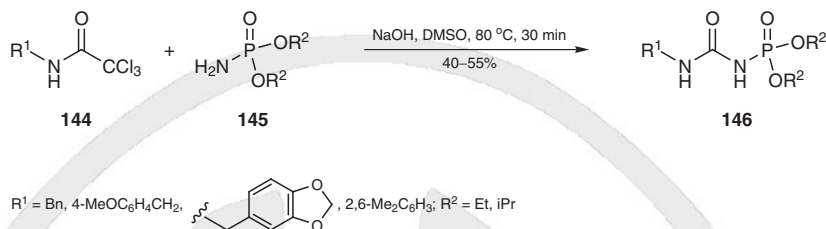
Product Subclass 9: N-Phosphorylureas

18.8.9.1

Synthesis of Product Subclass 9

Ureas undergo N-phosphorylation upon treatment with a mixture of phosphoryl chloride and methanol (molar ratio 1:2) in the presence of triethylamine. The reaction occurs at 25 °C and the product crystallizes from the reaction mixture at –10 °C.^[233]

Similar low yields of the products are obtained by using trichloroacetamides and diethyl phosphoramidate. The starting trichloroacetamides **144** are added to a suspension of dialkyl phosphoramidates **145** (molar ratio 1:2) and powdered sodium hydroxide in dimethyl sulfoxide; the mixture is stirred at 80 °C for 30 minutes affording 1-alkyl- or 1-aryl-3-(dialkoxyphosphoryl)ureas **146** (Scheme 61).^[234] Partial hydrolysis of the product **146** occurs under the reaction conditions, which accounts for the relatively low yields.

Scheme 61 Synthesis of *N*-Phosphorylureas^[234]**1-(Diethoxyphosphoryl)-3-(2,6-dimethylphenyl)urea (146, R¹ = 2,6-Me₂C₆H₃; R² = Et);****Typical Procedure:**^[234]

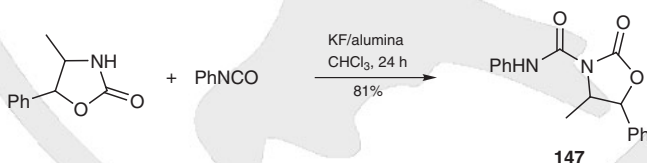
2,2,2-Trichloro-*N*-(2,6-dimethylphenyl)acetamide (**144**, R¹ = 2,6-Me₂C₆H₃; 1.33 g, 5 mmol) was added to a stirred suspension of diethyl phosphoramidate (**145**, R² = Et; 1.53 g, 10 mmol) and powdered NaOH (0.5 g, 12.5 mmol) in DMSO (5 mL). The mixture was stirred at 80 °C for 30 min, and after cooling was poured into H₂O (50 mL). The resultant mixture was basified to pH 12 with 40% aq NaOH and the soln was extracted with CH₂Cl₂ (2 × 20 mL). The aqueous layer was separated, filtered, and acidified to pH 2 with concd H₂SO₄. The mixture was extracted with CH₂Cl₂, the solvent was distilled off and the crude product was purified by crystallization (EtOH) affording the product; yield: 0.83 g (55%); mp 121–123 °C.

18.8.10 Product Subclass 10:
***N*-(Alkoxyalkyl)ureas**
18.8.10.1 Synthesis of Product Subclass 10

N-(Alkoxyalkyl)ureas such as 2-oxooxazolidine-3-carboxamides possess a wide range of biological activity including antidepressant, antifungal, and antihypertensive activity.^[235]

The most common methods for the preparation of *N*-functionalized oxazolidinones require the use of strong bases and an aqueous workup.^[236]

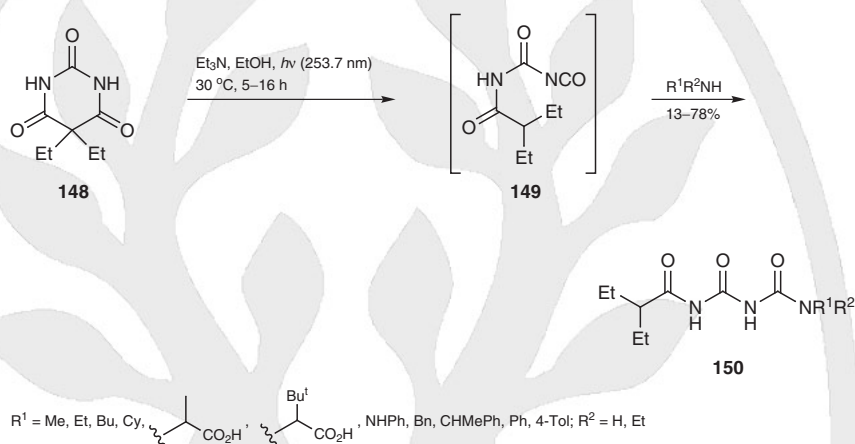
An easy method for the production of this subclass of compounds is based on the *N*-acylation of linear or cyclic carbamates with different electrophilic reagents. For example, addition of phenyl isocyanate to 4-methyl-5-phenyloxazolidin-2-one and potassium fluoride/alumina in chloroform with vigorous stirring for 24 hours affords 4-methyl-2-oxo-*N*,5-diphenyloxazolidine-3-carboxamide (**147**) in 81% yield (Scheme 62).^[237]

Scheme 62 An Example of the *N*-Acylation of an Oxazolidin-2-one^[237]
18.8.11 Product Subclass 11:
Biurets
18.8.11.1 Synthesis of Product Subclass 11

The 1-acylbiurets (*N*-acyl-*N'*-substituted imidodicarbonic acid derivatives) show various biological activities, e.g. sedative and hypnotic or anti-inflammatory and antipyretic properties.^[238]

Preparation of 5-substituted 1-acylbiurets is restricted by the very limited availability of the appropriate substrates. Photolysis of 5,5-diethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**148**) in ethanol solution in the presence of different amines yields biurets **150** via the isocyanate intermediate **149**, which is subsequently trapped by nucleophilic attack of the amine (Scheme 63). This method can be applied on a preparative scale using various primary and secondary aliphatic, alicyclic, or aromatic amines, as well as phenylhydrazine and amino acids as the nucleophilic reagents for the trapping step. Triethylamine is necessary to produce the monoionized form of **148**.^[239]

Scheme 63 Preparation of 1-Acylbiurets^[239]



The reaction of isocyanates with ureas is one of the most frequently utilized methods for the synthesis of these compounds. The reaction of 4,4'-methylenedi(phenyl isocyanate) with ammonia at room temperature gives the corresponding 4,4'-methylenedi(phenylurea), which in dimethylformamide affords 4,4'-methylenedi(1-phenyl-5-tosylbiuret) upon treatment with 4-toluenesulfonyl isocyanate in almost quantitative yield.^[240]

1-(1-Carboxyethyl)-5-(2-ethylbutanoyl)biuret (150, R¹ = CHMeCO₂H; R² = H);

Typical Procedure:^[239]

Alanine (2.3 g, 25 mmol) was dissolved in 1 M NaOH (25 mL) and the soln was diluted with hot EtOH (200 mL). After cooling to 30 °C, 5,5-diethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**148**; 2.25 g, 12.5 mmol) was dissolved in the mixture, which was then irradiated for 5 h in a photoreactor tube (height 58 cm, diameter 5.5 cm, thickness of irradiated layer 2.5 mm) equipped with cooling jacket and immersion low-pressure Hg lamp TUV 30W protected by a quartz tube. The mixture was acidified with 1 M HCl (25 mL), evaporated under reduced pressure to a volume of 50 mL, basified with 1 M NaOH to pH 8, diluted with phosphate buffer (pH 8; 50 mL) and extracted with EtOAc (3 × 50 mL). The H₂O layer was acidified with 1 M HCl to pH 1 and evaporated to a volume of 20 mL. Then H₂O was decanted and the oily residue was crystallized twice (EtOH/H₂O) affording the product as white crystals; yield: 0.44 g (13%); mp 174–175 °C.

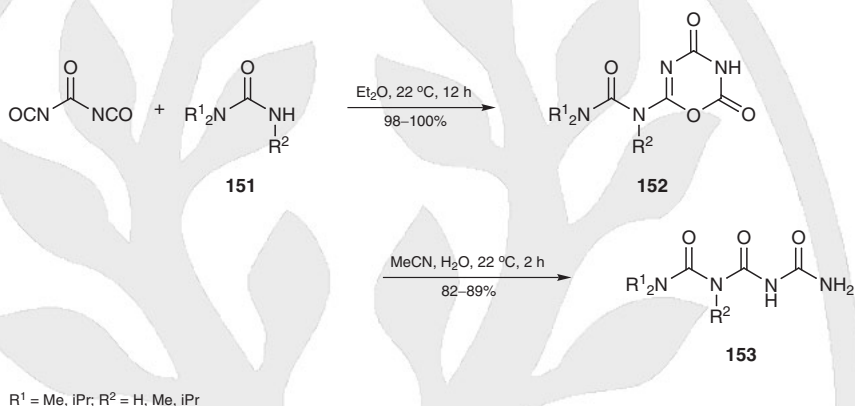
18.8.12 Product Subclass 12:
Triurets

18.8.12.1 Synthesis of Product Subclass 12

Carbonyl diisocyanate is a useful starting reagent for the preparation of triurets. A solution of substituted ureas **151** in diethyl ether is added to a mixture of carbonyl diisocya-

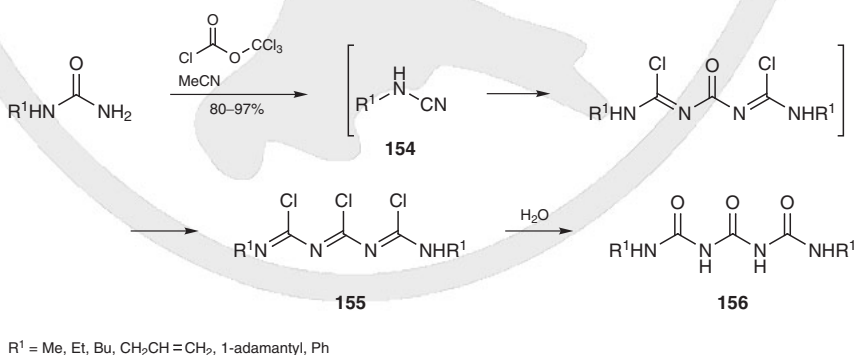
nate in the same solvent and is reacted for 12 hours affording the corresponding 6-ureido-2*H*-1,3,5-oxadiazine-2,4(3*H*)-diones **152**. These compounds are decarboxylated simply by treatment with water in acetonitrile giving triurets **153** (Scheme 64).^[241] The methodology can be applied to the preparation of different pentaurets. Thus, reaction of carbonyl diisocyanate with methylamine (molar ratio 1:2) in tetrahydrofuran followed by addition of formic acid and water gives 1,11-dimethylpentauret as a colorless powder in 23% yield. Different primary and secondary amines are utilized in this reaction and six examples of pentaurets are produced with 23–92% yield.^[241]

Scheme 64 Preparation of Triurets from Carbonyl Diisocyanate^[241]



Triurets can also be prepared from trichloromethyl chloroformate (diphosgene) and substituted ureas. The reaction is readily performed by addition of trichloromethyl chloroformate to a solution of the *N*-alkylurea in acetonitrile at room temperature and allowing the reaction to proceed for 15 minutes. The entire process requires two molecules of *N*-alkylurea for one molecule of trichloromethyl chloroformate. When the substituted cyanamide intermediate **154** is allowed to react with trichloromethyl chloroformate, the 2,4,6-trichloro-1,3,5,7-tetraazahepta-1,3,5-triene **155** is isolated as a hygroscopic solid, which is readily transformed into 1,7-disubstituted triuret **156** upon decomposition with water (Scheme 65). Different *N*-substituted ureas are utilized.^[242] The reaction can also be extended to 1,3-disubstituted ureas such as 1,1-dimethyl- and 1,1-diethylurea affording the 1,1,7,7-tetrasubstituted triurets; three examples are reported in 15–90% yield.^[242]

Scheme 65 Synthesis of Triurets from Trichloromethyl Chloroformate^[242]



1,7-Di(1-adamantyl)triuret (156, R¹ = 1-Adamantyl); Typical Procedure:^[242]**CAUTION:** Trichloromethyl chloroformate (diphosgene) can produce monomeric phosgene; handle and manipulate it in a well-ventilated hood.

In a well-ventilated hood, trichloromethyl chloroformate (11.9 g, 20 mmol) was added dropwise to a cold (0–5 °C) soln of 1-adamantylurea (3.9 g, 20 mmol) in MeCN (20 mL) (Note: this is as stated in the original procedure; however, 11.9 g of trichloromethyl chloroformate is 60 mmol and the correct ratio of trichloromethyl chloroformate/1-adamantylurea is not known. An excess of trichloromethyl chloroformate must be used as it has to decompose to phosgene and some phosgene can be lost during the reaction). After stirring at rt for 15 min, H₂O (40 mL) was slowly added. A white precipitate was collected by filtration and recrystallized (EtOH/H₂O) to give the analytically pure product; yield: 3.8 g (91%); mp 295–300 °C.

18.8.13**Product Subclass 13:****N-Acyl-, N,N-Diacyl-, and N,N'-Diacylureas**

N-Acylureas and related derivatives, particularly cyclic examples, are used in various asymmetric catalytic studies due to their chelating bidentate properties. In addition to this, these compounds are utilized as useful heterocyclic building blocks that are prominent structural elements of compounds showing a wide variety of interesting biochemical and pharmacological properties.^[243] As a consequence of this, a number of synthetic approaches have been developed that provide access to derivatives of these classes of ureas. Moreover, these compounds can be readily prepared from low-cost starting materials and are highly crystalline, facilitating purification.

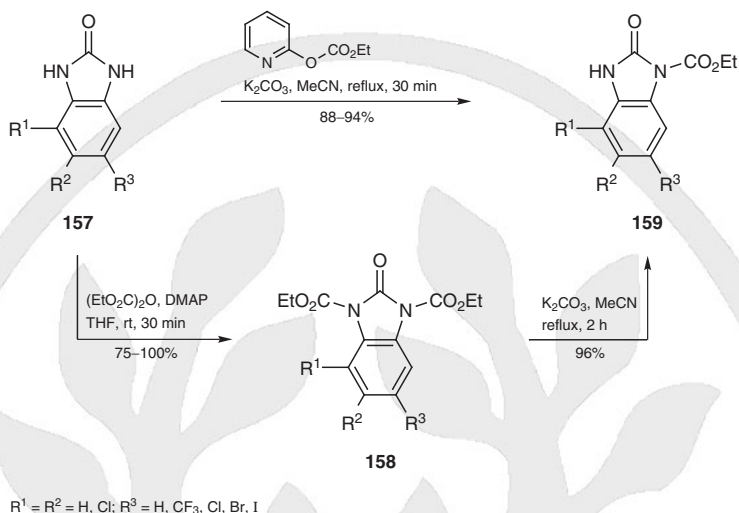
18.8.13.1**Synthesis of Product Subclass 13****18.8.13.1.1****Method 1:****From Ureas**

The most viable methods for the production of N-acyl-, N,N-diacyl-, and N,N'-diacylureas are based on two main synthetic strategies, namely the direct N-acylation of ureas with various carboxylic acid derivatives and the selective oxidation of an α -carbon.

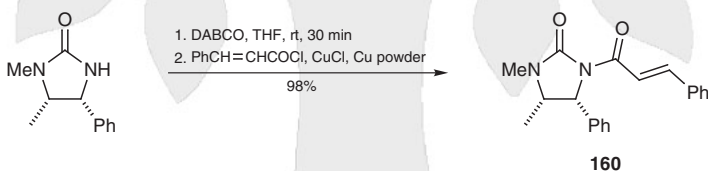
18.8.13.1.1.1**Variation 1:****By Acylation with Carboxylic Acid Derivatives**

A solution of racemic octahydro-*trans*-2H-benzimidazol-2-one in tetrahydrofuran treated with 2 equivalents of butyllithium at –78 °C and isobutanoyl chloride gives 1,3-diisobutanoyloctahydro-*trans*-2H-benzimidazol-2-one in 87% yield. This compound can be converted into the 1-isobutanoyloctahydro-*trans*-2H-benzimidazol-2-one in 100% yield by treatment with potassium hexamethyldisilazide in tetrahydrofuran (–78 °C, 24 h).^[244]

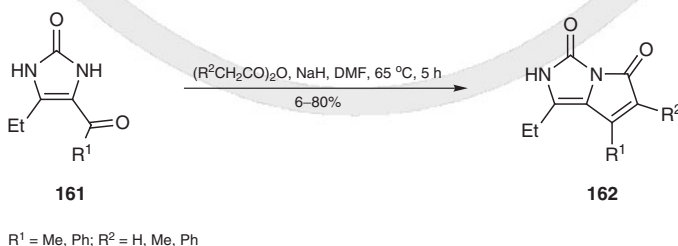
The selective protection of one of the degenerate nitrogen atoms of cyclic ureas as a carbamate derivative is an interesting method. Depending on the nature of the substituents, the selective monoprotection of **157** to produce monoacylated **159** is performed either directly with ethyl 2-pyridyl carbonate or by double protection and selective monoprotection via disproportionation of **158** in the presence of **157** and potassium carbonate (Scheme 66). The process is sensitive to steric factors of the group R¹.^[245] All products can be isolated by crystallization without the need to resort to chromatographic methods of purification.

Scheme 66 Selective Monoprotection of Degenerate Nitrogen Atoms of Cyclic Ureas^[245]

Chiral 1-acylimidazolidin-2-ones, utilized as face-selective dienophiles in Diels–Alder cycloaddition reactions, are efficiently prepared by *N*-acylation of imidazolidin-2-ones containing one NH group with freshly distilled cinnamoyl chlorides in the presence of 1,4-diazabicyclo[2.2.2]octane, copper(I) chloride, and copper(0) powder. Five examples are reported with a yield range of 57–98%; an example is shown in Scheme 67 for the formation of the 1-methyl-3-(3-phenylprop-2-enoyl)imidazolidin-2-one **160**.^[246] The precise role of the copper remains to be established, whereas 1,4-diazabicyclo[2.2.2]octane is the base of choice as it is able to abstract the NH proton of the reagent.

Scheme 67 Formation of a 1-Methyl-3-(3-phenylprop-2-enoyl)imidazolidin-2-one^[246]

An interesting application of this process concerns a cascade reaction between 4-acyl-1,3-dihydro-2*H*-imidazol-2-ones **161** and carboxylic acid anhydrides in the presence of sodium hydride affording bicyclic compounds **162** via the intramolecular aldol condensation of a 3,4-diacylimidazol-2-one intermediate (Scheme 68).^[247]

Scheme 68 Synthesis of 3*H*-Pyrrolo[1,2-*c*]imidazole-3,5(2*H*)-diones^[247]

Trichloromethyl chloroformate (diphosgene) is utilized for the N-chloroformylation of 1-acetylimidazolidin-2-ones. The reaction does not require a catalyst, the product is obtained in high yield and selectivity.^[248] The sole drawback is connected with the use of highly toxic phosgene, which is produced directly from trichloromethyl chloroformate.

More interestingly, from both environmental and synthetic points of view, is the selective mono-N-chloroformylation of imidazolidin-2-ones with bis(trichloromethyl) carbonate (triphosgene), a safer reagent. The reaction occurs in tetrahydrofuran at 60 °C and does not require a catalyst.^[249]

N-Acylation of ureas can also be performed by electrochemical methods. Thus, a mixture of 1,3-dihydro-2*H*-imidazol-2-one, tetramethylammonium tetrafluoroborate, and methanol is electrolyzed at a constant current of 0.5 A until $2 \text{ F} \cdot \text{mol}^{-1}$ electricity is passed; after addition of excess acetic anhydride, 1,3-diacetyl-1,3-dihydro-2*H*-imidazol-2-one is obtained in 40% yield.^[250] Similarly, a mixture of urea itself and methyl benzoate can be converted into 1-benzoylurea at a controlled current of $20 \text{ mA} \cdot 4 \text{ cm}^{-2}$ until $5 \text{ F} \cdot \text{mol}^{-1}$ has passed; three examples are reported in 50–67% yield.^[251]

(4*R*,5*S*)-1,5-Dimethyl-4-phenyl-3-[(*Z*)-3-phenylprop-2-enoyl]imidazolidin-2-one (160);

Typical Procedure:^[246]

(4*R*,5*S*)-1,5-Dimethyl-4-phenylimidazolidin-2-one (0.30 g, 1.58 mmol) and DABCO (0.23 g, 2.05 mmol) in anhyd THF were stirred at rt for 30 min. Then Cu powder (0.10 g, 1.58 mmol) and CuCl (0.16 g, 1.58 mmol) were added. Freshly distilled cinnamoyl chloride (0.53 g, 3.16 mmol) was added slowly and the mixture was stirred overnight. The THF was removed under reduced pressure, and the crude was purified by column chromatography (basic alumina, CH_2Cl_2) affording the product as white crystals; yield: 0.50 g (98%); mp 164–165.5 °C.

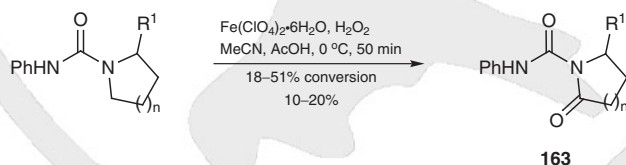
18.8.13.1.1.2

Variation 2:

Oxidation of Pyrrolidine- and Piperidine-1-carboxamides

Oxidation of pyrrolidine- and piperidine-1-carboxamides with iron(II) perchlorate and hydrogen peroxide in 95% aqueous acetonitrile gives the corresponding 2-oxopyrrolidine-1-carboxamides **163** ($n = 1$) and 2-oxopiperidine-1-carboxamides **163** ($n = 2$) (Scheme 69).^[252] The methylene group in the α -position to the nitrogen rather than the methine group is attacked preferentially by the oxidant; moreover derivatives of pyrrolidine are more reactive than those of piperidine. A limitation of this method is the requirement for a stoichiometric amount of iron(II) perchlorate with respect to the starting nitrogen heterocycle.

Scheme 69 Oxidative Preparation of Pyrrolidin-2-ones and Piperidin-2-ones^[252]



$\text{R}^1 = \text{H, Me, Ph, CO}_2\text{Me}; n = 1, 2$

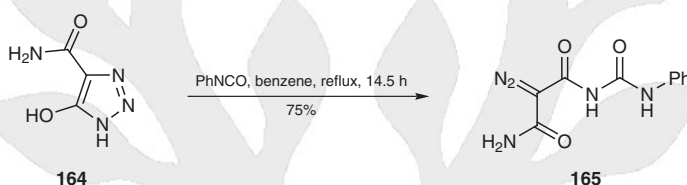
18.8.13.1.2

**Method 2:
From Isocyanates**

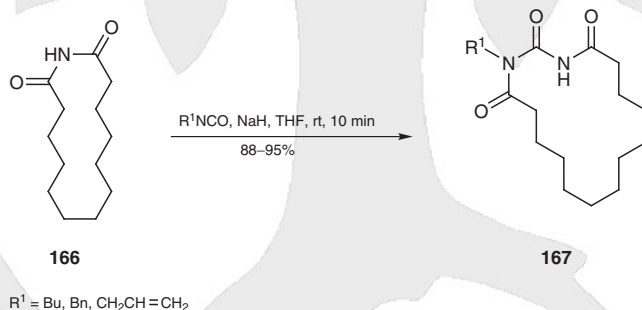
A well-known and extensively applied urea synthesis by nucleophilic addition of amines to isocyanates can be successfully used in the preparation of *N*-acylureas. Accordingly, reaction of amines with carbonyl isocyanates or simple isocyanates with amides or imides results in the production of *N*-acylureas.

Acetanilides react with 1-chloro-2,2,2-trifluoro-1-phenylethyl isocyanate at 60°C in the presence of triethylamine in benzene affording 1-acyl-3-alkylideneureas with the simultaneous elimination of a chloride anion. Five examples are reported with a yield range of 51–76%.^[253]

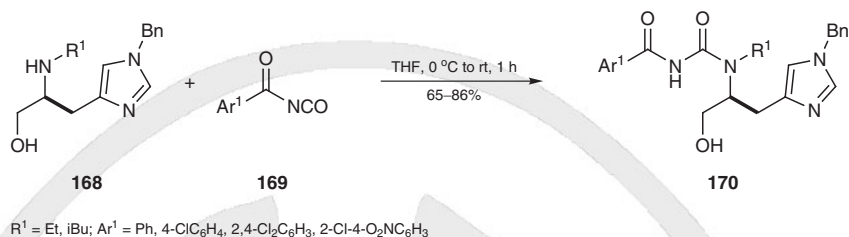
N-Carbamoyl-2-diazomalonamide (**165**) is produced in 75% yield by a cascade reaction involving addition of 5-hydroxy-1*H*-1,2,3-triazole-4-carboxamide (**164**) to phenyl isocyanate followed by opening of the triazole ring in benzene without additional reagents (Scheme 70).^[254]

Scheme 70 Synthesis of *N*-Carbamoyl-2-diazomalonamide^[254]

Macrocyclic analogues of barbituric acid **167** are synthesized by ring enlargement of macrocyclic imide **166** through reaction with isocyanates via an $[n+2]$ -zip process (Scheme 71). Sodium hydride is utilized to enhance the nucleophilicity of the NH group of the cyclic imide and the entire reaction occurs at room temperature in a few minutes.^[255]

Scheme 71 Synthesis of Macroyclic Analogues of Barbituric Acid^[255]

The synthesis of some biologically active compounds such as the imidazolidin-2-one analogue of pilocarpine is performed by addition of amines to acyl isocyanates. Thus, reaction of 1-benzyl-4-[2-(ethylamino)-3-hydroxypropyl]-1*H*-imidazole (**168**, R¹ = Et) with benzoyl isocyanate (**169**, Ar¹ = Ph) in tetrahydrofuran at room temperature for 1 hour affords the 1-benzoylurea **170** (R¹ = Et, Ar¹ = Ph) in 86% yield (Scheme 72). The conversion of **168** into **170** can lead to mixtures of both O- and N-acylated products, however the reaction in Scheme 72 gives selectively the products of N-acylation.^[256]

Scheme 72 Pilocarpine Analogue Synthesis^[256]

A simple and easy method for the synthesis of *N*-formylureas is based on the reductive C–N coupling of alkyl isocyanates. The reaction takes place in the presence of the tetranuclear cluster anion $[\text{Ru}_4\text{H}_3(\text{CO})_{12}]^-$ as catalyst and it fails with phenyl isocyanate and with branched alkyl isocyanates. In each case the final reaction mixture contains the intact cluster anion, the catalytic activity of which remains unchanged. Three examples are reported with yield of 41–56%.^[257]

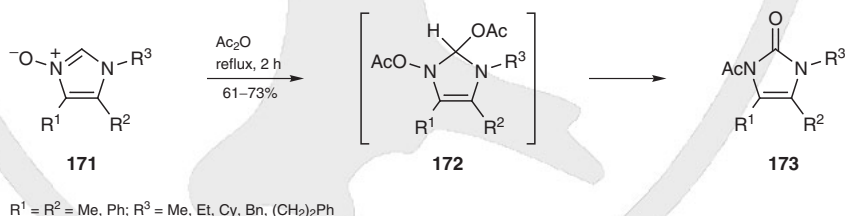
1-Benzoyl-3-[(*S*)-2-(1-benzyl-1*H*-imidazol-4-yl)-1-(hydroxymethyl)ethyl]-3-ethylurea (170, $\text{R}^1 = \text{Et}$; $\text{Ar}^1 = \text{Ph}$); Typical Procedure:^[256]

A soln of benzoyl isocyanate (**169**, $\text{Ar}^1 = \text{Ph}$; 0.31 mL, 2.4 mmol) in THF (5 mL) was added over 1 h via a syringe pump to a soln of 1-benzyl-4-[2-(ethylamino)-3-hydroxypropyl]-1*H*-imidazole (**168**, $\text{R}^1 = \text{Et}$; 0.57 g, 2.2 mmol) in THF (15 mL) cooled in an ice bath. The mixture was stirred at rt for 1 h and evaporated. The crude product was purified by low-pressure chromatography (EtOAc/MeOH 9:1) to give a white foam; yield: 0.78 g (86%).

18.8.13.1.3

Methods 3:
Miscellaneous Reactions

Different types of isomerization reactions are utilized for the preparation of *N*-acylureas. These include, for example, the thermal conversion of 1,4,5-trialkyl-1*H*-imidazole 3-oxides **171**, prepared by a literature method,^[258] into the *N*-acetyl derivatives **173** simply by reflux in acetic anhydride without additional reagents (Scheme 73). In analogy to the mechanistic interpretation of the reaction of pyridine 1-oxide with acetic anhydride leading to 2-acetoxypyridine, the formation of intermediates **172** is proposed.^[259]

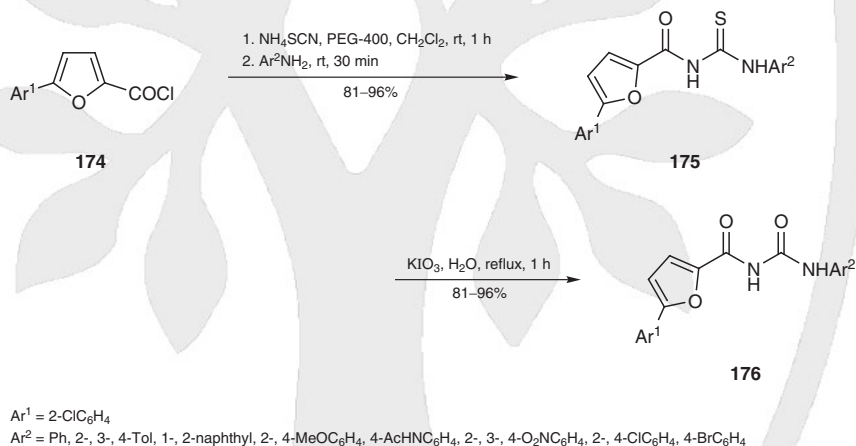
Scheme 73 Preparation of 1-Acetyl-1,3-dihydro-2*H*-imidazol-2-ones^[259]

Similarly, imidazol-2-ones fused to aromatic rings are prepared by an aza-oxy-Cope rearrangement of *N*-arylbenzohydroxamic acids and cyanogen bromide in equimolar ratio at room temperature. Ten examples are reported in 52–99% yield.^[260] In both cases products are isolated as crystalline solids directly from the final reaction mixture. A limitation in the latter case is the use of cyanogen bromide, which is highly toxic and may explode when heated. Cyanogen bromide must be used in a chemical fume hood; hydrogen cyanide and hydrogen bromide may arise from its combustion or decomposition.

In a second approach *N*-acylthioureas are converted into the corresponding *N*-acylureas. The general strategy seems to be particularly attractive since thioureas are readily prepared by various, simple methods in high yields. Treatment of a dichloromethane solution of 1,3-dipropionyloctahydro-*trans*-benzimidazole-2-thione with a stoichiometric amount of mercury(II) acetate for 12 hours at room temperature gives the corresponding octahydro-2*H*-benzimidazol-2-one in 88% yield. The starting thione is simply prepared from the corresponding diamine and carbon disulfide.^[261] The role of mercury is to enhance the leaving group ability of the sulfur due to its thiophilicity. The development of this conversion of thiourea into urea allows the latter type of compounds to be synthesized from 1,2-diamines in three steps in an overall yield of 70–80% depending on the substituents. Seventeen examples are available with a yield of 42–97% for the diacylation step and a yield of 70–99% for the dethionation step.^[262] The great drawback of this synthetic route is the requirement of a stoichiometric amount of mercury(II) acetate.

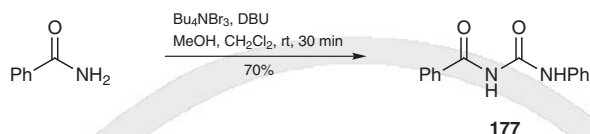
Another attractive method based on the dethionation of thioureas is the reaction of the thioureas with potassium iodate in water. Thioureas **175** are obtained by the reaction of 5-(2-chlorophenyl)-2-furoyl chloride (**174**) with ammonium thiocyanate catalyzed by polyethylene glycol 400 (PEG-400) and then addition of aromatic amines to the mixture at room temperature. Further treatment of **175** with potassium iodate in water at reflux affords compounds **176** (Scheme 74). The reaction tolerates the presence of aromatic halides, nitro groups, ketones, and phenol ethers.^[263]

Scheme 74 Preparation of 1-Aryl-3-[5-(2-chlorophenyl)-2-furoyl]ureas^[263]



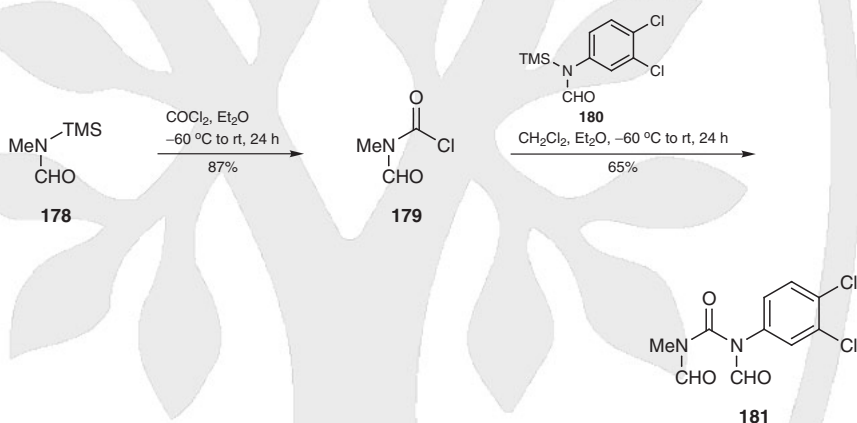
1-Formyl-4-amino-5-hydroxy-1,5-dihydro-2*H*-imidazol-2-one is obtained in 66% yield via oxidative ring contraction of cytosine through the (*C,N*)-1,4-diformyl intermediate produced by ozonolysis of C4=C5 bond followed by cyclization to the five-membered heterocycle. Twelve examples are available in 7–66% yield.^[264]

The ability of tetraalkylammonium polyhalides to act as selective halogenating reagents is utilized in a simple and attractive synthesis of *N*-acylureas, some of which show physiological activity on insects. The reaction is performed by mixing amides with tetrabutylammonium tribromide and 1,8-diazabicyclo[5.4.0]undec-7-ene in the presence of little methanol in dichloromethane at room temperature. The entire process is quite complex from a mechanistic point of view and probably involves the initial production of methyl hypobromite that then converts the amide into the isocyanate. *N*-Acylureas are thus prepared in fairly good yields from both aromatic and aliphatic acid amides. An example is shown in Scheme 75 for the preparation of 1-benzoyl-3-phenylurea (**177**) in 70% yield, in total 12 examples are reported with a yield range of 45–93%.^[265]

Scheme 75 The Preparation of 1-Benzoyl-3-phenylurea^[265]

1,3-Diacetyl-1,3-dihydro-2*H*-benzimidazol-2-one is prepared in good yield from 1*H*-benzimidazole by an acylation–oxidation process; nine examples are available in 40–84% yield. The reaction has the advantage of using inexpensive reagents, but it can only be used for small-scale production since it utilizes 2 equivalents of acyl chloride and 2 equivalents of potassium permanganate as the oxidant; it is consequently problematic from the point of view of atom economy.^[266]

The synthesis of the interesting 1,3-diformylurea **181** is performed by reaction of *N*-methyl-*N*-(trimethylsilyl)formamide (**178**) with phosgene, resulting in the production of *N*-formyl-*N*-methylcarbamoyl chloride (**179**) which upon treatment with *N*-(3,4-dichlorophenyl)-*N*-(trimethylsilyl)formamide (**180**) affords compound **181** in 65% yield (Scheme 76).^[267]

Scheme 76 Synthesis of a 1,3-Diformylurea^[267]**1-Benzoyl-3-phenylurea (177); Typical Procedure:**^[265]

To a soln of benzamide (0.48 g, 4.0 mmol) and Bu₄NBr₃ (1.0 g, 2.07 mmol) in CH₂Cl₂ (containing a catalytic amount of MeOH) (20 mL), DBU (0.64 g, 4.2 mmol) in CH₂Cl₂ (5 mL) was added at rt. The mixture was stirred for 30 min and the solvent was then distilled in vacuo. Small amounts of Et₂O and H₂O were then added to the residue and the precipitate obtained was filtered and washed with Et₂O and H₂O to give the product as colorless crystals; yield: 0.33 g (70%); mp 206–207 °C.

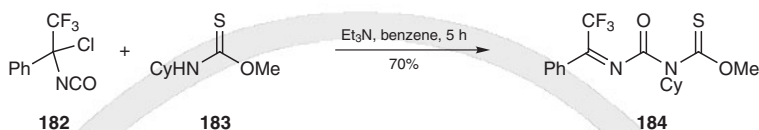
18.8.14

**Product Subclass 14:
N-Organooxythiocarbonyl Ureas**

18.8.14.1

Synthesis of Product Subclass 14

The addition of thiocarbamate to isocyanates is a further application of isocyanate chemistry in urea synthesis. 1-[(Methoxy)thiocarbonyl]-3-(2,2,2-trifluoro-1-phenylethylene)urea (**184**) is produced in 70% yield simply by addition of *O*-methyl thiocarbamate **183** to the chloroalkyl isocyanate **182** in one portion in benzene followed by triethylamine which can abstract the NH proton of **183** enhancing its nucleophilicity (Scheme 77).^[268]

Scheme 77 Preparation of 1-[(Methoxy)thiocarbonyl]-3-(2,2,2-trifluoro-1-phenylethylene)urea^[268]

18.8.15

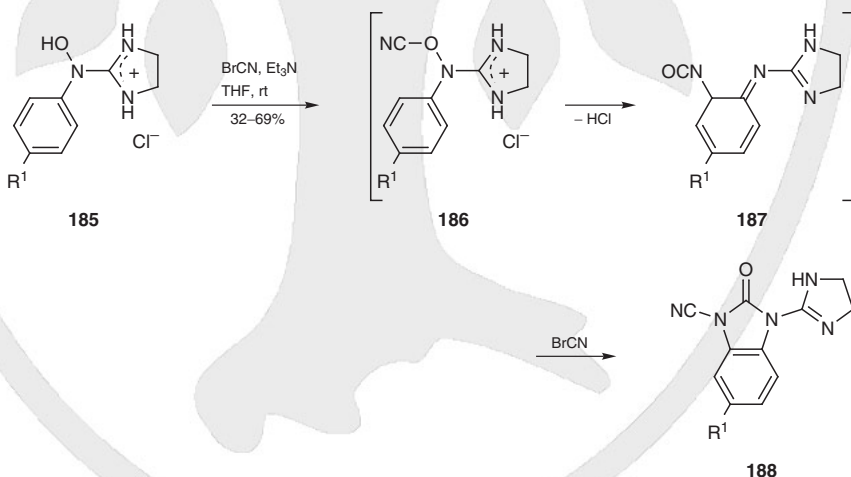
**Product Subclass 15:
N-Cyanoureas**

18.8.15.1

Synthesis of Product Subclass 15

These compounds are multifunctional intermediates that are utilized in heterocyclic and natural product chemistry.

2-Oxo-2,3-dihydro-1*H*-benzimidazole-1-carbonitriles **188** are prepared under mild reaction conditions starting from an aromatic hydroxylamine **185** and cyanogen bromide (Scheme 78). The starting reagent **185** is prepared in 48% yield from readily available *N*-phenylhydroxylamine by treatment with 2-chloro-4,5-dihydro-1*H*-imidazole in dichloromethane at room temperature. Reaction of **185** with cyanogen bromide in the presence of triethylamine in polar aprotic solvents such as acetone or tetrahydrofuran at room temperature directly affords 3-(4,5-dihydro-1*H*-imidazol-2-yl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-1-carbonitriles **188**.^[269] The entire process involves *O*-cyanation of the hydroxylamine **185**, rearrangement of the *N*-cyanato derivative **186**, prototropic rearomatization and internal nucleophilic addition in the resulting isocyanate **187**, and finally reaction of the thus formed cyclic benzimidazolone intermediate with a second molecule of cyanogen bromide to give to the final product **188**.

Scheme 78 Synthesis of *N*-Cyanoureas^[269] $\text{R}^1 = \text{H}, \text{Me}, \text{Cl}, \text{OMe}$

18.8.16

**Product Subclass 16:
N-Carbamimidoylureas**

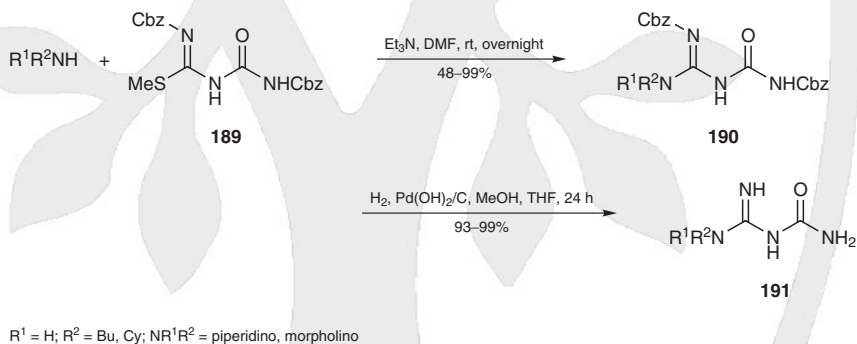
18.8.16.1

Synthesis of Product Subclass 16

The classic methods utilized for the synthesis of ureas and guanidines can be used in the preparation of *N*-carbamimidoylureas, which are ureas that contain a nitrogen atom shared with a guanidine group.

A simple and efficient method for the preparation of these compounds is based on the displacement of a methoxy group from methyl 2,6-dimethylphenylcarbamate by 1-methylguanidine. The reaction occurs in dimethyl sulfoxide at 100 °C for 1 hour giving the corresponding *N*-carbamimidoylurea–dimethyl sulfoxide adduct, namely the lidamidine–dimethyl sulfoxide adduct. Removal of dimethyl sulfoxide can be performed in de-ionized water at 50 °C. The method is superior to other known routes since it does not require poisonous, hazardous, and strongly acidic compounds.^[270]

Addition of primary or secondary amines to 1-(benzyloxycarbonyl)-3-[(benzyloxycarbonyl)imino](methylsulfanyl)methylurea (**189**) in dimethylformamide and in the presence of triethylamine results in the production of the 1-[(amino)l(benzyloxycarbonyl)imino]methyl-3-(benzyloxycarbonyl)ureas **190**. Intermediates **190** are then hydrogenated in methanol/tetrahydrofuran (1:2) solution at 4 atm in the presence of a little 20% palladium hydroxide on carbon affording the carbamimidoylureas **191** (Scheme 79); the method is efficient and mild.^[271]

Scheme 79 Preparation of *N*-Carbamimidoylureas^[271]**1-[(Cyclohexylamino)iminomethyl]urea (191, R¹ = H; R² = Cy); Typical Procedure:**^[271]

To a mixture of 1-(benzyloxycarbonyl)-3-[(benzyloxycarbonyl)imino](methylsulfanyl)methylurea (**189**; 401 mg, 1.0 mmol) in DMF (9 mL) were added cyclohexylamine (149 mg, 1.5 mmol) and Et₃N (303 mg, 3.0 mmol). The resulting mixture was stirred overnight at rt. The mixture was poured into CH₂Cl₂ and washed with 1 M HCl, sat. NaHCO₃, and brine, then dried (Na₂SO₄), filtered, concentrated, and separated by column chromatography (silica gel, CH₂Cl₂/EtOAc/MeOH 15:4:1) to afford 1-(benzyloxycarbonyl)-3-[(benzyloxycarbonyl)imino](cyclohexylamino)methylureas (**190**, R¹ = H; R² = Cy); yield: 448 mg (99%). To a soln of **190** (R¹ = H, R² = Cy; 285 mg, 0.63 mmol) in MeOH (3 mL) and THF (6 mL) was added 20% Pd(OH)₂/C (30 mg). The reaction vessel was charged with H₂ and the mixture was hydrogenated at 4 atm for 24 h. The mixture was then purged with N₂ and filtered to remove the catalyst. The filtrate was concentrated and dried in vacuo to give the product **191** (R¹ = H; R² = Cy); yield: 108 mg (93%).

18.8.17

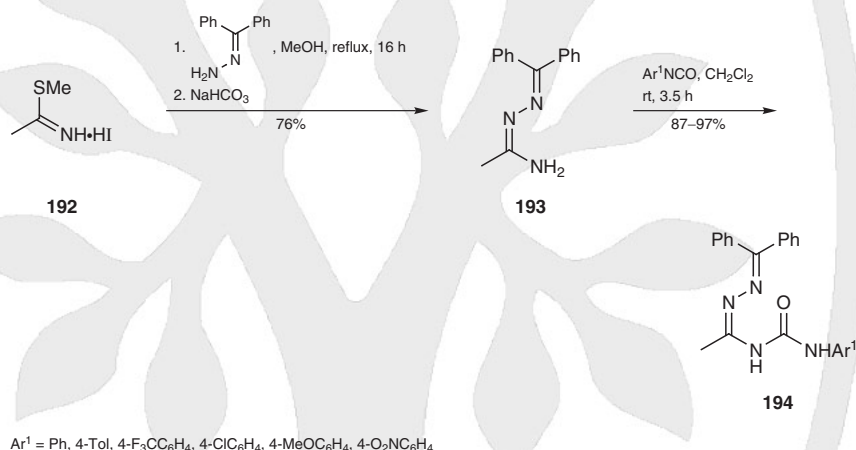
Product Subclass 17:
***N*-(Iminomethyl)ureas**

18.8.17.1

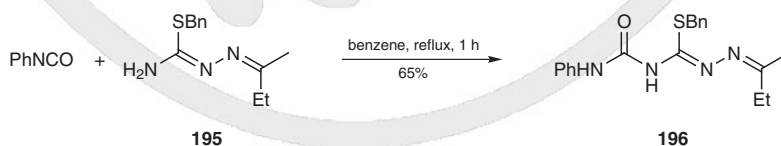
Synthesis of Product Subclass 17

This method represents an extension of the general approach to urea synthesis by nucleophilic addition of amines to isocyanates (see Section 18.8.1.1.4.1). In a similar way, nucleophilic amines containing a C=N functional group (i.e., azines, amidines, thiosemicarbazones) in the α -position react with isocyanates affording *N*-(iminomethyl)ureas. Due to the complexity of the compounds obtained, the reaction is frequently accompanied by further steps (isomerization, ring closure) that make every process specific to that starting material.

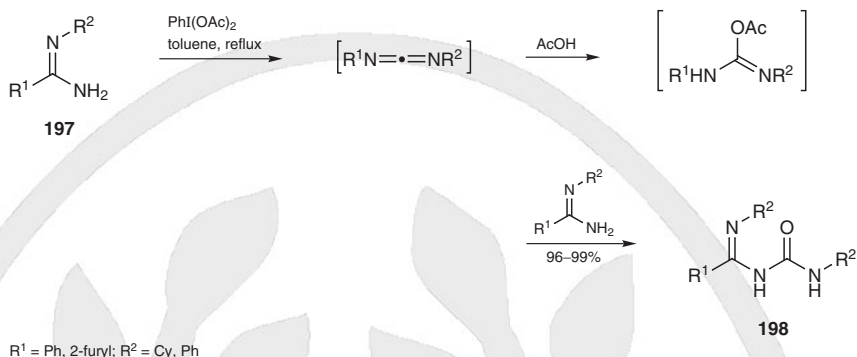
The reaction of methyl thioacetimidate hydroiodide (**192**) with benzophenone hydrazone, followed by neutralization with sodium hydrogen carbonate solution, gives benzophenone 1-aminoethylidenehydrazone (**193**), which is converted into 1-{1-[(diphenylmethylene)hydrazono]ethyl}ureas **194** by reaction with aryl isocyanates (Scheme 80).^[272]

Scheme 80 Synthesis of *N*-(Iminomethyl)ureas^[272]

S-Benzyl isothiosemicarbazones are similarly obtained by benzylation of thiosemicarbazones with benzyl chloride in methanol. These compounds react further with phenyl isocyanate yielding solid products identified as 1-[(benzylsulfanyl)(1-methylpropylidene)hydrazono]methyl-3-phenylurea which can be in turn converted into thiazolidine heterocycles (see Section 18.8.18). An example is shown in Scheme 81 for the formation of **196** from the 2-benzyl-3-(1-methylpropylideneamino)isothioureia (**195**), in total four examples are reported with a yield range of 61–71%.^[273]

Scheme 81 Synthesis of an *N*-(Iminomethyl)urea^[273]

N-(Iminomethyl)ureas **198** are obtained in quantitative yield when a solution of compound **197** in toluene is added to a solution of iodobenzene diacetate in the same solvent at reflux (Scheme 82).^[274] The entire process is hypothesized to occur via a carbodiimide intermediate produced by a Hofmann-like rearrangement.

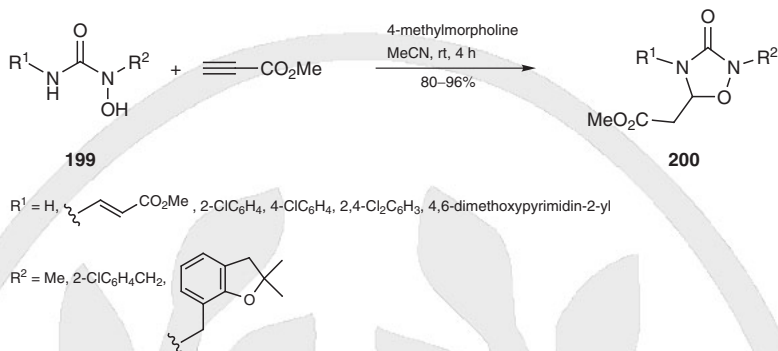
Scheme 82 Synthesis of *N*-(Iminomethyl)ureas via a Dimerization Process^[274]**1-((Benzylsulfanyl)((1-methylpropylidene)hydrazono)methyl)-3-phenylurea (196);****Typical Procedure:**^[273]

Phenyl isocyanate (2.02 g, 16.9 mmol) and 2-benzyl-3-(1-methylpropylideneamino)isothio-urea (**195**; 4.0 g, 16.9 mmol) in dry benzene (25 mL) (**CAUTION: carcinogen**) were heated under reflux for 1 h. After evaporation of excess of solvent under reduced pressure the crude was washed with petroleum ether (bp 40–60 °C), and after crystallization (EtOH) the product was obtained; yield: 3.90 g (65%); mp 130 °C.

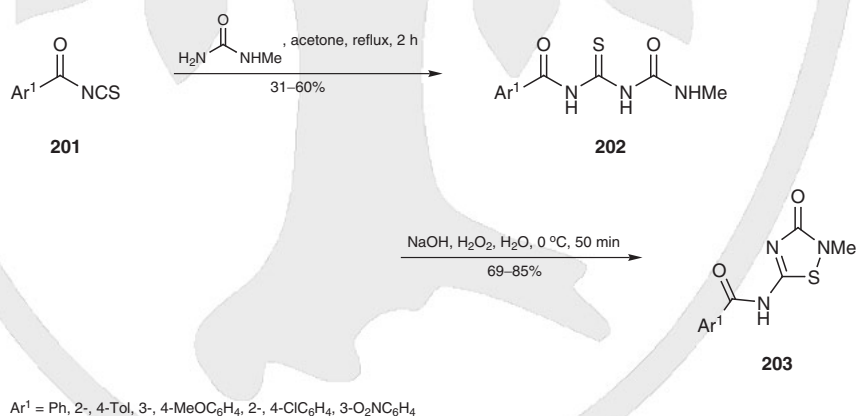
18.8.18**Product Subclass 18:****1,2,4-Oxadiazolidin-3-ones, 1,2,4-Thiadiazolidin-3-ones, 1,2,4-Triazolidinones, and 1,2,4-Triazolones****18.8.18.1****Synthesis of Product Subclass 18**

The compounds of this subclass are saturated or unsaturated five-membered ring ureas containing an additional heteroatom (O, S, N).

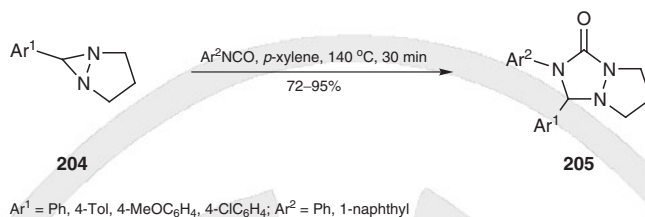
The useful methods for the preparation of 1,2,4-oxadiazolidin-3-ones are mainly based on *O,N*-dialkylation of hydroxyureas with dihalomethanes.^[275] A more convenient synthetic approach to these compounds is based on the tandem *O,N*-addition of *N*-hydroxyureas **199** to methyl propynoate in the presence of 4-methylmorpholine in acetonitrile. With 1,3-disubstituted 1-hydroxyureas the cyclization reaction is complete within 4 hours and no significant byproducts are detected. By contrast, when a free amino group is present ($R^1 = \text{H}$), the use of sodium hydride in tetrahydrofuran is required to afford the cyclized products **200** (Scheme 83).^[276] The starting *N*-hydroxyureas **199** can be prepared by treatment of hydroxyamines with the corresponding isocyanates.

Scheme 83 Preparation of 1,2,4-Oxadiazolidin-3-ones^[276]

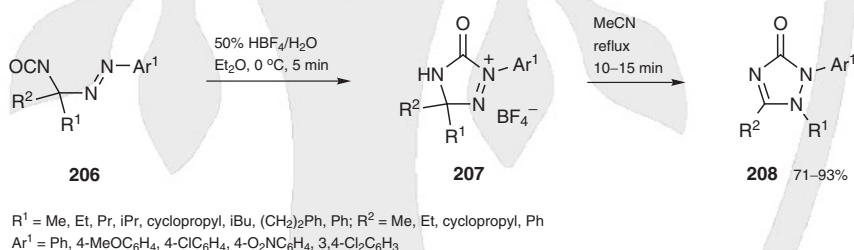
Two different routes are available for the synthesis of 1,2,4-thiadiazolidin-3-ones: reaction of 1,2,4-dithiazolidin-3-ones with isocyanates or ring closure of 1-[(alkylidenehydrazono)(benzylsulfanyl)methyl]-3-phenylureas (see Section 18.8.17). The first process, a [3+2] cycloaddition–elimination reaction, requires refluxing conditions in toluene for 24 hours; four examples are reported in 36–97% yield.^[277] The second process, the oxidative debenzylation and ring closure of 1-[(alkylidenehydrazono)(benzylsulfanyl)methyl]-3-phenylureas is carried out with molecular bromine; four examples are reported in 61–63% yield.^[273] A further advantage of this approach is the easy synthesis of 1-[(alkylidenehydrazono)(benzylsulfanyl)methyl]-3-phenylureas (Section 18.8.17). Oxidative cyclization of 2-thiobiurets **202** with hydrogen peroxide in an alkaline solution constitutes an additional method for the synthesis of 1,2,4-thiadiazolidin-3-ones **203** (Scheme 84). The starting 2-thiobiurets **202** are prepared by reacting methylurea with benzoyl isothiocyanates **201**, in turn prepared from benzoyl chlorides and potassium thiocyanate.^[278]

Scheme 84 Preparation of 1,2,4-Thiadiazolidin-3-ones by Oxidative Cyclization of 2-Thiobiurets^[278]

1,2,4-Triazolidin-3-ones **205** are obtained by reaction of diaziridines **204** with aryl isocyanates (Scheme 85). The process involves the initial thermal decomposition of the diaziridine (rate-determining step) affording an intermediate ylide that next gives regioselective 1,3-dipolar cycloaddition reaction with the aryl isocyanate. This second step occurs faster than the competitive hydride shifting and affords triazolidinones **205** in high yield and selectivity.^[279] The entire process occurs without additional reagents and products are directly obtained by crystallization from the final reaction mixture.

Scheme 85 Preparation of 1,2,4-Triazolidin-3-ones^[279]

The preparation of 1,5-disubstituted 2-aryl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones **208** can be achieved by acid-induced rearrangement of 1-(aryloxy)alkyl isocyanates **206**, prepared in turn by 1,3-dipolar cycloaddition of isocyanic acid (generated in situ) to arylhydrazones followed by oxidation with potassium permanganate of the so obtained triazolidinones. 1-(Aryloxy)alkyl isocyanates **206** are converted into 3,3-disubstituted 1-aryl-5-oxo-4,5-dihydro-3*H*-1,2,4-triazolium tetrafluoroborates **207** by simply stirring with tetrafluoroboric acid in diethyl ether. Compounds **207** can be isolated as crystals and characterized. Their stability depends strongly on both the nature of the substituents R^1 and R^2 and the substitution pattern on the aromatic ring. Triazolium tetrafluoroborates **207** rearrange under mild reaction conditions with a 1,2-shift of one of the substituents from position 3 to the nitrogen atom at position 2 to yield the salts of 1,5-disubstituted 2-aryl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones **208** (Scheme 86). Extension of the reaction to various examples of **207** shows that the nature of the substituents determines their migratory aptitude for the rearrangement; important differences in the migration rates of the substituents ensures that, when $\text{R}^1 \neq \text{R}^2$, the formation of mixtures of two possible isomers is not observed.^[280]

Scheme 86 Synthesis of 1,5-Disubstituted 2-Aryl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones^[280]

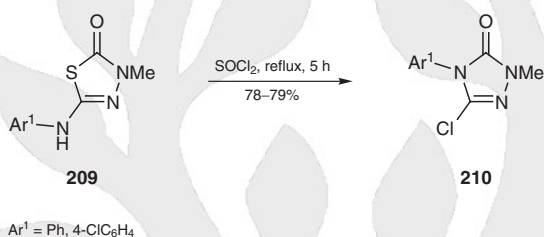
By using 5-spiro-substituted 2-phenyl-1,2,4-triazolidin-3-ones as starting materials several 1,5-annulated 2-aryl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones can be prepared by isocyclic ring expansion; 16 examples are reported with a wide yield range of 15–98%.^[281] Following the same strategy, 1-aza-2-azoniaallene salts react with isocyanates affording 5-oxo-4,5-dihydro-3*H*-1,2,4-triazolium salts. Mechanistically, reaction of 1-aza-2-azoniaallene with isocyanates would resemble 1,3-dipolar cycloaddition with the cumulene acting as 1,3-dipole and the isocyanate as dipolarophile. It is worthy of note that if the substituent at position 4 is an electron-withdrawing group, these products are unstable and rearrange at room temperature to the more stable 5-oxo-4,5-dihydro-1*H*-1,2,4-triazolium salts by 1,2-alkyl shift. A large number of examples is reported (22) with a yield range of 42–93%.^[282]

Another strategy for the synthesis of 1,2,4-triazol-3-ones involves the use of linear ureas containing a single N–N bond bearing a further functional group, usually a C=O or C=S bond, which allows the cyclization process via addition–elimination steps. Starting materials such as 1-acylsemicarbazides in the presence of sodium hydroxide undergo intramolecular nucleophilic attack and, after water elimination, afford mono- and disub-

stituted 1,2,4-triazol-3-ones, very useful intermediates in the manufacture of medications, herbicides, and polymers. Six examples are reported with 31–90% yield.^[283]

2,4-Dihydro-3*H*-1,2,4-triazol-3-ones **210** are prepared by rearrangement of 1,3,4-thiadiazol-2(3*H*)-ones **209** by a hypothetical triazole–thione intermediate followed by chlorination. The starting reagents **209** are prepared by multistep reaction from methyl 2-methyldithiocarbamate and isocyanates in the presence of an excess of thionyl chloride. The mechanism seems to involve the initial formation of a chloro sulfide, followed by intramolecular transfer of chlorosulfinyl group and subsequent cyclization to 1,3,4-thiadiazol-2(3*H*)-ones **209** that then rearrange on treatment with thionyl chloride to the isomeric triazole–thione followed by chlorination to give the final products **210** (Scheme 87).^[284]

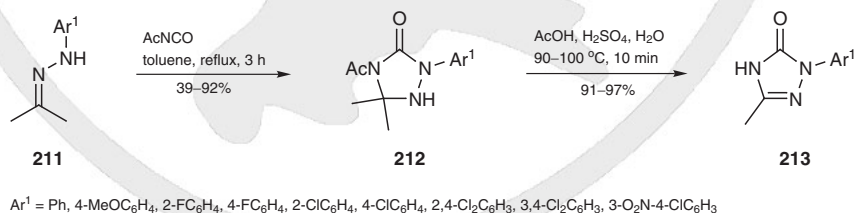
Scheme 87 Synthesis of 2,4-Dihydro-3*H*-1,2,4-triazol-3-ones by Rearrangement of 1,3,4-Thiadiazol-2(3*H*)-ones^[284]



N-Nitrosoureas cyclize to the corresponding 2,4-dihydro-3*H*-1,2,4-triazol-3-ones on heating in acetone, chloroform, or diethyl ether; two examples are reported with 62–86% yield.^[285] No significant solvent dependence of the yields is reported.

A final strategy is based on the use of a reagent containing a single N–N bond that reacts with (1-chlorovinyl)carbamoyl chloride or acetyl isocyanate affording substituted 1,2,4-triazol-3-ones. For example, treatment of *N*-(1-chlorovinyl)carbamoyl chloride in acetonitrile with formohydrazide in the presence of triethylamine affords the product in 97% yield and high purity after workup with aqueous hydrogen chloride.^[286] Similarly, treatment of acetyl isocyanate in toluene with arylhydrazones **211** affords 2-aryl-5,5-dimethyl-1,2,4-triazolidin-3-ones **212** that after acid hydrolysis produce the desired heterocycles **213** (Scheme 88). The one-pot cyclization–hydrolysis procedure can be performed by carrying out the reaction in toluene, replacing it with a mixture of acetic acid and aqueous sulfuric acid and refluxing; the products are obtained without isolation of intermediates **212**.^[287]

Scheme 88 Synthesis of Substituted 2,4-Dihydro-3*H*-1,2,4-triazol-3-ones from Arylhydrazones and Acetyl Isocyanate^[287]



Methyl [4-(4-Chlorophenyl)-2-methyl-3-oxo-1,2,4-oxadiazolidin-5-yl]acetate (200, R¹ = 4-ClC₆H₄; R² = Me); Typical Procedure:^[276]

To a soln of 3-(4-chlorophenyl)-1-hydroxy-1-methylurea (**199**, R¹ = 4-ClC₆H₄; R² = Me; 201 mg, 1.0 mmol) and methyl propynoate (88 mg, 1.05 mmol) in MeCN was added 4-methylmorpholine (20.2 mg, 0.2 mmol) at rt. The mixture was stirred for 4 h and then

concentrated under reduced pressure. The crude product was recrystallized (Et₂O/hexane) to afford the product as crystals; yield: 273 mg (96%); mp 83–85 °C.

2-Methyl-5-(4-methylbenzoylamino)-1,2,4-thiadiazol-3(2H)-one (203, Ar¹ = 4-Tol);

Typical Procedure:^[278]

5-Methyl-1-(4-methylbenzoyl)-2-thiobiuret (**202**, Ar¹ = 4-Tol; 1.0 g, 4.18 mmol) was completely dissolved in 2 M NaOH (20 mL) at 0 °C. 30% H₂O₂ (0.13 mL, 5.51 mmol) was added dropwise to the mixture. The mixture was stirred for 50 min at the same temperature and then acidified to pH 4.5 with concd HCl. The resulting colorless solid was separated and collected with suction (0.78 g, 75%). Recrystallization (EtOH) gave the product; yield: 0.57 g (55%); mp 278–280 °C.

3-(4-Methoxyphenyl)-2-phenyltetrahydro-1H,5H-pyrazolo[1,2-*a*][1,2,4]triazol-1-one

(205, Ar¹ = 4-MeOC₆H₄; Ar² = Ph); Typical Procedure:^[279]

A mixture of 6-(4-methoxyphenyl)-1,5-diazabicyclo[3.1.0]hexane (**204**, Ar¹ = 4-MeOC₆H₄; 0.38 g, 2 mmol) and PhNCO (0.24 g, 2 mmol) in dry *p*-xylene (8 mL) was stirred and heated at 140 °C for 20 min. The solvent was removed under reduced pressure and the residue was recrystallized [benzene (**CAUTION: carcinogen**)/hexane] to give the product; yield: 0.59 g (95%); mp 166 °C.

2-(4-Methoxyphenyl)-1,5-dimethyl-1,2-dihydro-3H-1,2,4-triazol-3-one (208, R¹ = R² = Me;

Ar¹ = 4-MeOC₆H₄); Typical Procedure:^[280]

A soln of 2-(4-methoxyphenyl)-5,5-dimethyl-1,2,4-triazolidin-3-one (3.32 g, 15 mmol) in Et₂O (225 mL) and 2% KMnO₄/H₂O (150 mL) were mixed by shaking in a separatory funnel for 30 min. Then the aqueous layer was separated (the MnO₂ formed can be dissolved by addition of NaHSO₃) and extracted with Et₂O (2 × 30 mL); the combined ether solns were washed with H₂O until neutral and dried (MgSO₄). After removal of the solvent in vacuo 1-(4-methoxyphenylazo)-1-methylethyl isocyanate (**206**, R¹ = R² = Me; Ar¹ = 4-MeOC₆H₄) was obtained; yield: 3.19 g (97%). This compound **206** (R¹ = R² = Me; Ar¹ = 4-MeOC₆H₄; 2.19 g, 10 mmol) was dissolved in Et₂O (75 mL) and the soln was cooled to 0 °C. 50% HBF₄/H₂O (10 mL) was added dropwise over 10 min with stirring, whereupon the yellow crystalline 1-(4-methoxyphenyl)-3,3-dimethyl-5-oxo-4,5-dihydro-3H-1,2,4-triazolium tetrafluoroborate (**207**; R¹ = R² = Me; Ar¹ = 4-MeOC₆H₄) precipitated. Stirring was continued for 5 min, the product was filtered, washed with a small quantity of ice-cold Et₂O and dried in vacuo over CaCl₂. This product (1.54 g, 5 mmol) was dissolved in MeCN (10 mL) and refluxed for 10–15 min, during which time the initially bright yellow color fades. The solvent was removed under reduced pressure, and the crystalline residue was dissolved in a minimum quantity of MeCN. Precipitation of the product was induced by careful addition of Et₂O, or better *t*-BuOMe; yield: 1.00 g (91%); mp >185 °C (dec).

2-(3,4-Dichlorophenyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one

(213, Ar¹ = 3,4-Cl₂C₆H₃); Typical Procedure:^[287]

Under a dry N₂ atmosphere, a soln of acetyl isocyanate (0.94 g, 11 mmol) in toluene was added dropwise to a stirred soln of acetone 3,4-dichlorophenylhydrazone (**211**, Ar¹ = 3,4-Cl₂C₆H₃; 2.17 g, 10 mmol) in toluene (20 mL). The mixture was stirred at rt for 15 min, then heated at gentle reflux for 3 h. The solvent was removed under reduced pressure and then AcOH (50 mL), concd H₂SO₄ (1 mL), and H₂O (5 mL) were successively added and the mixture was heated between 90–100 °C for 10 min. The solvent was removed under reduced pressure and the residue was triturated with H₂O; the resulting solid was collected by filtration at the pump, washed well with H₂O, and dried in vacuo at 80 °C affording the product; yield: 2.12 g (87%); mp 249–250 °C.

18.8.19

Product Subclass 19:**1,3,5-Oxadiazin-4-ones, 1,3,5-Thiadiazin-4-ones, 1,3,5-Triazin-2-ones, and 1,2,4-Triazin-3-ones**

18.8.19.1

Synthesis of Product Subclass 19

The compounds of this subclass are saturated or unsaturated six-membered ring ureas with an additional heteroatom (O, S, N).

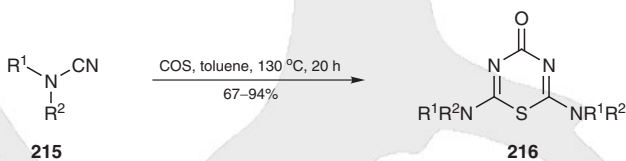
Tetrahydro-4*H*-1,3,5-oxadiazin-4-ones (urons) are prepared by reacting formaldehyde with 1-alkyl-3-arylureas without activating groups in the aromatic ring. The reaction is carried out in 1,2-dichloroethane in the presence of trifluoroacetic acid at room temperature and involves 1,3-bishydroxymethylation of the starting urea followed by ring closure with elimination of a molecule of water. An example is shown in Scheme 89 for the formation of 3-phenyl-5-(2-phenylethyl)tetrahydro-4*H*-1,3,5-oxadiazin-4-one (**214**); in total five examples are reported with 46–90% yield.^[288] It is notable that with 1-alkyl-3-arylureas containing activating groups on the aromatic ring, the reaction takes a different pathway leading to the formation of substituted tetrahydroquinolines via intramolecular Mannich reaction.

Scheme 89 The Formation of 3-Phenyl-5-(2-phenylethyl)tetrahydro-4*H*-1,3,5-oxadiazin-4-one^[288]



Substituted 4*H*-1,3,5-thiadiazin-4-ones **216** are prepared through cycloaddition processes. The strategy utilizes dialkylcyanamides **215** and carbonyl sulfide in toluene at high pressure (800 MPa) and temperature (130 °C) (Scheme 90). The reaction is highly selective and the formation of 2,6-bis(dialkylamino)-4*H*-1,3,5-thiadiazin-4-ones **216** is presumably due to repeated cycloaddition–reversion processes.^[289]

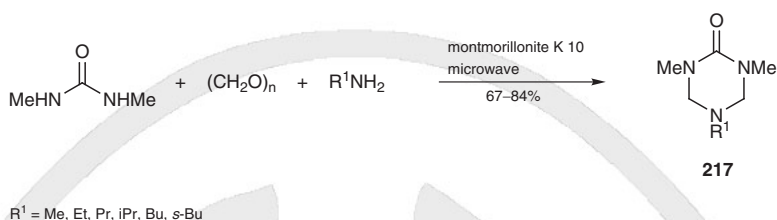
Scheme 90 Synthesis of 4*H*-1,3,5-Thiadiazin-4-ones by Cycloaddition of Dialkylcyanamides with Carbonyl Sulfide^[289]



$\text{R}^1 = \text{R}^2 = \text{Me}$; $\text{NR}^1\text{R}^2 = \text{pyrrolidin-1-yl, piperidino, morpholino}$

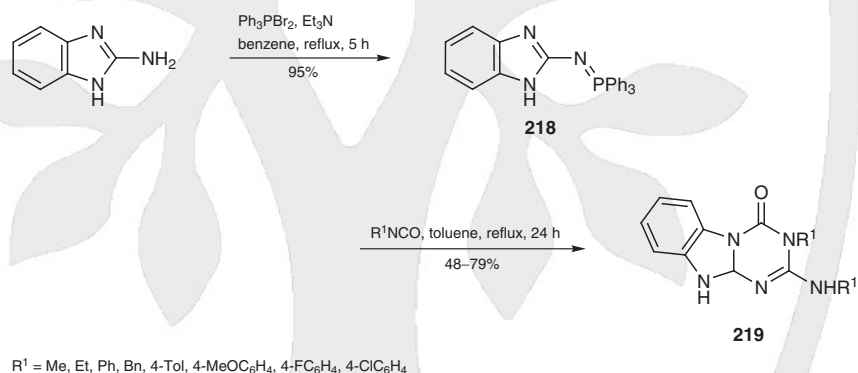
Tetrahydro-1,3,5-triazin-2(1*H*)-ones, 3,4-dihydro-1,3,5-triazin-2(1*H*)-ones, and 1,3,5-triazin-2(1*H*)-ones are generally prepared via cyclization process, if possible employing a three-component strategy.

The preparation of tetrahydro-1,3,5-triazin-2(1*H*)-ones is carried out following the multicomponent approach. Ureas can react with paraformaldehyde and primary amines affording heterocycles such as **217** in a mild and rapid procedure (Scheme 91). The process is catalyzed by a clay, namely montmorillonite K 10, and is carried out in solvent-free conditions under microwave irradiation.^[290] The role of the solid catalyst is presumably to promote the depolymerization of paraformaldehyde.

Scheme 91 Three-Component Synthesis of Tetrahydro-1,3,5-triazin-2(1*H*)-ones^[290]

An elegant three-component approach is represented by the reaction involving aryl isocyanates and 1,3,5-trisubstituted hexahydrotriazines; the reaction is believed to occur by the sequential addition to the isocyanate of two molecules of the monomeric *N*-methyleneamines derived from the thermal decomposition of the corresponding hexahydrotriazines. Eighteen examples are reported with a yield range of 40–90%.^[291]

The preparation of triazinones containing an endocyclic C=N bond can be performed by reacting alkyl or aryl isocyanates with double-functionalized compounds. For example, by using iminophosphoranes **218**, readily derived from 1*H*-benzimidazol-2-amine and dibromotriphenylphosphorane in the presence of triethylamine, a variety of 10,10a-dihydro-1,3,5-triazino[1,2-*a*]benzimidazol-4(3*H*)-ones **219** are produced by an aza-Wittig reaction (Scheme 92).^[292]

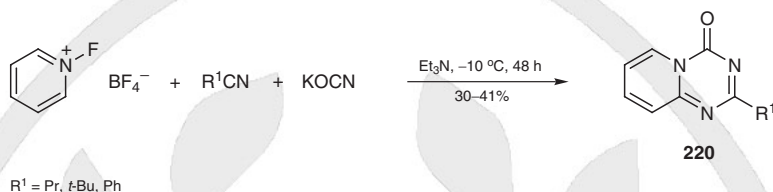
Scheme 92 Synthesis of Triazinones from Iminophosphoranes and Isocyanates^[292]

Following the same strategy, *N*-substituted benzimidamides react with isocyanates in boiling toluene and in the presence of a little quinuclidine affording *N,N'*-disubstituted benzimidamides that are immediately cyclized to the corresponding 3,4-dihydro-1,3,5-triazin-2(1*H*)-ones. Six examples are reported with a yield range of 31–85%.^[293] If mild conditions are employed (no catalyst and lower temperatures) the cyclization reaction does not take place.

1,3,5-Triazin-2(1*H*)-ones are obtained by utilizing as the starting materials *N*-acylthiobiurets. Thus by refluxing 1-acyl-2-methylthioureac-3-carboxamides in methanol for 24 hours, 4,6-disubstituted 1,3,5-triazin-2(1*H*)-ones are prepared without additional reagents {see also *Science of Synthesis*, Vol. 17 [Six-Membered Heteroarenes with Two Unlike or More than Two Heteroatoms and Fully Unsaturated Larger-Ring Heterocycles (Section 17.2.3.1.1.3.1.3)]}.^[294] More interestingly, the same class of triazinones can be synthesized by multicomponent reactions. Following a three-component procedure, nitriles, potassium cyanate, and 1-fluoropyridinium tetrafluoroborate are reacted under nitrogen at -10°C affording 2-substituted 4*H*-pyrido[1,2-*a*]-1,3,5-triazin-4-ones **220** (Scheme 93).^[295] Even if the reaction is not highly selective [*N*-(2-pyridyl)amide byproducts are isolated in

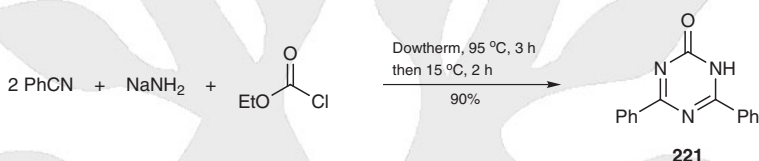
12–30% yield from the final reaction mixture], the process represents a novel synthetic approach for the preparation of compounds structurally similar to molecules displaying potent 5-HT₂ antagonist activity.^[296]

Scheme 93 Three-Component Synthesis of 4*H*-Pyrido[1,2-*a*]-1,3,5-triazin-4-ones^[295]



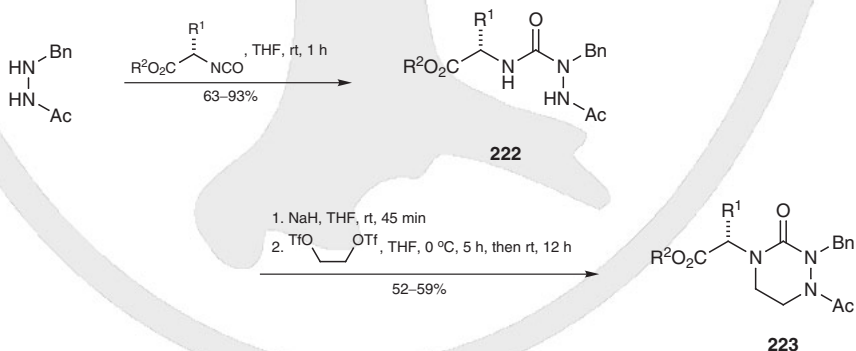
A four-component approach has also been studied. By reacting two molecules of benzonitrile with ethyl chloroformate and sodium amide, the 4,6-diphenyl-1,3,5-triazin-2(1*H*)-one **221** is isolated in 90% yield and in such high purity that it can be conveniently further processed without isolation (Scheme 94).^[297] This product represents a useful intermediate for the synthesis of UV absorbers.

Scheme 94 Four-Component Synthesis of 4,6-Diphenyl-1,3,5-triazin-2(1*H*)-one^[297]



Special 1,4,5,6-tetrahydro-1,2,4-triazin-3(2*H*)-ones **223** are prepared in a one-pot reaction by sodium hydride catalyzed cyclization of 1,2-bis(triflyloxy)ethane with azapeptides **222**, in turn prepared by reacting 1-acetyl-2-benzylhydrazine and isocyanates (Scheme 95). These so obtained tetrahydrotriazinones **223** are dipeptide-mimetic units and can be incorporated into longer chains by the usual techniques of peptide synthesis.^[298]

Scheme 95 Synthesis of 1,4,5,6-Tetrahydro-1,2,4-triazin-3(2*H*)-ones by Cyclization of Azapeptides^[298]

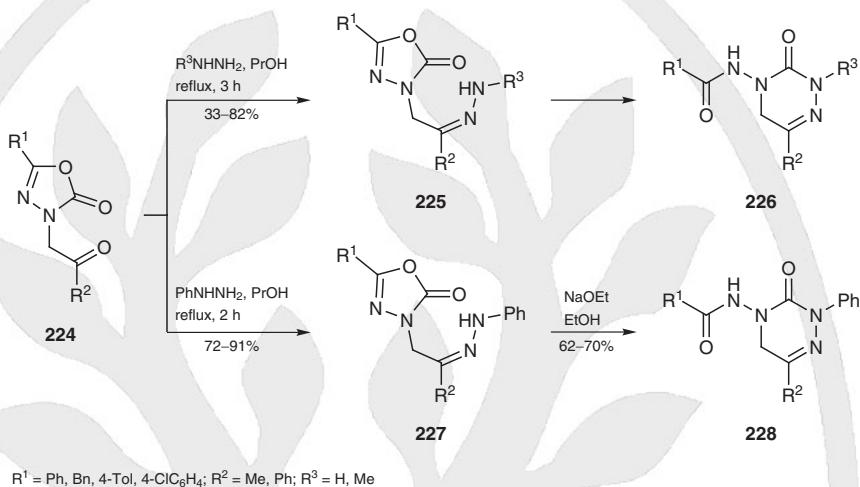


$R^1 = \text{H, Me, } s\text{-Bu, } i\text{Bu, Bn; } R^2 = \text{Me, Et}$

4,5-Dihydro-1,2,4-triazin-3(2*H*)-ones **226** and **228** are generally prepared from 1,3,4-oxadiazol-2(3*H*)-ones **224** by reaction with hydrazines (Scheme 96). The synthesis is performed by refluxing the solution of reagents in ethanol^[299] or propanol for 3 hours.^[300] The mech-

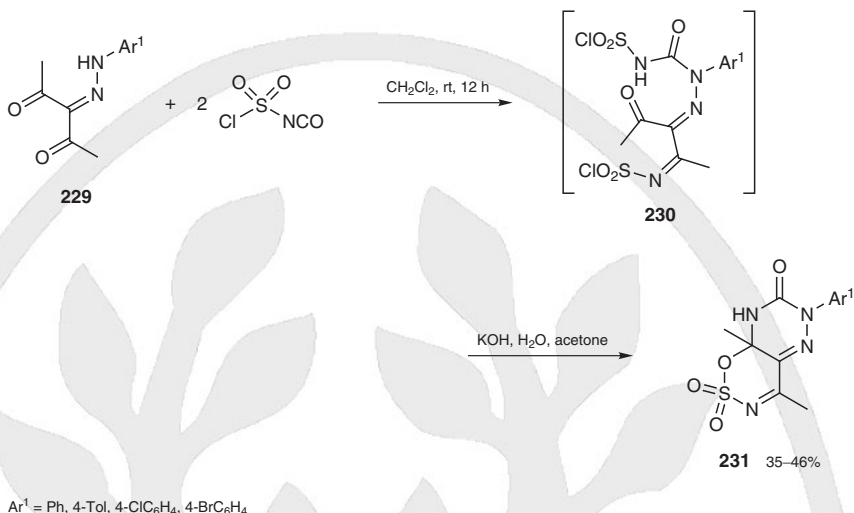
anistic pathway implies first attack of the hydrazine on the ketone group of **224** with initial formation of the corresponding hydrazones **225** or **227** which then undergo a ring-opening/cyclization process. If phenylhydrazine is employed, the reaction must be catalyzed by sodium ethoxide.

Scheme 96 Synthesis of 4,5-Dihydro-1,2,4-triazin-3(2*H*)-ones from 1,3,4-Oxadiazol-2(3*H*)-ones and Hydrazines^[299,300]

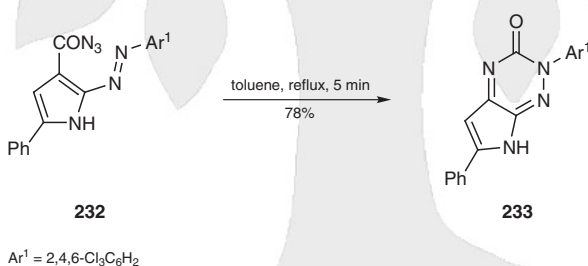


The same class of compounds can be obtained by reaction of phenylcarbamates and benzenediazonium chloride. For example by using ethyl 3-hydroxyphenylcarbamate in the presence of pyridine, the 2-phenyl-1,2,4-benzotriazine-3,6(2*H*,4*H*)-dione is isolated in 72% yield.^[301]

A convenient synthetic route to 4,5-dihydro-1,2,4-triazin-3(2*H*)-ones is by the three-component reaction between 3-(arylhyaazono)pentane-2,4-diones **229** and two molecules of chlorosulfonyl isocyanate (Scheme 97). The formation of the corresponding 4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **231** can be rationalized through an addition of two molecules of chlorosulfonyl isocyanate to hydrazones **229** affording the intermediates **230** that successively cyclize in the presence of potassium hydroxide to give the final products **231**.^[302]

Scheme 97 Three-Component Synthesis of 4,5-Dihydro-1,2,4-triazin-3(2*H*)-ones^[302]

1,2,4-Triazin-3(2*H*)-ones are obtained via isomerization of bicyclic isoureas, namely dihydroimidazooloxadiazines. The reaction is carried out in methanol and under high-pressure mercury-lamp irradiation at 330 nm.^[303] An alternative strategy is the intramolecular cycloaddition of isocyanates, derived from the corresponding carboxylic acid azides by Curtius rearrangement, to diazo compounds. Thus heating 1-[3-(azidocarbonyl)-5-phenyl-1*H*-pyrrol-2-yl]-2-(2,4,6-trichlorophenyl)diazene (**232**) at reflux for 5 minutes results in the production of 6-phenyl-2-(2,4,6-trichlorophenyl)-2,7-dihydro-3*H*-pyrrolo[3,2-*e*]-1,2,4-triazin-3-one (**233**) in 78% yield (Scheme 98).^[304]

Scheme 98 Synthesis of 1,2,4-Triazin-3(2*H*)-ones by Intramolecular Cycloaddition^[304]

3-Phenyl-5-(2-phenylethyl)tetrahydro-4*H*-1,3,5-oxadiazin-4-one (**214**);

Typical Procedure:^[288]

To a soln of 1-phenyl-3-(2-phenylethyl)urea (0.48 g, 2 mmol) in 1,2-dichloroethane (10 mL) was added paraformaldehyde (0.12 g, 4 mmol) and TFA (1 mL). The soln was stirred at rt for 3 h. H₂O (50 mL) was added, and the soln was extracted with CH₂Cl₂ (3 × 20 mL). The combined extracts were dried (Na₂SO₄) and concentrated; the crude was purified by column chromatography (neutral alumina, Et₂O/CH₂Cl₂) affording the product as colorless oil; yield: 0.51 g (90%).

2,6-Bis(dimethylamino)-4H-1,3,5-thiadiazin-4-one (216, R¹ = Me); Typical Procedure:^[289]

CAUTION: Carbonyl sulfide is a colorless, flammable, and toxic gas with an unpleasant odor similar to rotten eggs.

Dimethylcyanamide (**215**, R¹ = R² = Me; 0.77 g, 11 mmol) was dissolved in toluene (10 mL) saturated with COS (~9 mmol). The soln was sealed in a poly(tetrafluoroethylene) capsule and compressed to 800 Mpa, and kept at 130 °C for 20 h. After evaporation of the solvent and the cyanamide under reduced pressure, the crude was crystallized [benzene (**CAUTION: carcinogen**)] and the product was obtained; yield: 1.01 g (92%); mp 214 °C.

5-Butyl-1,3-dimethyltetrahydro-1,3,5-triazin-2(1H)-one (217, R¹ = Bu);**Typical Procedure:**^[290]

1,3-Dimethylurea (0.26 g, 3 mmol), paraformaldehyde (1.0 g, 33 mmol), BuNH₂ (0.22 g, 3 mmol), and montmorillonite K 10 (2 g) were irradiated by microwave in a Teflon vessel. The mixture was then filtered and washed with H₂O. The organic phase was separated, dried (Na₂SO₄), and concentrated by vacuum distillation. Purification of the crude by column chromatography (CH₂Cl₂) afforded the product; yield: 0.47 g (84%).

3-(4-Fluorophenyl)-2-[(4-fluorophenyl)amino]-10,10a-dihydro-1,3,5-triazino[1,2-a]benzimidazol-4(3H)-one (219, R¹ = 4-FC₆H₄); Typical Procedure:^[292]

To a soln of 2-(triphenylphosphoranylideneamino)-1H-benzimidazole (**218**; 0.5 g, 1.3 mmol) in dry toluene (15 mL) was added 4-fluorophenyl isocyanate (0.36 g, 2.6 mmol). The mixture was stirred at reflux for 24 h. After cooling, the solvent was removed under reduced pressure and the residual material was slurried with cold EtOH (2 × 15 mL) and the separated solid was collected by filtration. Recrystallization (EtOH) afforded the product as white crystals; yield: 0.36 g (72%); mp 273–274 °C.

4,6-Diphenyl-1,3,5-triazin-2(1H)-one (221); Typical Procedure:^[297]

NaNH₂ (100 g, 2.56 mol) in Dowtherm (500 mL) was stirred at rt for 12 h in the presence of glass beads. The glass beads were then separated and washed with Dowtherm (500 mL). The resultant suspension was heated to 90 °C and PhCN (232 g, 2.25 mol) was added dropwise over 1 h such that the temperature did not rise above 105 °C. Heating was continued at 95 °C for 3 h, then the mixture was cooled to 15 °C and ethyl chloroformate (260.4 g, 2.4 mol) was added dropwise over 2 h. The mixture is then heated to 170 °C and the pressure was lowered to 150–80 mbar, whereupon a mixture consisting of EtOH, carbamic acid, and Dowtherm (300 g) was distilled over. After 2 h, the batch was cooled, filtered, and the filter residue was washed with MeOH (1 L) giving the product as a white solid; yield: 255.4 g (90%); mp 296 °C.

Methyl (S)-2-(1-Acetyl-2-benzyl-3-oxohexahydro-1,2,4-triazin-4-yl)propanoate**(223, R¹ = R² = Me); Typical Procedure:**^[298]

To a soln of 1-acetyl-2-benzylhydrazine (1.0 g, 6.09 mmol) in anhyd THF (100 mL) methyl (S)-2-isocyanatopropanoate (0.8 g, 6.20 mmol) in anhyd THF (50 mL) was added dropwise at 0 °C under stirring. The soln was stirred at rt for 1 h, then concentrated under vacuum; purification by column chromatography (silica gel, CH₂Cl₂/MeOH 19:1) afforded methyl (S)-2-[[2-(2-acetyl-1-benzylhydrazino)carbonyl]amino]propanoate (**222**); yield: 1.55 g (87%). To a soln of **222** (1.00 g, 3.41 mmol) in anhyd THF (200 mL) was added NaH (180 mg, 7.49 mmol). The suspension was stirred at rt for 45 min, then 1,2-bis(triflyloxy)ethane (1.1 g, 3.41 mmol) in anhyd THF (100 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 5 h, and at rt for 12 h. The soln was evaporated and the residue was dissolved in H₂O (20 mL) and extracted with EtOAc (4 × 40 mL). The extracts were dried (Na₂SO₄), and the residue was purified by column chromatography (CH₂Cl₂/MeOH 24:1) affording the product as colorless oil; yield: 0.63 g (58%); mp 100–101 °C.

4-(Benzoylamino)-2,6-diphenyl-4,5-dihydro-1,2,4-triazin-3(2H)-one (228, $R^1 = R^2 = \text{Ph}$);**Typical Procedure:**^[300]

To a soln of 3-(2-oxo-2-phenylethyl)-5-phenyl-1,3,4-oxadiazole-2(3H)-one (**224**, $R^1 = R^2 = \text{Ph}$; 4.2 g, 15 mmol) in PrOH (60 mL) was added PhNHNH_2 (1.7 g, 15 mmol) and the mixture was refluxed for 2 h. After removal of the solvent under reduced pressure, the resulting solid was recrystallized (PrOH) affording the phenylhydrazone derivative **227**; yield: 4.1 g (73%); mp 180 °C. This compound (3.7 g, 10 mmol) was added to soln of NaOEt (0.7 g, 10 mmol) in abs EtOH (40 mL). The mixture was refluxed for 1.5 h, cooled to rt, and poured into a soln of ice water (100 mL) and AcOH (2 mL). The resulting precipitate was filtered and recrystallized (EtOH) affording the product; yield: 2.5 g (67%); mp 210 °C.

18.8.20

Product Subclass 20:

1,3,5-Oxadiazine-4,6-diones, 1,3,5-Thiadiazine-4,6-diones, 1,3,5-Triazine-4,6-diones, 1,2,4-Triazine-3,5-diones, and 1,2,4-Triazine-3,6-diones

18.8.20.1

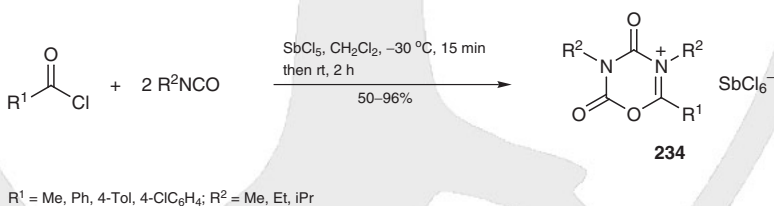
Synthesis of Product Subclass 20

The compounds of this subclass are saturated or unsaturated six-membered ring ureas with an additional heteroatom (O, S, N) and an additional $\text{C}=\text{O}$ group.

Isocyanates are the basic starting materials for the preparation of these kinds of compounds. In a first strategy, 1,4-diisocyanatobutane is converted by a catalytically induced reaction into a 3-(ω -isocyanatoalkyl)-5,6,7,8-tetrahydro-2H-1,3,5-oxadiazino[3,2-*a*][1,3]diazepine-2,4(3H)-dione. The process is carried out at 120 °C in the presence of hexamethyl-disilazane and the product is obtained with high selectivity (>90%).^[305] This conversion is very surprising because usually 1,4-diisocyanates, in the presence of different catalysts, tend to oligomerize with the formation of high-molecular-weight compounds.

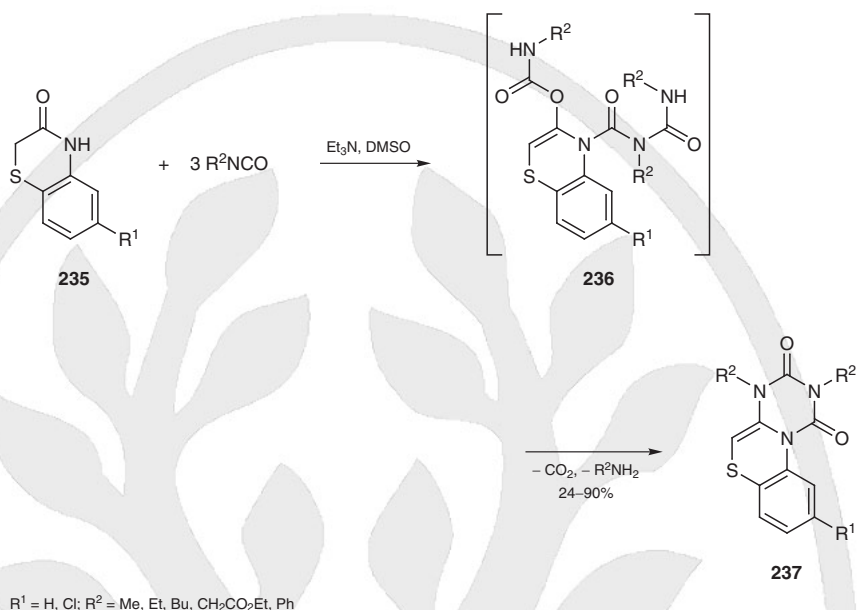
Alternatively, alkyl isocyanates react with acyl chlorides in a 2:1 ratio affording 3,5,6-trialkyl-2,4-dioxo-3,4-dihydro-2H-1,3,5-oxadiazinium salts **234**. The process is carried out in the presence of hard Lewis acids such as antimony(V) chloride (Scheme 99).^[306] The reaction fails with phenyl isocyanates.

Scheme 99 Synthesis of 2,4-Dioxo-3,4-dihydro-2H-1,3,5-oxadiazinium Salts by Three-Component Reaction of Acyl Chlorides and Alkyl Isocyanates^[306]

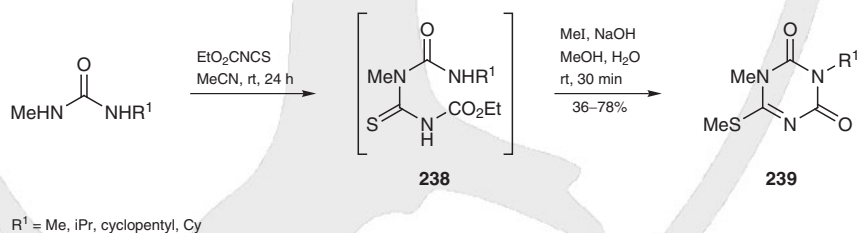


For the synthesis of substituted 1,3,5-thiadiazine-4,6-diones, thioamides can be reacted with chlorocarbonyl isocyanate. The process is carried out in benzene at 70 °C in the presence of a stoichiometric amount of triethylamine. Six examples are reported with a yield of 54–71%.^[307]

For the preparation of dihydro-1,3,5-triazine-2,4(1H,3H)-diones, a strategy used is the reaction of dihydrobenzothiazinones **235** with an excess of isocyanate in the presence of tertiary amines; in this case [1,3,5]triazino[2,1-*c*][1,4]benzothiazine-1,3(2H,4H)-diones **237** are isolated (Scheme 100). The process probably proceeds through the stepwise addition of three isocyanate molecules to dihydrobenzothiazinones **235** with the formation of intermediates **236**. Finally ring closure with liberation of amine and carbon dioxide gives the products **237**.^[308]

Scheme 100 Four-Component Synthesis of [1,3,5]Triazino[2,1-*c*][1,4]benzothiazine-1,3(2*H*,4*H*)-diones^[308]

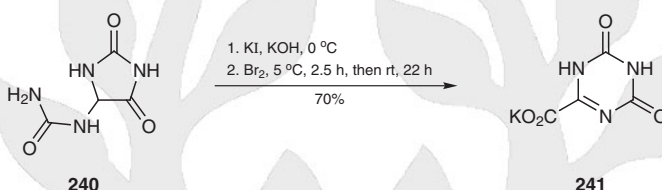
Various methodologies are utilized for the synthesis of 1,3,5-triazine-2,4(1*H*,3*H*)-diones, mainly based on the use of ureas and thioureas as starting reagents. One process involves the use of easily accessible 1-alkyl-3-methylureas that react with ethoxycarbonyl isothiocyanate in acetonitrile at room temperature affording 1-carbamoyl-3-(ethoxycarbonyl)-thioureas **238** that are then converted into 1,3,5-triazine-2,4(1*H*,3*H*)-diones **239** by treatment with aqueous sodium hydroxide followed by *S*-methylation (Scheme 101).^[309] The so obtained compounds are of interest from a phytotoxic standpoint^[310] and as herbicide precursors.^[311]

Scheme 101 Synthesis of 1,3,5-Triazine-2,4(1*H*,3*H*)-diones from Ureas and Ethoxycarbonyl Isothiocyanate^[309]

Following a rather similar strategy, thioureas are treated with silver cyanate in the presence of triethylamine in acetonitrile affording 6-amino-1,3,5-triazine-2,4(1*H*,3*H*)-diones. Five examples are reported with yields in the range 46–89%.^[312] Substituted 1,3,5-triazine-2,4(1*H*,3*H*)-diones can be also prepared by ring closure of special difunctionalized ureas. For example, an important class of herbicides containing this framework can be synthesized by treating 6-(3-{ethoxy[(methoxycarbonyl)imino]methyl}ureido)-7-fluoro-4-propyl-2*H*-1,4-benzoxazin-3(4*H*)-one in methanol with sodium methoxide at reflux. The product, 6-ethoxy-3-(7-fluoro-3-oxo-4-propyl-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)-1,3,5-triazine-2,4(1*H*,3*H*)-dione is isolated in 69% yield.^[313]

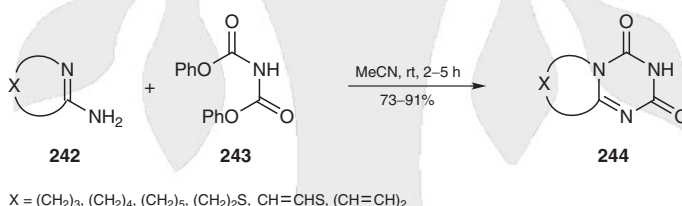
A further example of this strategy is the preparation of potassium oxonate (**241**, potassium 4,6-dioxo-3,4,5,6-tetrahydro-1,3,5-triazine-2-carboxylate), a compound useful in alleviating side effects resulting from the use of a 5-fluorouracil-type anticancer agent. The process, even though utilizing bromine, is based on a method that avoids the use of compounds having an adverse affect on the Earth's environment. The starting material is allantoin (**240**, 5-ureidohydantoin) which is initially reacted with potassium iodide and aqueous potassium hydroxide solution and then treated with bromine. Workup with acetic acid and cooling affords potassium oxonate (**241**) in 70% yield (Scheme 102).^[314] The mechanism involves the ring opening of the hydantoin moiety and subsequent intramolecular ring closure involving the ureidic part of the molecule.

Scheme 102 Preparation of Potassium Oxonate from Allantoin^[314]



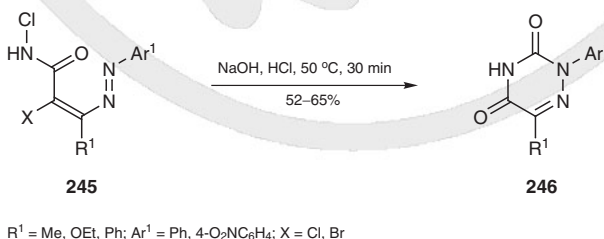
Cyclic amidines **242** and diphenyl iminodicarbonate **243** can also be utilized as useful reagents for the preparation of particular 1,3,5-triazine-2,4-diones **244** that are important moieties of compounds with 5-HT₂ antagonist activity (Scheme 103). The reaction is carried out in acetonitrile at room temperature for 2–5 hours with aliphatic amidines, whereas higher temperatures (refluxing 1,4-dioxane) and longer reaction times are required when aromatic amidines are utilized.^[315]

Scheme 103 Preparation of 1,3,5-Triazine-2,4-diones from Cyclic Amidines^[315]



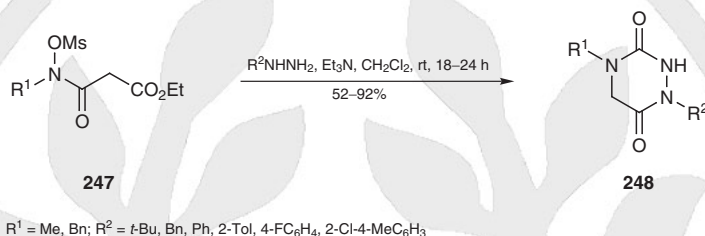
1,2,4-Triazine-3,5(2*H*,4*H*)-diones **246** are obtained by heating 3-(aryloxy)-*N*-chloroacrylamides **245**, obtained from 3-(aryloxy)acrylamides and sodium hypochlorite, with sodium hydroxide; the process proceeds via a Hofmann degradation reaction (Scheme 104).^[316]

Scheme 104 Synthesis of 1,2,4-Triazine-3,5(2*H*,4*H*)-diones from 3-(Aryloxy)-*N*-chloroacrylamides^[316]



A simple and direct method for the preparation of tetrahydro-1,2,4-triazine-3,6-diones **248** is the reaction of hydrazines with α -lactams derived from ethyl (*N*-hydroxycarbamoyl)acetates **247** (Scheme 105). The process, catalyzed by an amine, involves the formation of an urea hydrazone that cyclizes affording the products **248** via the α -lactam group.^[317]

Scheme 105 Synthesis of Tetrahydro-1,2,4-triazine-3,6-diones from (*N*-Hydroxycarbamoyl)acetates and Hydrazines^[317]



3,5-Diisopropyl-2,4-dioxo-6-phenyl-3,4-dihydro-2H-1,3,5-oxadiazinium Hexachloroantimonate (234, R¹ = Ph; R² = iPr); Typical Procedure:^[306]

At -30°C a soln of SbCl_5 (2.99 g, 10 mmol) in CH_2Cl_2 (10 mL) was added to a soln of BzCl (1.41 g, 10 mmol) and iPrNCO (1.70 g, 20 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at -30°C for 15 min, and then at rt for 2 h and after filtration the product was obtained as a moisture-sensitive colorless powder; yield: 5.84 g (96%); mp $180\text{--}183^\circ\text{C}$ (dec).

Potassium 4,6-Dioxo-1,4,5,6-tetrahydro-1,3,5-triazine-2-carboxylate (241, Potassium Oxonate):^[314]

CAUTION: Bromine is a severe irritant of the eyes, mucous membranes, lungs, and skin. Liquid bromine causes severe and painful burns on contact with eyes and skin.

At 0°C allantoin (15.8 g, 0.1 mol) and KI (0.79 g, 0.005 mol) were added to a soln of 16.6% $\text{KOH}/\text{H}_2\text{O}$ (271 g). Thereafter Br_2 (32.0 g, 0.2 mol) was added dropwise at such a rate as to keep the internal temperature at $\sim 5^\circ\text{C}$ for ca. 2.5 h. After completion of the addition of Br_2 , the internal temperature was raised to rt, followed by stirring for ca. 22 h. Then, the mixture was neutralized with AcOH (20 mL) to a pH ~ 6 to precipitate crystals. Subsequently, the soln was cooled to 5°C , followed by stirring for 2 h. Thereafter, the crystals were filtered off, washed with cold H_2O (66 mL) and cold acetone (22 mL). Then, the crystals were dried to obtain the product; yield: 13.7 g (70%); mp $>300^\circ\text{C}$.

4-Benzyl-1-phenyltetrahydro-1,2,4-triazine-3,6-dione (248, R¹ = Bn; R² = Ph); Typical Procedure:^[317]

To a soln of ethyl {[benzyl(mesyloxy)amino]carbonyl}acetate (**247**, R¹ = Bn; 1.0 g, 3.17 mmol) and PhNHNH_2 (0.84 g, 7.77 mmol) in CH_2Cl_2 was added Et_3N (202 mg, 2.1 mmol) in CH_2Cl_2 (24 mL) over a period of 6 h. The mixture was stirred for 18–24 h, then the solvent was removed, and the residue was diluted with EtOAc (60 mL), washed with H_2O (4×20 mL) and brine (20 mL), and dried (MgSO_4). After rotary evaporation, the crude was purified by recrystallization (hexanes/ CHCl_3 4:1) to give the product; yield: 530 mg (62%); mp $148\text{--}149^\circ\text{C}$.

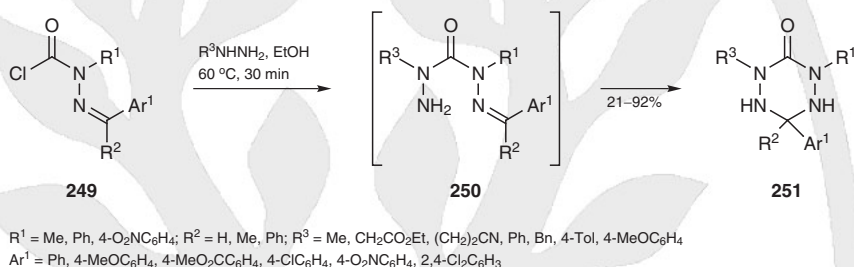
18.8.21 Product Subclass 21: Tetrazinones

18.8.21.1 Synthesis of Product Subclass 21

The compounds of this subclass are saturated or unsaturated six-membered ring ureas with two additional nitrogen atoms.

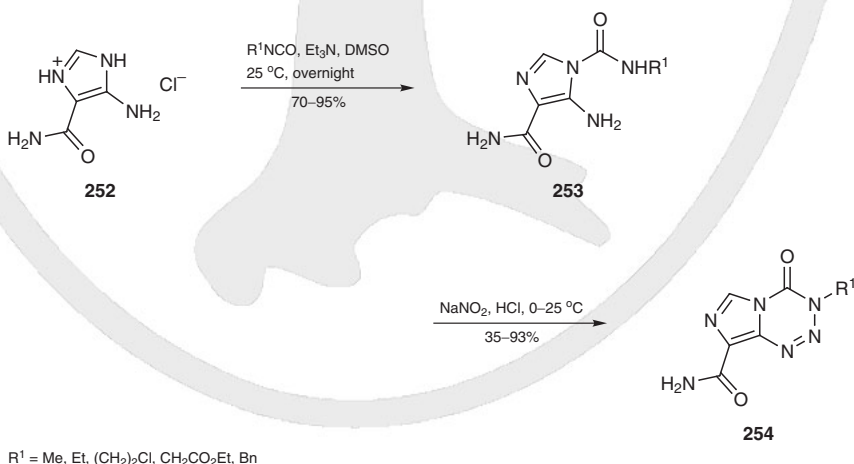
Tetrahydro-1,2,4,5-tetrazin-3(2H)-ones **251** are prepared by a cyclization reaction between (chloroformyl)hydrazones **249** and various hydrazines. The process proceeds through the formation of the 1-alkylidenecarbonohydrazide **250** that cyclizes immediately affording the corresponding tetrahydrotetrazinones **251** (Scheme 106).^[318]

Scheme 106 Synthesis of Tetrahydro-1,2,4,5-tetrazin-3(2H)-ones by Cyclization of (Chloroformyl)hydrazones with Hydrazines^[318]



Reaction of 5-amino-1H-imidazole-4-carboxamide hydrochloride **252** with alkyl isocyanates in dimethyl sulfoxide leads to regioselective carbamoylation of **252** with the formation of ureas **253** despite the availability of competing sites; nitrosative cyclization of **253** affords 4-oxo-3,4-dihydroimidazo[5,1-d]-1,2,3,5-tetrazine-8-carboxamides **254** that are potential antitumor drugs (Scheme 107); four examples are reported in a yield range of 35–93%.^[319]

Scheme 107 Synthesis of 4-Oxo-3,4-dihydroimidazo[5,1-d]-1,2,3,5-tetrazine-8-carboxamides from 5-Amino-1H-imidazole-4-carboxamide Hydrochloride and Isocyanates^[319]



6-(4-Nitrophenyl)-2,4-diphenyltetrahydro-1,2,4,5-tetrazin-3(2H)-one (251, $R^1 = R^3 = \text{Ph}$; $R^2 = \text{H}$; $\text{Ar}^1 = 4\text{-O}_2\text{NC}_6\text{H}_4$); **Typical Procedure**:^[318]

To a stirred soln of PhNHNH_2 (2.16 g, 20 mmol) in EtOH (50 mL) 1-(chloroformyl)-2-(4-nitrobenzylidene)-1-phenylhydrazine (**249**, $R^1 = \text{Ph}$; $R^2 = \text{H}$; $\text{Ar}^1 = 4\text{-O}_2\text{NC}_6\text{H}_4$; 3.04 g, 10 mmol) was added. The mixture was stirred at 60 °C for 30 min and after cooling to rt was poured into ice water (150 mL). The resulting precipitate was filtered and then crystallized twice (PrOH) to afford the product; yield: 3.45 g (92%); mp 226 °C.

References

- [1] Tafesh, A. M.; Weiguny, J., *Chem. Rev.*, (1999) **96**, 2035.
- [2] Bigi, F.; Maggi, R.; Sartori, G., *Green Chem.*, (2000) **2**, 140.
- [3] Dales, N. A.; Bohacek, R. S.; Satyshur, K. A.; Rich, D. A., *Org. Lett.*, (2001) **3**, 2313.
- [4] de la Torre, M. F.; Campos, E. G.; Gonzalez, S.; Morán, J. R.; Cruz Caballero, M., *Tetrahedron*, (2001) **57**, 3945.
- [5] Tejeda, A.; Oliva, A. I.; Simón, L.; Grande, M.; Caballero, M. C.; Morán, J. R., *Tetrahedron Lett.*, (2000) **41**, 4563.
- [6] Wada, M.; Kajimoto, N.; Nagata, T., EP 248 220, (1987); *Chem. Abstr.*, (1988) **108**, 112 508.
- [7] Nagata, T.; Wada, M.; Tamaoki, A., JP 62 181 264, (1987); *Chem. Abstr.*, (1987) **107**, 236 710.
- [8] Henkelmann, J.; Heider, M.; Ruehl, T., EP 752 417, (1997); *Chem. Abstr.*, (1997) **126**, 157 923.
- [9] Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-i., *J. Am. Chem. Soc.*, (1988) **110**, 3994.
- [10] Balko, T. W.; Brinkmeyer, R. S.; Terando, N. H., *Tetrahedron Lett.*, (1989) **30**, 2045.
- [11] Cardillo, G.; Orena, M.; Penna, M.; Sandri, S.; Tomasini, C., *Tetrahedron*, (1991) **47**, 2263.
- [12] Shiau, C. Y.; Chern, J. W.; Tien, J. H.; Liu, K. C., *J. Heterocycl. Chem.*, (1989) **26**, 595.
- [13] Markwalder, J. A.; Pottorf, R. S.; Seitz, S. P., *Synlett*, (1997), 521.
- [14] Wendeborn, S.; Winkler, T.; Foisy, I., *Tetrahedron Lett.*, (2000) **41**, 6387.
- [15] Kamal, A.; Sattur, P. B., *Tetrahedron Lett.*, (1989) **30**, 1133.
- [16] Kim, T. H.; Lee, G.-J., *J. Org. Chem.*, (1999) **64**, 2941.
- [17] Fülöp, F.; Wamhoff, H.; Sohár, P., *Synthesis*, (1995), 863.
- [18] Ramadas, K.; Srinivasan, N., *Org. Prep. Proced. Int.*, (1993) **25**, 600.
- [19] Yang, Y.; Lu, S., *Org. Prep. Proced. Int.*, (1999) **31**, 559.
- [20] Mojtahedi, M. M.; Saidi, M. R.; Bolourtchian, M., *J. Chem. Res., Synop.*, (1999), 710.
- [21] Kondo, T.; Kotachi, S.; Watanabe, Y., *J. Chem. Soc., Chem. Commun.*, (1992), 1318.
- [22] Akester, J.; Cui, J.; Fraenkel, G., *J. Org. Chem.*, (1997) **62**, 431.
- [23] Shouyou, K.; Kato, K.; Yamamoto, Y., JP 11 158 152, (1999); *Chem. Abstr.*, (1999) **131**, 44 823.
- [24] Kramer, A.; Siegel, W., EP 906 905, (1999); *Chem. Abstr.*, (1999) **130**, 283 683.
- [25] Mabire, F.; Blanc, A., EP 141 755, (1985); *Chem. Abstr.*, (1985) **103**, 106 265.
- [26] Bakibaev, A. A.; Savchenko, T. I.; Filimonov, V. D.; Yagovkin, A. Y.; Novikov, A. N., *Zh. Org. Khim.*, (1988) **24**, 2581; *Chem. Abstr.*, (1989) **111**, 39 257.
- [27] Zav'yalov, S. I.; Kulikova, L. B., *Khim.-Farm. Zh.*, (1992) **26**, 88; *Chem. Abstr.*, (1992) **117**, 150 650.
- [28] Mizuta, H.; Takaoka, M.; Nagata, T., EP 823 427, (1998); *Chem. Abstr.*, (1998) **128**, 167 422.
- [29] Kim, Y. B.; Kim, C. S.; Lee, C. K., *J. Heterocycl. Chem.*, (1994) **31**, 1653.
- [30] Srivastava, M.; Lakhan, R., *Org. Prep. Proced. Int.*, (1993) **25**, 708.
- [31] Von Itter, F. A., DE 3 906 855, (1990); *Chem. Abstr.*, (1991) **114**, 23 694.
- [32] Rapole, K. R.; Siddiqui, A. H.; Dayal, B.; Batta, A. K.; Rao, S. J.; Kumar, P.; Salen, G., *Synth. Commun.*, (1996) **26**, 3511.
- [33] Armstrong, J. D., III; Wolfe, C. N.; Keller, J. L.; Lynch, J. L.; Bhupathy, M.; Volante, R. P., *Tetrahedron Lett.*, (1997) **38**, 1531.
- [34] Xu, D.; Ciszewski, L.; Li, T.; Repic, O.; Blacklock, T. J., *Tetrahedron Lett.*, (1998) **39**, 1107.
- [35] Addison, S. J.; Cunningham, B. D. M.; Gate, E. N.; Shah, P. Z.; Threadgill, M. D., *J. Chem. Soc., Perkin Trans. 1*, (1985), 75.
- [36] Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W., *J. Am. Chem. Soc.*, (1993) **115**, 2622.
- [37] Kohler, B.; Meyer, R. V., DE 3 724 621, (1989); *Chem. Abstr.*, (1989) **111**, 78 022.
- [38] Dömling, A.; Herdtweck, E.; Ugi, I., *Acta Chem. Scand.*, (1998) **52**, 107.
- [39] Lombardo, M.; Trombini, C., In *Seminars in Organic Synthesis*, XXIII Summer School "A. Corbella", Società Chimica Italiana: Rome, (1998); p 7.

- [40] Trost, B. M., *Angew. Chem.*, (1995) **107**, 285; *Angew. Chem. Int. Ed. Engl.*, (1995) **34**, 259.
- [41] Lu, J.; Ma, H., *Synlett*, (2000), 63.
- [42] Ranu, B. C.; Hajra, A.; Jana, U., *J. Org. Chem.*, (2000) **65**, 6270.
- [43] Yadav, J. S.; Subba Reddy, B. V.; Srinivas, R.; Venugopal, C.; Ramalingam, T., *Synthesis*, (2001), 1341.
- [44] Yadav, J. S.; Reddy, B. V. S.; Reddy, E. J.; Ramalingam, T., *J. Chem. Res., Synop.*, (2000), 354.
- [45] Bussolari, J. C.; McDonnell, P. A., *J. Org. Chem.*, (2000) **65**, 6777.
- [46] Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B., *Synlett*, (2001), 863.
- [47] Dondoni, A.; Massi, A.; Sabbatini, S., *Tetrahedron Lett.*, (2001) **42**, 4495.
- [48] Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G., *Tetrahedron Lett.*, (1999) **40**, 3465.
- [49] Peng, J.; Deng, Y., *Tetrahedron Lett.*, (2001) **42**, 5917.
- [50] Valverde, M. G.; Dallinger, D.; Kappe, C. O., *Synlett*, (2001), 741.
- [51] Hu, E. H.; Sidler, D. R.; Dolling, U.-H., *J. Org. Chem.*, (1998) **63**, 3454.
- [52] Kumar, K. A.; Kasthuraiah, M.; Reddy, C. S.; Reddy, C. D., *Tetrahedron Lett.*, (2001) **42**, 7873.
- [53] Kappe, C. O.; Kumar, D.; Varma, R. S., *Synthesis*, (1999), 1799.
- [54] Stefani, H. A.; Gatti, P. M., *Synth. Commun.*, (2000) **30**, 2165.
- [55] Ma, Y.; Qian, C.; Wang, L.; Yang, M., *J. Org. Chem.*, (2000) **65**, 3864.
- [56] Stadler, A.; Kappe, C. O., *J. Comb. Chem.*, (2001) **3**, 624.
- [57] Dondoni, A.; Massi, A., *Tetrahedron Lett.*, (2001) **42**, 7975.
- [58] Wipf, P.; Cunningham, A., *Tetrahedron Lett.*, (1995) **36**, 7819.
- [59] Kappe, C. O., *Acc. Chem. Res.*, (2000) **33**, 879.
- [60] Rosser, M.; Parker, D.; Ferguson, G.; Gallagher, J. F.; Howard, J. A. K.; Yufit, D. S., *J. Chem. Soc., Chem. Commun.*, (1993), 1267.
- [61] Mathias, L. J., *Synthesis*, (1979), 561.
- [62] Giuliano, R. M.; Duong, T. T.; Deisenroth, T. W.; McMahon, W. G.; Boyko, W. J., *Synthesis*, (1991), 86.
- [63] Kishikawa, K.; Sankhavasi, W.; Yoshizaki, K.; Kohmoto, S.; Yamamoto, M.; Yamada, K., *J. Chem. Soc., Perkin Trans. 1*, (1994), 1205.
- [64] Clegg, W.; Collinwood, S. P.; Golding, B. T.; Hodgson, S. M., *Chem. Commun. (Cambridge)*, (1998), 1175.
- [65] Frindeisen, K.; König, K.; Sundermann, D., In *Houben–Weyl*, (1983); Vol. E 4, p 738.
- [66] Richter, R.; Ulrich, H.; In *The Chemistry of Cyanates and Their Thio Derivatives*, Patai, S., Ed.; Wiley: New York, (1977); Part 2, p 619.
- [67] Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G., *Angew. Chem.*, (1995) **107**, 2746; *Angew. Chem. Int. Ed. Engl.*, (1995) **34**, 2497.
- [68] Kissener, W.; Franke, J.; Fiege, H.; Wedemeyer, K., DE 3 636 190, (1988); *Chem. Abstr.*, (1988) **109**, 128610.
- [69] Feng, Z.; Lubell, W. D., *J. Org. Chem.*, (2001) **66**, 1181.
- [70] Jiménez Blanco, J. L.; Sitz Barria, C.; Benito, J. M.; Ortiz Mellet, C.; Fuentes, J.; Santoyo-González, F.; García Fernández, J. M., *Synthesis*, (1999), 1907.
- [71] Fort, Y.; Gottardi, C.; Caubère, P., *Tetrahedron Lett.*, (1993) **34**, 3857.
- [72] Phoon, C. W.; Sim, M. M., *Synlett*, (2001), 697.
- [73] Eames, J.; Watkinson, M., *Eur. J. Org. Chem.*, (2001), 1213.
- [74] König, B.; Pelka, M.; Subat, M.; Dix, I.; Jones, P. G., *Eur. J. Org. Chem.*, (2001), 1943.
- [75] Buysch, H. J.; Klipper, R.; Lange, P. M.; Mues, P., DE 3 324 903, (1985); *Chem. Abstr.*, (1985) **103**, 6838.
- [76] Xin, Z.; Pei, Z.; von Geldern, T.; Jirousek, M., *Tetrahedron Lett.*, (2000) **41**, 1147.
- [77] Khajavi, M. S.; Hajihadi, M.; Naderi, R., *J. Chem. Res., Synop.*, (1996), 92.
- [78] Vovk, M. V.; Dorokhov, V. I.; Samarai, L. I., *Zh. Org. Khim.*, (1989) **25**, 2394; *Chem. Abstr.*, (1990) **113**, 23872.
- [79] Molina, P.; Aller, E.; Lorenzo, A., *Synthesis*, (1998), 283.
- [80] Snellink-Ruël, B. H. M.; Antonisse, M. M. G.; Engbersen, J. F. J.; Timmerman, P.; Reinhoudt, D. N., *Eur. J. Org. Chem.*, (2000), 165.
- [81] Butler, D. C. D.; Inman, G. A.; Alper, H., *J. Org. Chem.*, (2000) **65**, 5887.
- [82] Baeg, J.-O.; Bensimon, C.; Alper, H., *J. Am. Chem. Soc.*, (1995) **117**, 4700.
- [83] Handke, I.; Schaumann, E.; Ketcham, R., *J. Org. Chem.*, (1988) **53**, 5298.
- [84] Daniel, J.; Dhar, D. N., *Synth. Commun.*, (1993) **23**, 2151.
- [85] Elliott, M. C.; Kruiswijk, E., *Chem. Commun. (Cambridge)*, (1997), 2311.

- [86] Dorokhov, V. A.; Gordeev, M. F.; Komkov, A. V.; Bogdanov, V. S., *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1991), 2593; *Chem. Abstr.*, (1992) **116**, 105 956.
- [87] Shibata, I.; Toyota, M.; Baba, A.; Matsuda, H., *J. Org. Chem.*, (1990) **55**, 2487.
- [88] Woo, E. P.; Price, D. R., US 4 642 351, (1987); *Chem. Abstr.*, (1987) **107**, 23 338.
- [89] Ohe, K.; Matsuda, H.; Morimoto, T.; Ogoshi, S.; Chatani, N.; Murai, S., *J. Am. Chem. Soc.*, (1994) **116**, 4125.
- [90] Aiman, C. E.; Daus, E. D., US 5 338 862, (1994); *Chem. Abstr.*, (1994) **121**, 280 646.
- [91] Lyle, T. A.; Tucker, T. J.; Wiscount, C. M., WO 95 12 583, (1995); *Chem. Abstr.*, (1995) **123**, 256 755.
- [92] Aresta, M., *Chem. Ind. (Milan)*, (1998) **80**, 1051.
- [93] Petersen, I., In *Houben-Weyl*, (1983); Vol. E 4, p 334.
- [94] Ogura, H.; Takeda, K.; Tokue, R.; Kobayashi, T., *Synthesis*, (1978), 394.
- [95] Yamazaki, N.; Higashi, F.; Iguchi, T., *Tetrahedron Lett.*, (1974), 1191.
- [96] Nomura, R.; Yamamoto, M.; Matsuda, H., *Ind. Eng. Chem. Res.*, (1987) **26**, 1056.
- [97] Nomura, R.; Hasegawa, Y.; Ishimoto, M.; Toyosaki, T.; Matsuda, H., *J. Org. Chem.*, (1992) **57**, 7339.
- [98] Fournier, J.; Bruneau, C.; Dixneuf, P. H.; Lécolier, S., *J. Org. Chem.*, (1991) **56**, 4456.
- [99] McGhee, W.; Riley, D.; Christ, K.; Pan, Y.; Parnas, B., *J. Org. Chem.*, (1995) **60**, 2820.
- [100] Aresta, M.; Quaranta, E., *Tetrahedron*, (1992) **48**, 1515.
- [101] Cooper, C. F.; Falcone, S. J., *Synth. Commun.*, (1995) **25**, 2467.
- [102] Charbonnier, F.; Marsura, A.; Roussel, K.; Kovács, J.; Pintér, I., *Helv. Chim. Acta*, (2001) **84**, 535.
- [103] Wagner, M.; Engrand, P.; Regnouf-de-Vains, J.-B.; Marsura, A., *Tetrahedron Lett.*, (2001) **42**, 5207.
- [104] Nudelman, N. S.; Lewkowicz, E. S.; Pérez, D. G., *Synthesis*, (1990), 917.
- [105] McCusker, J. E.; Abboud, K. A.; McElwee-White, L., *Organometallics*, (1997) **16**, 3863.
- [106] McCusker, J. E.; Main, A. D.; Johnson, K. S.; Grasso, C. A.; McElwee-White, L., *J. Org. Chem.*, (2000) **65**, 5216.
- [107] McCusker, J. E.; Grasso, C. A.; Main, A. D.; McElwee-White, L., *Org. Lett.*, (1999) **1**, 961.
- [108] Yoshida, T.; Kambe, N.; Murai, S.; Sonoda, N., *Tetrahedron Lett.*, (1986) **27**, 3037.
- [109] Yoshida, T.; Kambe, N.; Murai, S.; Sonoda, N., *Bull. Chem. Soc. Jpn.*, (1987) **60**, 1793.
- [110] Yoshida, T.; Kambe, N.; Murai, S.; Sonoda, N., *J. Org. Chem.*, (1987) **52**, 1611.
- [111] Sonoda, S., *Pure Appl. Chem.*, (1993) **65**, 699.
- [112] Kondo, K.; Murata, K.; Miyoshi, N.; Murai, S.; Sonoda, N., *Synthesis*, (1979), 735.
- [113] Yang, Y.; Lu, S., *Tetrahedron Lett.*, (1999) **40**, 4845.
- [114] Sundermann, R.; Scholl, H. J., *Reductive Carbonylation of Nitro Compounds In Applied Homogeneous Catalysis with Organometallic Compounds*, Cornils, B.; Herrmann, W. A., Eds.; VCH: Weinheim, Germany, (1996); Vol. 2, p 1072.
- [115] Bassoli, A.; Rindone, B.; Cenini, S., *J. Mol. Catal.*, (1991) **66**, 163.
- [116] Giannoccaro, P.; Nobile, C. F.; Mastrorilli, P.; Ravasio, N., *J. Organomet. Chem.*, (1991) **419**, 251.
- [117] Srivastava, S. C.; Shrimal, A. K.; Srivastava, A., *J. Organomet. Chem.*, (1991) **414**, 65.
- [118] Kim, K. D.; Lee, S. M.; Cho, N. S.; Oh, J. S.; Lee, C. W.; Lee, J. S., *J. Mol. Catal.*, (1992) **75**, L1–L6.
- [119] Goodall, B. L.; Terlouw, W., EP 319 111, (1989); *Chem. Abstr.*, (1989) **111**, 214245.
- [120] Choudary, B. M.; Rao, K. K.; Pirozhkov, S. D.; Lapidus, A. L., *Synth. Commun.*, (1991) **21**, 1923.
- [121] Shi, F.; Deng, Y.; SiMa, T.; Yang, H., *Tetrahedron Lett.*, (2001) **42**, 2161.
- [122] Ono, Y., *Appl. Catal., A*, (1997) **155**, 133.
- [123] Romano, U.; Fornasari, G.; Sgambato, U., EP 103 919, (1984); *Chem. Abstr.*, (1984) **101**, 54745.
- [124] Vauthey, I.; Valot, F.; Gozzi, C.; Fache, F.; Lemaire, M., *Tetrahedron Lett.*, (2000) **41**, 6347.
- [125] Izdebski, J.; Pawlak, D., *Synthesis*, (1989), 423.
- [126] Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G., *Synlett*, (1996), 502.
- [127] Knölker, H.-J.; Braxmeier, T., *Tetrahedron Lett.*, (1998) **39**, 9407.
- [128] Lamothe, M.; Perez, M.; Colovray-Gotteland, V.; Halazy, S., *Synlett*, (1996), 507.
- [129] Cotarca, L.; Delogu, P.; Nardelli, A.; Šunjić, V., *Synthesis*, (1996), 553.
- [130] Majer, P.; Randad, R. S., *J. Org. Chem.*, (1994) **59**, 1937.
- [131] Weiberth, F. J., *Tetrahedron Lett.*, (1999) **40**, 2895.
- [132] Ranganathan, D.; Lakshmi, C., *Chem. Commun. (Cambridge)*, (2001), 1250.
- [133] Songkram, C.; Yamasaki, R.; Tanatani, A.; Takaishi, K.; Yamaguchi, K.; Kagechika, H.; Endo, Y., *Tetrahedron Lett.*, (2001) **42**, 5913.
- [134] Degani, I.; Fochi, R.; Regondi, V., *Synthesis*, (1980), 375.
- [135] Leung, M.-K.; Lai, J. L.; Lau, K.-H.; Yu, H.-h.; Hsiao, H.-J., *J. Org. Chem.*, (1996) **61**, 4175.
- [136] Takeda, K.; Tsuboyama, K.; Takayanagi, H.; Shirokama, R.; Takeura, M.; Ogura, H., *Chem. Pharm. Bull.*, (1989) **37**, 2334.

- [137] Bon, E.; Réau, R.; Bertrand, G.; Bigg, D. C. H., *Tetrahedron Lett.*, (1996) **37**, 1217.
- [138] Matsumura, Y.; Satoh, Y.; Onomura, O.; Maki, T., *J. Org. Chem.*, (2000) **65**, 1549.
- [139] Gastaldi, F.; Weinreb, S.; Stien, D., *J. Org. Chem.*, (2000) **65**, 3239.
- [140] Miel, H.; Rault, S., *Tetrahedron Lett.*, (1998) **39**, 1565.
- [141] Anbazhagan, M.; Rakeeb, A.; Deshmukh, A. S.; Rajappa, S., *Tetrahedron Lett.*, (1998) **39**, 3609.
- [142] Thavonekham, B., *Synthesis*, (1997), 1189.
- [143] Liu, Q.; Luedtke, N. W.; Tor, Y., *Tetrahedron Lett.*, (2001) **42**, 1445.
- [144] Dressman, B. A.; Singh, U.; Kaldor, S. W., *Tetrahedron Lett.*, (1998) **39**, 3631.
- [145] Chong, P. Y.; Petillo, P. A., *Tetrahedron Lett.*, (1999) **40**, 4501.
- [146] Basha, A., *Tetrahedron Lett.*, (1988) **29**, 2525.
- [147] Fordon, K. J.; Crane, C. G.; Burrows, C. J., *Tetrahedron Lett.*, (1994) **35**, 6215.
- [148] Hulme, C.; Ma, L.; Romano, J. J.; Morton, G.; Tang, S.-Y.; Cherrier, M.-P.; Choi, S.; Salvino, J.; Labaudiniere, R., *Tetrahedron Lett.*, (2000) **41**, 1889.
- [149] Bhattacharyya, T.; Nilsson, U. J., *Tetrahedron Lett.*, (2001) **42**, 2873.
- [150] Lozanova, K.; Kalcheva, V.; Simov, D., *J. Prakt. Chem.*, (1989) **331**, 1007.
- [151] Leser, U.; König, B.; Mertens, A.; Zilch, H., DE 4 214 829, (1993); *Chem. Abstr.*, (1994) **120**, 164220.
- [152] Lozanova, K.; Kalcheva, V.; Simov, D., *Khim. Geterotsikl. Soedin.*, (1988), 1362; *Chem. Abstr.*, (1989) **111**, 57626.
- [153] Kant, J., *J. Heterocycl. Chem.*, (1990) **27**, 2129.
- [154] Kise, N.; Kashiwagi, K.; Watanabe, M.; Yoshida, J.-i., *J. Org. Chem.*, (1996) **61**, 428.
- [155] Park, Y. S.; Boys, M. L.; Beak, P., *J. Am. Chem. Soc.*, (1996) **118**, 3757.
- [156] Fabis, F.; Jolivet-Fouchet, S.; Robba, M.; Landelle, H.; Rault, S., *Tetrahedron*, (1998) **54**, 10789.
- [157] Ichikawa, Y., *Synlett*, (1991), 238.
- [158] Hassan, A. A.; Mourad, A. E., *Indian J. Chem., Sect. B*, (1992) **31**, 277.
- [159] Fredenburgh, L. E.; Larsen, R. D.; Liu, J.; Reamer, R. A.; Senanayake, C. H.; Verhoeven, T. R., US 5 424 432, (1995); *Chem. Abstr.*, (1995) **123**, 198803.
- [160] Leshner, G. Y.; Bacon, E. R.; Singh, B.; Kuo, G. H., US 4 963 561, (1990); *Chem. Abstr.*, (1991) **114**, 101994.
- [161] Hiremath, S. P.; Hiremath, D. M.; Purohit, M. G., *Indian J. Chem., Sect. B*, (1987) **26**, 1042.
- [162] Fabis, F.; Jolivet-Fouchet, S.; Rault, S., *Tetrahedron*, (1999) **55**, 6167.
- [163] Braverman, S.; Cherkinsky, M.; Kedrova, L.; Reiselman, A., *Tetrahedron Lett.*, (1999) **40**, 3235.
- [164] Ichikawa, Y.; Nishiyama, T.; Isobe, M., *J. Org. Chem.*, (2001) **66**, 4200.
- [165] Pihuleac, J.; Bauer, L., *Synthesis*, (1989), 61.
- [166] Messeri, T.; Sternbach, D. D.; Tomkinson, N. C. O., *Tetrahedron Lett.*, (1998) **39**, 1673.
- [167] Isobe, T.; Ishikawa, T., *J. Org. Chem.*, (1999) **64**, 5832.
- [168] Migawa, M. T.; Swayze, E. E., *Org. Lett.*, (2000) **2**, 3309.
- [169] Hasegawa, E.; Ishiyama, K.; Horaguchi, T.; Shimizu, T., *J. Chem. Soc., Chem. Commun.*, (1990), 549.
- [170] Faraj, M. K., US 5 155 267, (1992); *Chem. Abstr.*, (1993) **118**, 80639.
- [171] Watabe, Y.; Kondo, T.; Kotachi, S.; Tsuji, Y., JP 04 134 058, (1992); *Chem. Abstr.*, (1992) **117**, 191505.
- [172] Bigi, F.; Maggi, R.; Sartori, G.; Zambonin, E., *Chem. Commun. (Cambridge)*, (1998), 513.
- [173] Reddy, B. M.; Reddy, V. R., *Synth. Commun.*, (1999) **29**, 2789.
- [174] Bigi, F.; Frullanti, B.; Maggi, R.; Sartori, G.; Zambonin, E., *J. Org. Chem.*, (1999) **64**, 1004.
- [175] Batey, R. A.; Santhakumar, V.; Yoshina-Ishii, C.; Taylor, S. D., *Tetrahedron Lett.*, (1998) **39**, 6267.
- [176] Zhang, X.; Rodrigues, J.; Evans, L.; Hinkle, B.; Ballantyne, L.; Peña, M., *J. Org. Chem.*, (1997) **62**, 6420.
- [177] Katritzky, A. R.; Pleyne, D. P. M.; Yang, B., *J. Org. Chem.*, (1997) **62**, 4155.
- [178] Laban, G.; Guenther, W.; Kazmirowski, H. G.; Menzer, M.; Czernotzky, K.; Mueller, R.; Moeller, G., DD 272 841, (1989); *Chem. Abstr.*, (1990) **112**, 235310.
- [179] Brillion, D.; Sauve, G.; Boulos, Z.; Di Belleau, B., WO 91 01 976, (1991); *Chem. Abstr.*, (1991) **114**, 207838.
- [180] Miyata, T.; Mizuno, T.; Nishiguchi, I.; Hirashima, T.; Nakatani, S.; Nakahara, Y., *Chem. Express*, (1992) **7**, 949.
- [181] Yoon, S. C.; Kim, M., *Heterocycles*, (1995) **41**, 103.
- [182] Gala, D.; Puar, M. S.; Czarniecki, M.; Das, P. R.; Kugelman, M.; Kaminski, J. J., *Tetrahedron Lett.*, (2000) **41**, 5025.
- [183] Barluenga, J.; Tomás, M.; Ballesteros, A.; López, L. A., *Tetrahedron Lett.*, (1989) **30**, 4573.
- [184] Döpp, D.; Gomaa, M. A.-M.; Henkel, G.; Nour El-Din, A. M., *J. Heterocycl. Chem.*, (1995) **32**, 603.

- [185] Agami, C.; Dechoux, L.; Melaimi, M., *Tetrahedron Lett.*, (2001) **42**, 8629.
- [186] Yagovkin, A. Y.; Bakibaev, A. A.; Filimonov, V. D., SU 1 675 300, (1991); *Chem. Abstr.*, (1992) **116**, 194314.
- [187] Stewart, A. O.; Brooks, D. W., *J. Org. Chem.*, (1992) **57**, 5020.
- [188] Bertz, St. H.; Dabbagh, G.; Cotte, P., *J. Org. Chem.*, (1982) **47**, 2216.
- [189] Bock, V.; Klötzer, W.; Singewald, N.; Strieder, G., *Synthesis*, (1987), 1058.
- [190] Gehrer, E.; Klötzer, W.; Singewald, N.; Stadlwieser, J., *Synthesis*, (1987), 633.
- [191] Yoshida, H.; Ohtsuka, H.; Ogata, T.; Matsumoto, K., *Chem. Lett.*, (1987), 659.
- [192] Lachhein, S.; Willms, L., EP 467 251, (1992); *Chem. Abstr.*, (1992) **116**, 151 791.
- [193] Mueller, K. H., EP 559 044, (1993); *Chem. Abstr.*, (1994) **120**, 107069.
- [194] Moon, M. P., WO 89 09 214, (1989); *Chem. Abstr.*, (1990) **112**, 179 030.
- [195] Ulrich, H.; Sayigh, A. A. R., *Angew. Chem.*, (1966) **78**, 761; *Angew. Chem. Int. Ed. Engl.*, (1966) **5**, 704.
- [196] Besenyei, G.; Nemeth, S.; Simandi, L. I., *Angew. Chem.*, (1990) **102**, 1168; *Angew. Chem. Int. Ed. Engl.*, (1990) **29**, 1147.
- [197] Besenyei, G.; Nemeth, S.; Simandi, L. I., *Tetrahedron Lett.*, (1994) **35**, 9609.
- [198] Guirado, A.; Andreu, R.; Galvez, J., *Tetrahedron Lett.*, (1999) **40**, 8163.
- [199] Willms, L., DE 3 330 603, (1985); *Chem. Abstr.*, (1985) **103**, 54 094.
- [200] Cervelló, J.; Sastre, T., *Synthesis*, (1990), 221.
- [201] Nadir, U. K.; Basu, N., *Tetrahedron Lett.*, (1992) **33**, 7949.
- [202] Boeger, M.; Drabek, J., DE 3 521 892, (1986); *Chem. Abstr.*, (1986) **105**, 24 190.
- [203] de Tullio, P.; Pirotte, B.; Lebrun, P.; Fontaine, J.; Dupont, L.; Antoine, M.; Onedraogo, R.; Khelili, S.; Maggetto, C.; Masereel, B.; Diouf, O.; Podona, J.; Delarge, J., *J. Med. Chem.*, (1996) **39**, 937.
- [204] Kluth, J.; Mueller, K. H., DE 4 343 595, (1995); *Chem. Abstr.*, (1995) **123**, 286 041.
- [205] Affandi, H.; Bayquen, A. V.; Read, R. W., *Tetrahedron Lett.*, (1994) **35**, 2729.
- [206] Suzuki, H.; Nakaya, C.; Matano, Y., *J. Chem. Res., Synop.*, (1992), 34.
- [207] Wang, C.-I.; Wang, Y.-I.; Wang, X.; Li, J.; Ma, D.-I.; Wang, H., *Synth. Commun.*, (1997) **27**, 3723.
- [208] Wang, X.-Y.; Wang, Y. L.; Li, J.; Zhang, Z. Y., *Synth. Commun.*, (1999) **29**, 157.
- [209] Wang, C.; Wang, Y.; Wang, X.; Wang, X.; Wang, H.; Li, J., *Synth. Commun.*, (1999) **29**, 2597.
- [210] Wang, Y.; Shi, L.; Jia, X.; Pan, F.; Ma, D.; Wang, X., *Synth. Commun.*, (1999) **29**, 53.
- [211] Wang, Y.; Ru, C.; Li, J.; Wang, H.; Ma, D., *Synth. Commun.*, (1994) **24**, 1737.
- [212] Wang, H.; Wang, Y.; Li, Y.; Wang, X., *Org. Prep. Proced. Int.*, (1999) **31**, 462.
- [213] Starr, J. T.; Rai, G. S.; Dang, H.; McNelis, B. J., *Synth. Commun.*, (1997) **27**, 3197.
- [214] Ermakov, A. S.; Serkov, S. A.; Strelenko, Y. A., *Izv. Akad. Nauk, Ser. Khim.*, (1994), 2041; *Chem. Abstr.*, (1995) **123**, 227 617.
- [215] Bombek, S.; Lenarsic, R.; Kocevar, M.; Polanc, S., *Synlett*, (2001), 1237.
- [216] Attanasi, O. A.; Filippone, P.; Giovagnoli, D.; Mei, A., *Synth. Commun.*, (1994) **24**, 453.
- [217] Lenarsic, R.; Kocevar, M.; Polanc, S., *J. Org. Chem.*, (1999) **64**, 2558.
- [218] Evans, D. A.; Johnson, D. S., *Org. Lett.*, (1999) **1**, 595.
- [219] Yamamoto, Y.; Yumoto, M.; Yamada, J., *Tetrahedron Lett.*, (1991) **32**, 3079.
- [220] Attanasi, O. A.; Santeusano, S.; Serra-Zanetti, F., *Synthesis*, (1994), 372.
- [221] Palacios, F.; Retana, A. M.; Oyarzabal, J.; Ezpeleta, J. M., *Tetrahedron*, (1998) **54**, 2281.
- [222] Evans, D. R.; Herbert, R. B.; Baumberg, S.; Cove, J. H.; Southey, E. A.; Buss, A. D.; Dawson, M. J.; Noble, D.; Rudd, B. A. M., *Tetrahedron Lett.*, (1995) **36**, 2351.
- [223] Belley, M.; Scheigetz, J.; Dubé, P.; Dolmon, S., *Synlett*, (2001), 222.
- [224] Kajigaeshi, S.; Matsuoka, S.; Kanemasa, S.; Noguchi, M., *J. Heterocycl. Chem.*, (1986) **23**, 49.
- [225] Just, M., DD 287 255, (1991); *Chem. Abstr.*, (1991) **115**, 91 864.
- [226] Pilgram, K. H., *Synth. Commun.*, (1985) **15**, 697.
- [227] Murphy, A. M.; Dagnino, R.; Vallar, P. L., Jr.; Trippe, A. J.; Sherman, S. L.; Lumpkin, R. H.; Tamura, S. Y.; Webb, T. R., *J. Am. Chem. Soc.*, (1992) **114**, 3156.
- [228] Colotta, V.; Catarzi, D.; Varano, F.; Filacchioni, G.; Cecchi, L.; Galli, A.; Costagli, C., *J. Med. Chem.*, (1996) **39**, 2915.
- [229] Wang, X. W.; Li, Z.; Da, Y.; Chen, J., *Synth. Commun.*, (2000) **30**, 3405.
- [230] Milcent, R.; Barbier, G., *J. Heterocycl. Chem.*, (1992) **29**, 1081.
- [231] Bischoff, C.; Schroder, E., *J. Prakt. Chem.*, (1989) **331**, 537.
- [232] Jean-Claude, B. J.; Just, G., *J. Chem. Soc., Perkin Trans. 1*, (1991), 2525.
- [233] Moll, R.; Jentzsch, R.; Fischer, G. W., *J. Prakt. Chem.*, (1990) **332**, 439.
- [234] Petrov, J.; Atanassova, I.; Ognyanova, V., *Org. Prep. Proced. Int.*, (1994) **26**, 357.

- [235] Gemin, M.; Hutchinson, D.; Allwine, D.; Hester, J.; Emmert, D.; Garmon, S.; Ford, C.; Zurenko, G.; Hamel, J.; Shaadt, R.; Stapert, D.; Yagi, B.; Friis, J.; Shobe, E.; Adams, W., *J. Med. Chem.*, (1998) **41**, 5144.
- [236] Gage, J. R.; Evans, D. A., *Org. Synth., Coll. Vol. VIII*, (1993), 339.
- [237] Blass, B. E.; Drowns, M.; Harris, C. L.; Liu, S.; Portlock, D. E., *Tetrahedron Lett.*, (1999) **40**, 6545.
- [238] Eid, A. I.; Ragab, F. A.; Nour El-Din, H., *Bull. Fac. Pharm., Cairo Univ.*, (1975) **14**, 39; *Chem. Abstr.*, (1978) **88**, 22 323.
- [239] Bartón, H. J.; Paluchowska, M. H.; Mokrosz, J. L.; Szneler, E., *Synthesis*, (1987), 156.
- [240] Yoshikawa, K.; Shimada, S.; Suzuki, N.; Sato, H., JP 11 263 769, (1999); *Chem. Abstr.*, (1999) **131**, 235 800.
- [241] Akteries, B.; Jochims, J. C., *Chem. Ber.*, (1986) **119**, 669.
- [242] Mai, K.; Patil, G., *Synth. Commun.*, (1986) **16**, 1823.
- [243] Preston, P. M., *Chemistry of Heterocyclic Compounds*, Preston, P. M., Ed.; Wiley Interscience: New York, (1980); Vol. 40, p 531.
- [244] Bew, P. S.; Bull, S. D.; Davies, S. G.; Eames, J.; Baxter, A. D.; Mykytiuk, J., *Tetrahedron Lett.*, (1999) **40**, 7143.
- [245] Meanwell, N. A.; Sit, S. Y.; Gao, J.; Wong, H. S.; Gao, Q.; St. Laurent, D. R.; Balasubramanian, N., *J. Org. Chem.*, (1995) **60**, 1565.
- [246] Kriel, K. N.; Emslie, N. D.; Roos, G. H. P., *Tetrahedron Lett.*, (1997) **38**, 109.
- [247] Shaw, K. J.; Vartanian, M., *J. Org. Chem.*, (1991) **56**, 858.
- [248] Su, W. K.; Huang, K. W.; Zhang, Y. M., *Org. Prep. Proced. Int.*, (2000) **32**, 498.
- [249] Su, W. K.; Zhang, Y. M., *J. Chem. Res., Synop.*, (2000), 440.
- [250] Wang, P. C., *Heterocycles*, (1985) **23**, 3041.
- [251] Arai, K.; Tamura, S.; Kawai, K.; Nakajima, S., *Chem. Pharm. Bull.*, (1989) **37**, 3117.
- [252] Murata, S.; Miura, M.; Nomura, M., *J. Chem. Soc., Perkin Trans. 1*, (1987), 1259.
- [253] Vovk, M. V.; Dorokhov, V. I.; Pirozhenko, V. V.; Samarai, L. I., *Zh. Org. Khim.*, (1989) **25**, 1634; *Chem. Abstr.*, (1990) **112**, 198 018.
- [254] Akat'ev, V. E.; Bakulev, V. A.; Mokrushin, V. S.; Lebedev, A. T., *Khim. Geterotsikl. Soedin.*, (1992), 1347; *Chem. Abstr.*, (1993) **119**, 95 050.
- [255] Koch, T.; Hesse, M., *Synthesis*, (1995), 251.
- [256] Kim, T. H.; Rapoport, H., *J. Org. Chem.*, (1990) **55**, 3699.
- [257] Süß-Fink, G.; Herrmann, G., *Angew. Chem.*, (1986) **98**, 568; *Angew. Chem. Int. Ed. Engl.*, (1986) **25**, 570.
- [258] Młostoń, G.; Gendek, T.; Heimgartner, H., *Helv. Chim. Acta*, (1998) **81**, 1585.
- [259] Młostoń, G.; Celeda, M.; Prakash, G. K. S.; Olah, G. A.; Heimgartner, H., *Helv. Chim. Acta*, (2000) **83**, 728.
- [260] Almeida, P. S.; Lobo, A. M.; Prabhakar, S., *Heterocycles*, (1989) **28**, 653.
- [261] Allen, C. F. H.; Edens, C. O.; Vanallen, J., *Org. Synth., Coll. Vol. III*, (1955), 394.
- [262] Davies, S. G.; Mortlock, A. A., *Tetrahedron Lett.*, (1991) **32**, 4791.
- [263] Li, Z.; Wang, X.; Da, Y.; Chen, J., *Synth. Commun.*, (2000) **30**, 2635.
- [264] Matsui, M.; Shibata, K.; Muramatsu, H.; Nakazumi, H., *J. Org. Chem.*, (1991) **56**, 4987.
- [265] Fujisaki, S.; Tomiyasu, K.; Nishida, A.; Kajigaeshi, S., *Bull. Chem. Soc. Jpn.*, (1988) **61**, 1401.
- [266] Venkov, A. P.; Starkova-Abeghe, S., *Synth. Commun.*, (1998) **28**, 1857.
- [267] Kezerian, C., US 4 950 323, (1990); *Chem. Abstr.*, (1991) **114**, 121 768.
- [268] Vovk, M. V.; Davidyuk, Y. N.; Chernega, A. N.; Tsymbah, I. F.; Samarai, L. I., *Zh. Org. Khim.*, (1992) **28**, 2042; *Chem. Abstr.*, (1994) **120**, 76 648.
- [269] Saczewski, F.; Debowski, T., *Tetrahedron Lett.*, (1993) **34**, 2843.
- [270] Török, S.; Nagy, B.; Pribék, F.; Balogh, S., WO 88 07 990, (1988); *Chem. Abstr.*, (1989) **110**, 114 462.
- [271] Yuan, C.; Williams, R., *Tetrahedron Lett.*, (1996) **37**, 1945.
- [272] Lee, K.-J.; Kim, S. H.; Kim, S.; Park, H.; Cho, Y. R.; Chung, B. Y.; Schweizer, E. E., *Synthesis*, (1994), 1057.
- [273] Ali, M. R.; Verma, V. K., *Synthesis*, (1985), 691.
- [274] Ramsden, C. A.; Rose, H. L., *J. Chem. Soc., Perkin Trans. 1*, (1995), 615.
- [275] Becker, R.; Rohr, W., *Liebigs Ann. Chem.*, (1981) **2**, 191.
- [276] Zong, K.; Shin, S. I.; Kim, H. R.; Ryu, E. K., *Synlett*, (1998), 1217.
- [277] L'abbé, G.; Vandendriessche, A., *J. Heterocycl. Chem.*, (1990) **27**, 1629.
- [278] Cho, N. S.; Shon, H. I.; Párkányi, C., *J. Heterocycl. Chem.*, (1991) **28**, 1645.
- [279] Molchanov, A. P.; Sipkin, D. I.; Koptelov, Y. B.; Kostikov, R. R., *Synlett*, (2000), 1779.

- [280] Gstach, H.; Seil, P., *Synthesis*, (1990), 803.
- [281] Gstach, H.; Seil, P., *Synthesis*, (1990), 808.
- [282] Wang, Q.; Mohr, S.; Jochims, J. C., *Chem. Ber.*, (1994) **127**, 947.
- [283] Senet, J.-P.; Wolf, P.; Wooden, G. P., EP 301 946, (1989); *Chem. Abstr.*, (1989) **111**, 7413.
- [284] Molina, P.; Tárraga, A.; Espinosa, A., *Synthesis*, (1989), 923.
- [285] Kamiya, S.; Yamaguchi, K.; Miyahara, M.; Miyata, N., *Chem. Pharm. Bull.*, (1990) **38**, 3226.
- [286] Weckbecker, C.; Drauz, K., EP 784 053, (1997); *Chem. Abstr.*, (1997) **127**, 149 149.
- [287] Ray, P. S.; Hank, R. F., *J. Heterocycl. Chem.*, (1990) **27**, 2017.
- [288] Venkov, A. P.; Temnyalova, T. A., *Synth. Commun.*, (1996) **26**, 3217.
- [289] Yasumoto, M.; Tsuchiya, T.; Taguchi, Y.; Shibuya, I.; Yonemoto, K.; Goto, M., *Chem. Lett.*, (1991), 1229.
- [290] Balalaie, S.; Hashtroudi, M. S.; Sharifi, A., *J. Chem. Res., Synop.*, (1999), 392.
- [291] Verardo, G.; Giumanini, A. G.; Gorassini, F.; Strazzolini, P.; Benetollo, F.; Bombieri, G., *J. Heterocycl. Chem.*, (1995) **32**, 995.
- [292] Molina, P.; Lorenzo, A.; Aller, E., *Synthesis*, (1992), 297.
- [293] Kimmy, T.; Gasquez, F.; Compagnon, P.-L., *Synthesis*, (1988), 412.
- [294] Kohra, S.; Ueda, K.; Tominaga, Y., *Heterocycles*, (1996) **43**, 839.
- [295] Kiselyov, A. S.; Strekowski, L., *Tetrahedron Lett.*, (1994) **35**, 207.
- [296] Watanabe, J.; Usui, H.; Kabayashi, S.; Yoshiwara, H.; Shibano, T.; Tanaka, T.; Morishima, Y.; Yasuoka, M.; Kanao, M., *J. Med. Chem.*, (1992) **35**, 189.
- [297] Reinehr, D.; Bacher, J. P., EP 556 156, (1993); *Chem. Abstr.*, (1994) **119**, 271 207.
- [298] Gante, J.; Neunhoeffler, H.; Schmidt, A., *J. Org. Chem.*, (1994) **59**, 6487.
- [299] Beriger, E.; Kristinsson, H., CA 2 029 838, (1991); *Chem. Abstr.*, (1991) **115**, 232 296.
- [300] Milcent, R.; Yver, B.; Barbier, G., *J. Heterocycl. Chem.*, (1992) **29**, 959.
- [301] Ikesu, S.; Kita, H.; Kaneco, Y., JP 04 223 461, (1992); *Chem. Abstr.*, (1993) **118**, 90 736.
- [302] Daniel, J.; Dhar, D. N., *Synth. Commun.*, (1991) **21**, 1695.
- [303] Geissler, G.; Steiner, B.; Bloedorn, W. D.; Hetzheim, A., DD 295 836, (1991); *Chem. Abstr.*, (1992) **116**, 174 174.
- [304] Kirschke, K.; Costisella, B.; Ramm, M.; Schulz, B., *J. Prakt. Chem.*, (1990) **332**, 143.
- [305] Richter, F.; Mager, D.; Pedain, J., EP 849 268, (1998); *Chem. Abstr.*, (1998) **129**, 96 662.
- [306] Hamed, A.; Ismail, A.; Hitzler, M. G.; Jochims, J. C., *J. Prakt. Chem.*, (1995) **337**, 385.
- [307] Vovk, M. V., *Khim. Geterotsikl. Soedin.*, (1993), 1139; *Chem. Abstr.*, (1994) **120**, 244 999.
- [308] Musser, J. H.; Lewis, S. C.; Bender, R. H. W., *Heterocycles*, (1990) **31**, 1393.
- [309] Sanemitsu, Y., *Synthesis*, (1985), 429.
- [310] Fuchs, J. J.; Lin, K., DE 2 326 312, (1973); *Chem. Abstr.*, (1974) **80**, 59971.
- [311] Lin, K., US 3 902 887, (1975); *Chem. Abstr.*, (1976) **84**, 44 169.
- [312] Shibuya, I.; Honda, K.; Gama, Y.; Shimizu, M., *Heterocycles*, (2000) **53**, 929.
- [313] Schallner, O.; Santel, H.-J.; Dollinger, M., EP 640 600, (1995); *Chem. Abstr.*, (1995) **122**, 265 404.
- [314] Sugi, M.; Igi, M., EP 957 096, (1999); *Chem. Abstr.*, (1999) **131**, 337 037.
- [315] Usui, H.; Watanabe, Y.; Kanao, M., *J. Heterocycl. Chem.*, (1993) **30**, 551.
- [316] Lutze, G.; Kirschke, K.; Krauß, N., *J. Prakt. Chem.*, (1993) **335**, 616.
- [317] Hoffman, R. V.; Nayyar, N. K., *J. Org. Chem.*, (1995) **60**, 5992.
- [318] Milcent, R.; Barbier, G.; Capelle, S.; Catteau, J.-P., *J. Heterocycl. Chem.*, (1994) **31**, 319.
- [319] Wang, Y.; Lowe, P. R.; Thomson, W. T.; Clark, J.; Stevens, M. F. G., *J. Chem. Soc., Chem. Commun.*, (1997), 363.

Product Class 9: Polymeric Ureas and Their Phosphorus Analogues

G. Guichard

General Introduction

Previously published information on this product class can be found in *Houben–Weyl*, Vol. E 20.

Almost all of the polymers (and oligomers) covered in this product class are based on ureas, their phosphorus-containing analogues being limited to Section 18.9.10. With the exception of urea–aldehyde resins (see Section 18.9.7), which are formed by the condensation of urea with formaldehyde, the synthesis of polymers in this product class mainly involves polymerization reactions of monoisocyanates, diisocyanates, or polyisocyanates. Isocyanates are extremely versatile intermediates that can undergo a variety of reactions and polymerization processes.

The use of isocyanates in polymer chemistry was pioneered by O. Bayer at I. G. Farbenindustrie in the 1930s with the joint discovery of polyurethanes (see Section 18.7) and polyureas (see Section 18.9.8). Polyureas, originally synthesized by the polyaddition of diisocyanates and diamines and copoly(urethane ureas), still represent the most common isocyanate-derived polymers and are manufactured for a variety of applications, including coatings. Most commercial polyureas and polyurethanes are derived from a few aromatic diisocyanates, principally 1,1'-methylenebis(4-isocyanatobenzene) (diphenylmethane 4,4'-diisocyanate or MDI), its polymeric form (PMDI), and 2,4-diisocyanatotoluene (toluene 2,4-diisocyanate or TDI), which together represent about 90% of the world's production of isocyanates. Aliphatic diisocyanates such as 1,6-diisocyanatohexane (hexamethylene diisocyanate or HDI), isophorone diisocyanate [5-isocyanato-1-(isocyanatomethyl)-1,3,3-trimethylcyclohexane or IPDI] and 4,4'-methylenebis(cyclohexyl isocyanate) (dicyclohexylmethane 4,4'-diisocyanate), which are considerably more expensive than aromatic diisocyanates, are used to a much smaller extent and account for less than 5% of the total market for isocyanates.^[1]

The assembly of discrete oligomers, mainly oligoureas with amino acid side chains, by using solid-phase techniques has found some interesting applications in peptidomimetic chemistry.

SAFETY: Isocyanates are highly toxic upon inhalation and ingestion. They should be stored and handled with great care, and experiments should be conducted in a well-ventilated fume hood. There have been a number of cases of poisoning by isocyanates, mainly as a result of their widespread and large-scale use at a time before their hazards were fully understood. In Bhopal, India, in December 1984, an accidental release of 40 tons of highly volatile methyl isocyanate to the air caused the death of more than 3500 people in the area surrounding the plant.

Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms. Material safety data sheets should be read carefully before use. General considerations on the safety and environmental impact of diisocyanates can be found in the criteria document edited by the National Institute for Occupational Safety and Health,^[2] as well as in a monograph.^[1] Many countries, including the United States and the United Kingdom, have statutory regulations on the handling and use of isocyanates and on the medical testing of workers who are exposed to isocya-

nates. In some cases, the regulations cover laboratory workers who handle only small amounts of such materials.

18.9.1 **Product Subclass 1:** **Polyisocyanates (1-Nylons)**

Previously published information on the chemistry and synthesis of polyisocyanates can be found in several reviews.^[1,3,4]

The oligomerization reactions of isocyanates, particularly their cyclotrimerization to give isocyanurate [1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione] derivatives in the presence of appropriate catalysts, are well-known reactions.^[5] The polymerization of isocyanates to polyisocyanates was discovered in 1959 by Shashoua and co-workers at DuPont.^[6] These high-molecular-weight polymers were originally obtained by anionic polymerization of both aliphatic and aromatic monoisocyanates in the presence of sodium cyanide as the initiator. Alternative methods, including photochemical,^[7] cationic,^[8] and electrochemical polymerization,^[9] are moderately successful. Some research efforts have been focused on living organotitanium(IV)-catalyzed polymerization and anionic living polymerization. Poly(alkyl isocyanates) possess a low thermal stability and decompose to monomers and isocyanurates (cyclic trimers) at temperatures above 140 °C ($T_d = 180\text{--}200\text{ °C}$). Similarly, depolymerization of aromatic and aliphatic polyisocyanates occurs under the influence of bases.

Polyisocyanates have attracted considerable academic interest because of their unique optical properties^[10] and liquid-crystalline behavior.^[11] Polyisocyanates are stiff polymers that adopt stable helical conformations in solution and in the solid state. In the absence of chiral information relating to the starting isocyanate monomers, both left- and right-handed helices occur, giving rise to kinked helical reversal; however, the introduction of asymmetry in the side chain can be used to force one helical sense over the other.^[12,13] Poly(alkoxymethyl isocyanates) have potential applications arising from their adhesive properties.^[14]

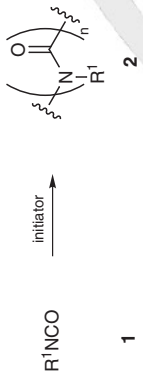
Polyisocyanates have a strong absorption band at about 1620 cm^{-1} in their infrared spectra, corresponding to the C=O bond stretching frequency, as well as a band in the region $1280\text{--}1390\text{ cm}^{-1}$ corresponding to the disubstituted amide structure. Aliphatic diisocyanates and triisocyanates also undergo polymerization to give cyclopolymers consisting of fused five- or six-membered rings. These are typically characterized by infrared spectra showing carbonyl absorption at about 1775 and 1695 cm^{-1} .

18.9.1.1 **Synthesis of Product Subclass 1**

18.9.1.1.1 **Method 1:** **By Anionic Polymerization of Monoisocyanates**

Anionic-catalyzed polymerization of monoisocyanates **1** gives high-molecular-weight polymers **2** classified as 1-nylons (Table 1).

Table 1 Anionic Polymerization of Monoisocyanates^[6,8,15–17]



Entry	R ¹	Initiator	[I] ₀ / [Initiator] ₀	Conditions	Yield (%)	M	PDI ^a	η _{inh} (dL·g ⁻¹) ^b	[η] (dL·g ⁻¹) ^c	Ref
1	Bu	NaCN in DMF	638	DMF, -55°C, 15 min	75	-	-	15.7 ^d	-	[6]
2	iPr	NaCN in DMF	366	DMF, -58°C, 15 min	0	-	-	-	-	[6]
3	3-Tol	NaCN in DMF	70	DMF, -58°C, 15 min	60	-	-	0.3 ^e	-	[6]
4	4-ClC ₆ H ₄	NaCN in DMF	156	DMF, -20°C, 15 min	0	-	-	-	-	[6]
5	(CH ₂) ₅ Me	NaCN in DMF	99	DMF, -58°C, 15 min	85	-	-	2.9 ^d	-	[6]
6	(CH ₂) ₅ Me	NaCN in DMF	39	toluene, -78°C	80	51 000 ^f	1.2	-	-	[15]
7	(CH ₂) ₅ Me	NaCN in DMF	80	toluene, -100°C	97	30 000 ^g	1.8	-	-	[15]
8	(R)-CH ₂ CHMe(CH ₂) ₂ CHMe ₂	NaCN in DMF	50	toluene, -78°C	99	72 000 ^g	1.8	-	-	[15]
9	(R)-CH ₂ CHMe(CH ₂) ₂ CHMe ₂	NaCN in DMF	200	toluene, -78°C	70	178 000 ^g	1.8	-	-	[15]
10	Bu	EtLi in benzene	89	toluene, -78°C, 20 h	43	-	-	-	11.6 ^d	[8]
11	Bu	EtLi in benzene	89	toluene, -78°C, 40 h	57	-	-	-	15.3 ^d	[8]
13	Ph	Na-naphthalene	76	DMF, -40°C, 15 min	60	-	-	-	-	[6]
14	(CH ₂) ₃ Si(OEt) ₃	Na-naphthalene in THF	86	THF, -98°C/10 ⁻⁶ Torr, 5 min	98	74 000 ^h	1.24	-	-	[16]
15	(CH ₂) ₅ Me	Na-naphthalene in THF	55	THF, -98°C/10 ⁻⁶ Torr, 10 min	100	36 500 ⁱ	1.21 ⁱ	-	-	[17]

^a PDI = polydispersity index.

^b η_{inh} = inherent viscosity.

^c [η] = intrinsic viscosity.

^d In benzene at 30°C.

^e In DMF at 30°C.

^f Viscosity-average molecular weight (M_v).

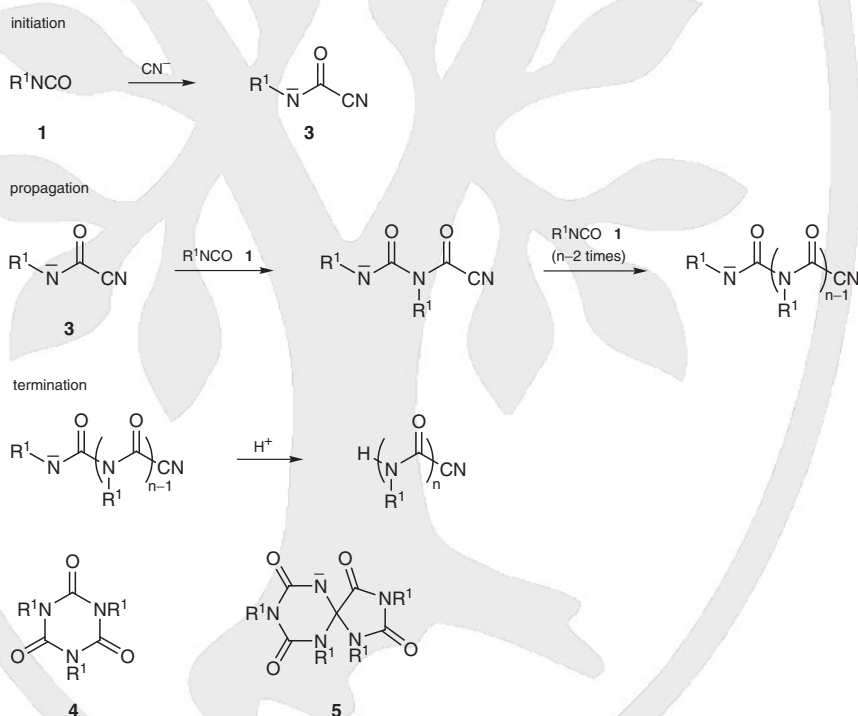
^g Weight-average molecular weight (M_w) by size-exclusion chromatography calibration.

^h Measured by size-exclusion chromatography (SEC) using polystyrene standard in THF at 40°C.

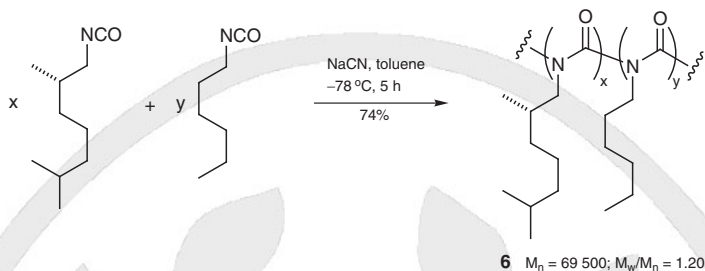
ⁱ Measured by size-exclusion chromatography–light scattering in THF at 40°C.

The polymerization is carried out by treating solutions of monoisocyanates **1** with anionic catalysts at a low temperature (-100°C to -20°C); the optimum temperature range is -70 to -50°C . Although sodium cyanide in dimethylformamide is the catalyst of choice (entries 1–9), other anionic initiators such as sodium benzophenone ketyl, sodium-naphthalene (entries 13–15), and sodium in dimethylformamide are also effective in promoting the polymerization.^[6] The low solubility in dimethylformamide at low temperatures of some monoisocyanates, e.g. **1** [$\text{R}^1 = (\text{CH}_2)_{15}\text{Me}$, 4- ClC_6H_4 (entry 4)], and steric hindrance at the isocyanate group, e.g. **1** [$\text{R}^1 = \text{iPr}$ (entry 2), Cy], prevent polymerization from occurring. Alkyl and aromatic isocyanates can be polymerized in nonpolar solvents by using ethyllithium as the initiator (entries 10 and 11).^[8] The mechanism for the homopolymerization of isocyanates involves an initiation step involving attack by the base at the electrophilic carbon of the isocyanate **1** to generate an amidate anion **3** (Scheme 1). The anion **3** is the propagating species and can react with more monomers or can be terminated by a proton source. This polymerization is not living, and a number of side reactions prevent control of the molecular weight and production of monodispersed polyisocyanates. Side reactions include early events, such as the formation of trimers **4** and chiral spirotetramers **5** when the polymerization is conducted above a certain temperature, as well as backbiting by the living polymer chain to form trimers.^[6,15]

Scheme 1 Mechanism of Anionic Polymerization of Monoisocyanates^[6,15]



The addition of toluene to dimethylformamide during sodium cyanide initiated polymerization can greatly improve the polymerization process by allowing lower temperatures (-100°C) to be reached (dimethylformamide freezes at -58°C) and by overcoming the problems of low solubility of various monomers in dimethylformamide.^[15] This simple procedure, which is suitable for scaling up, has also been used in the random copolymerization of isocyanates, e.g. to give polyisocyanate **6** (Scheme 2).^[18] Sodium-naphthalene in tetrahydrofuran at a very low temperature (-98°C) can also be used to initiate the polymerization.^[16,17,19]

Scheme 2 Random Anionic Copolymerization of Isocyanates^[18]

In the polymerization of isocyanates **1** [$R^1 = (\text{CH}_2)_5\text{Me}$; $(\text{CH}_2)_3\text{Si}(\text{OEt})_3$], the yields of the polymers increase rapidly with reaction time and approach quantitative values at 5 and 10 minutes, respectively. If the reaction time is increased further, however, the yield starts to decrease, and the formation of trimers (but not monomers) is observed, suggesting that when propagation is complete, depolymerization begins. Thus, in addition to the temperature and the nature of the initiator, the reaction time is critical for obtaining polyisocyanates **2** in high yields.

Random Copolyisocyanate 6 from Hexyl Isocyanate and (S)-2,6-Dimethylheptyl Isocyanate; Typical Procedure:^[18]

CAUTION: Cyanide salts can be absorbed through the skin and are extremely toxic. Isocyanates are highly toxic upon inhalation and ingestion.

CAUTION: Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms. Hexyl isocyanate is a lachrymator.

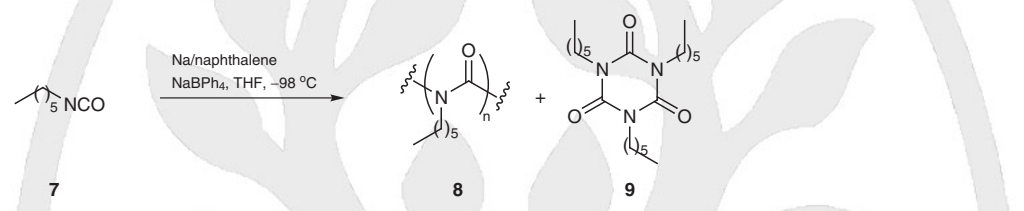
The polymerization was carried out in a 15-cm test tube equipped with a magnetic bar and a rubber septum under an atmosphere of dry argon. $\text{Me}(\text{CH}_2)_5\text{NCO}$ was dried overnight (CaH_2) and vacuum-distilled ($50^\circ\text{C}/7$ Torr) just before use. (S)-2,6-Dimethylheptyl isocyanate was prepared from (S)-citronellol. To form the initiator soln, NaCN (120 mg, 2.5 mmol) was dried under vacuum and dissolved in DMF (5 mL) freshly distilled under vacuum over P_2O_5 ($45^\circ\text{C}/10$ Torr). Toluene was distilled over Na under argon just before use. Dry syringes were used to transfer the exact amount of the two monomers and solvent to the reaction tube. The transfers and the polymerization were conducted under an argon atmosphere in a drybox.

$\text{Me}(\text{CH}_2)_5\text{NCO}$ (878.1 mg, 6.91 mmol) and (S)-2,6-dimethyl isocyanate (122.4 mg, 0.72 mmol) in toluene (5 mL) were placed in the polymerization tube under argon. The tube was cooled to -78°C with an acetone/dry ice bath, and the initiator soln (200 μL) was injected into the tube quickly by a 1-mL syringe. The viscosity of the soln increased after 5 min and kept increasing with time. A transparent gel was formed after 2 h. Polymerization was continued for 3 h before the reaction was quenched by injection of chilled MeOH (10 mL); this destroyed the gel in the tube and led to the formation of a precipitate of a polymer at the bottom of the polymerization tube. The MeOH was removed from the tube by a glass pipette, and CHCl_3 (15 mL) was injected into the tube. The polymer completely dissolved within 10 min. The polymer soln in CHCl_3 was added to a flask of MeOH (250 mL) with vigorous stirring. The polymer that precipitated was collected by filtration through a 5-mm fritted-disk filter and dried overnight under a high vacuum; yield: 0.74 g (74%); M_w (SEC) $84\,000\text{ g}\cdot\text{mol}^{-1}$; number-average molecular weight (M_n) (SEC) $69\,500\text{ g}\cdot\text{mol}^{-1}$; M_w/M_n 1.20 (SEC–light scattering); $[\alpha]_D^{20}$ 440 (c 0.1, toluene).

18.9.1.1.1

**Variation 1:
Living Anionic Polymerization**

Backbiting of the active polymer chain end in anionic isocyanate polymerization can be prevented by the use of large counteranions. The living character of the polymerization can be demonstrated in the case of several ligands, including a sodium(1+)-15-crown-5 complex^[16] and sodium tetraphenylborate (Table 2).^[17,19] In the latter case, polymerization of hexyl isocyanate (**7**) to polyisocyanate **8** is quantitative after 20 minutes, and no formation of trimer **9** is detected after a reaction time of 40 minutes, indicating that the amidate anions are still stable in the presence of sodium tetraphenylborate. A total of 19% of trimer is formed after 120 minutes (Table 2).

Table 2 Living Anionic Polymerization of Hexyl Isocyanate in the Presence of Sodium Tetraphenylborate^[17,19]


[NaBPh ₄] ₀ / [Na-naphthalene] ₀	[7] ₀ / [Na-naphthalene] ₀	Time (min)	M _n		M _w /M _n ^a	Yield (%)	Ref
			Calculated	Observed			
9.9	48.9	10	11 000	12 800	1.08	89 (11) ^b	[17,19]
10.6	39.0	20	9 300	10 700	1.11	99	[17,19]
10.3	88.2	20	21 500	22 200	1.11	96	[17,19]
9.9	48.0	40	11 800	12 800	1.12	96	[17,19]
9.5	49.6	60	11 500	10 800	1.13	93 (7) ^c	[17,19]
11.0	52.7	120	11 400	10 600	1.05	81 (19) ^c	[17,19]

^a The number-average molecular weight (M_n) and the polydispersity index (M_w/M_n) were measured by size-exclusion chromatography–light scattering in THF at 35 °C.

^b Yield of monomer **7** given in parentheses.

^c Yield of trimer **9** given in parentheses.

The relationship between the molecular weight of the polymer and the molar ratio of monomer to initiator is linear, and the molecular-weight distributions are narrow (polydispersity index M_w/M_n 1.07–1.12). The living character of the polymerization is further confirmed by postpolymerization experiments with hexyl isocyanate (**7**), which give the postpolymer (M_n 25 700; M_w/M_n 1.10) almost quantitatively. It is believed that the formation of the trimer is suppressed essentially by two factors: tight-contact ion pairs with sodium tetraphenylborate, and steric hindrance of bulky tetraphenylborate groups.

Polyisocyanate 8 from Hexyl Isocyanate (7); Typical Procedure:^[17,19]

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms. Hexyl isocyanate is a lachrymator.

The polymerization was carried out under a high vacuum in a glass apparatus equipped with break-seals. 97% Me(CH₂)₅NCO (**7**) was dried (CaH₂) under vacuum for 24 h and distilled under reduced pressure. The resulting monomer was redistilled before use from CaH₂ under vacuum. Na/naphthalene in THF (100 mL) was prepared by the reaction of a

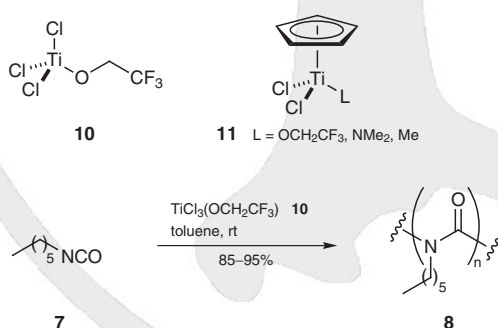
small excess of naphthalene (2.9 g, 22.65 mmol) with Na (0.5 g, 21.75 mmol) at rt. The reaction soln, which turned green, was degassed by connection to a high vacuum (10^{-6} Torr) after freezing in liq N_2 . After complete degassing of the soln, the initiator was divided into aliquots (ca. 0.1 mmol) in glass ampules with break-seals. The concentration of Na/naphthalene was determined by colorimetric titration to a colorless end point with octanol in a sealed reactor through break-seals under a vacuum at rt.

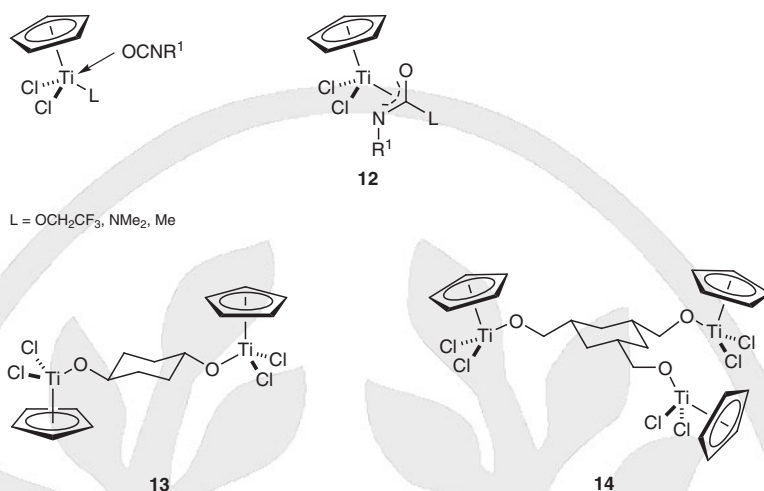
The initiator soln, Na/naphthalene (0.10 mmol) in THF (10 mL), was transferred into the reaction flask through a break-seal followed by a tenfold excess of $NaBPh_4$ (319 mg, 0.93 mmol) in THF (15 mL). The soln was cooled to $-98^\circ C$ in a liq N_2 /MeOH bath. Polymerization was carried out by adding $Me(CH_2)_5NCO$ (**7**; 576 mg, 4.53 mmol) in THF (11 mL) to the initiator soln. The color of the reaction soln changed to light brown. The polymerization was terminated after 20 min by adding HCl (0.5 mL) in MeOH (10 mL) to the polymer soln, and the polymer was precipitated into MeOH (100 mL), filtered, and dried under reduced pressure; yield: 0.570 g (99%); dec $198^\circ C$.

18.9.1.1.2

Method 2:**By Living Polymerization Using Organotitanium(IV) Catalysts**

In the presence of organotitanium(IV) compounds such as trichloro(2,2,2-trifluoroethoxy)titanium(IV) (**10**) and the dichloro(η^5 -cyclopentadienyl)titanium(IV) complexes **11** ($L = OCH_2CF_3$, NMe_2 , Me), monoisocyanates polymerize in high yield without the formation of cyclic trimers (Scheme 3).^[20–22] The polymerization has a living character that permits the synthesis of block copolymers and polymers of a controlled molecular weight. The polymerization of hexyl isocyanate (**7**) in the presence of a titanium(IV) complex **10** proceeds in yields of 85–95% (Scheme 3). The use of dichloro(η^5 -cyclopentadienyl)titanium(IV) complexes **11**, prepared from trichloro(η^5 -cyclopentadienyl)titanium(IV),^[22] as catalysts gives similar results, but polymerization is noticeably slower. Whereas organotitanium catalyst **10** cannot polymerize monomers that possess donor functional groups, organotitanium catalysts **11**, as a consequence of their lower Lewis acidity, polymerize most isocyanates, including the highly functionalized 2-isocyanatoethyl 2-methylacrylate.^[21] They do not polymerize secondary and tertiary isocyanates, aryl isocyanates, or isocyanates with enolizable protons.

Scheme 3 Living Anionic Polymerization Catalyzed by Organotitanium(IV) Complexes^[20–22]



The polydispersities of these polymerizations are typically within the range 1.1–1.2 for organotitanium catalyst **10** and 1.05–1.15 for organotitanium catalyst **11**. Other evidence for the living character of the polymerization is the linear variation of the number-average molecular weight M_n as a function of both the monomer/initiator ratio and the percentage conversion of the polymerization. Polymerizations of isocyanates by using organotitanium complexes **10** and **11** are fully reversible between the polymer and monomer. As a result, the yield is strongly dependent on the initial monomer concentration, and polymerization must be performed either in the bulk or in a concentrated solution, as no polymerization will occur when the initial monomer concentration is equal to the equilibrium monomer concentration. In the case of catalysts **11**, the proposed mechanism for the initiation step involves a migratory insertion of an isocyanate into the metal–ligand bond to form an η^2 -amidate complex **12** (Scheme 3), with the migrating ligand becoming the polymer chain end. Similarly, propagation is thought to occur by insertion of the isocyanate monomer into the titanium–amidate propagating end-group species through a bifunctional activation mechanism.^[22] The titanium complex stays active throughout the polymerization until quenched by the addition of a proton source. In addition, the relative stability of the titanium–amidate end group allows the synthesis of well-defined block copolymers.^[20,22] The bimetallic titanium alkoxide catalyst **13** and the trimetallic complex **14** (Scheme 3) polymerize hexyl isocyanate (**7**) to give two-arm (“once-broken worms”) and three-arm (“star”) polymers, respectively, in yields of 65–88%.^[23,24]

Polyisocyanate **8** from Hexyl Isocyanate (**7**) by Organotitanium-Catalyzed Polymerization; Typical Procedure:^[20]

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms. Hexyl isocyanate is a lachrymator.

In a drybox, an appropriate amount of catalyst, depending on the required monomer/initiator ratio, was weighed into a 25-mL Schlenk tube equipped with a magnetic stirring bar. A drop or two of solvent was added to ensure rapid dissolution of the catalyst, and the tube was connected to a Schlenk line. Me(CH₂)₅NCO (**7**; 1 mL, 865 mg, 6.80 mmol) was added from a syringe. The Schlenk tube was fitted with a ground-glass stopper, and the soln was stirred for 24 h. After the polymerization was complete, the solid orange mass was dissolved in a 5% soln of MeOH in THF (20 mL), and a white solid precipitated. The polymer was isolated by filtration through a 0.2-mm nylon filter and washed with

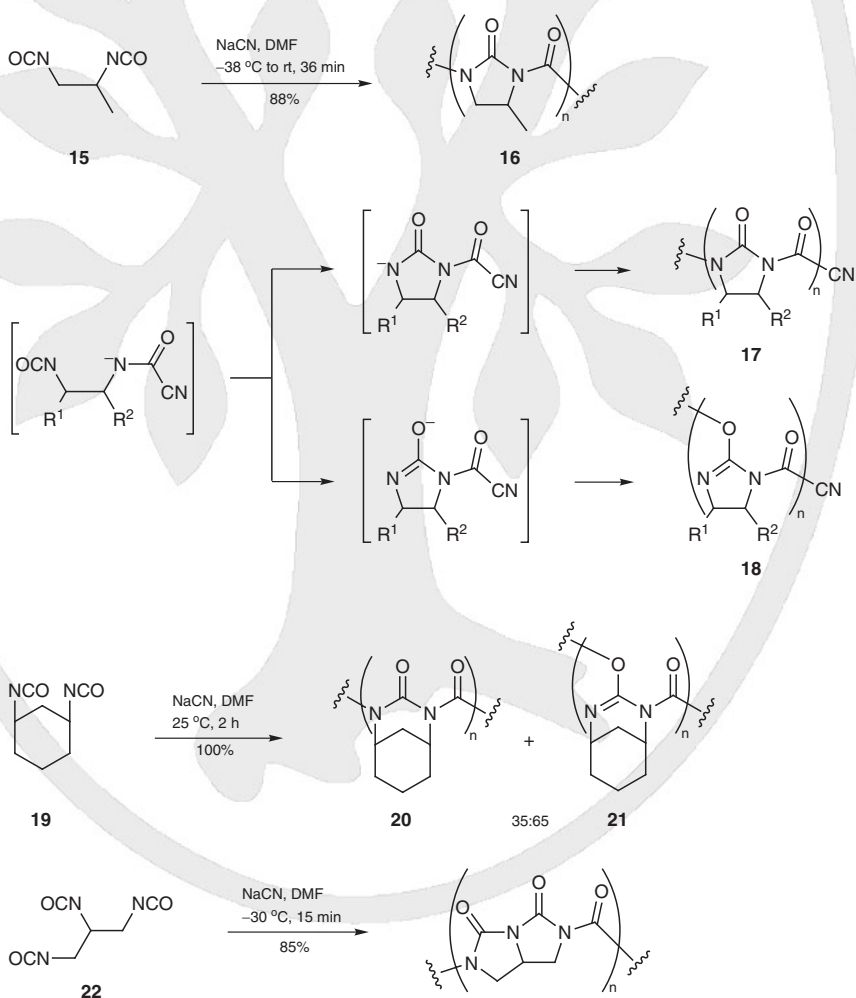
MeOH. Volatile materials were removed under vacuum and the polymer was purified by reprecipitation from THF with MeOH; yield: 74–95%; IR (thin film) $\tilde{\nu}_{\text{max}}$: 1700 (C=O), 1349, 1265 (disubstituted amide) cm^{-1} .

18.9.1.1.3

Method 3:**By Anionic Cyclopolymerization of Diisocyanates and Triisocyanates**

Cyclopolymerization, which was originally discovered with 1,6-dienes, is a useful addition polymerization technique that leads to the introduction of cyclic structures into the main chain of a polymer.^[25] Compared with their acyclic analogues, cyclopolymers often display enhanced properties, such as increased thermal stability. Under anionic conditions, 1,2-diisocyanates with primary and secondary centers, such as 1,2-diisocyanatoethane, 1,2-diisocyanatopropane (**15**), 1,2-diisocyanatocyclopropane, and 1,2-diisocyanatocyclohexane, polymerize to give linear cyclopolymers (e.g., **16**) in high yields (Scheme 4).^[26–29]

Scheme 4 Anionic Cyclopolymerization of 1,2-Diisocyanates, 1,3-Diisocyanates, and Triisocyanates^[26–31]



According to the mechanism proposed by King on the basis of infrared spectroscopy,^[27] stepwise intramolecular ring closure and intermolecular ring extension occur through addition of the amidate anion at the C=N bond to yield linear polymers **17** that contain imidazolidinonediylicarbonyl recurring units (Scheme 4). A second mechanism has, however, been proposed in which alternating anion addition to the C=N and C=O bonds results in a linear polymer **18** composed of dihydroimidazolediylloxycarbonyl units (Scheme 4). Although aminolysis studies performed on the cyclopolymer derived from 1,2-diisocyanatoethane suggest that the dihydroimidazole form (**18**) is obtained exclusively,^[28] more convincing evidence for the regiochemistry is needed.

In a similar fashion to 1,2-diisocyanates, 1,3-diisocyanates such as 1,3-diisocyanatopropane and (1R,3S)-1,3-diisocyanatocyclohexane (**19**) also undergo cyclopolymerization to give cyclopolymer **20** (Scheme 4).^[29–31] Aminolysis of the polymer suggests that the two possible substructures **20** and **21** are obtained in a 35:65 ratio.^[30,31] Typically, the resulting polymers give two characteristic absorption bands in their infrared spectra at about 1720 and 1685 cm⁻¹, corresponding to the inter-ring C=O and intra-ring C=O (or C=N) stretching frequencies, respectively.

1,2- and 1,3-Diisocyanates are extremely moisture sensitive and 1,2-diisocyanatoethane polymerizes immediately in cold dimethylformamide in the absence of a catalyst, and thus they should be stored under argon and handled with great care. For most diisocyanates, the polymerization reaction is markedly exothermic, so efficient stirring and cooling must be employed to keep the temperature low.

Similarly, polyisocyanates having more than two vicinal isocyanate groups [e.g., 1,2,3-triisocyanatopropane (**22**)] polymerize under anionic conditions to give the corresponding linear cyclopolymers (Scheme 4).^[26,27,32]

Cyclopolymer 16 from 1,2-Diisocyanatopropane (**15**); Typical Procedure:^[26,27]

CAUTION: Cyanide salts can be absorbed through the skin and are extremely toxic.

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

A 100-mL, three-necked flask equipped with a mechanical stirrer, a CaCl₂ tube, and a low-temperature thermometer was charged with freshly distilled dry DMF (50 mL) and cooled to -38 °C. Monomeric 1,2-diisocyanatopropane (**15**; 5.2 g, 41 mmol) was then added under stirring. NaCN in DMF (1 mL) was added to the stirred mixture from a hypodermic syringe over 3 min. The temperature rose to -14 °C within 6 min of adding the initiator, and the polymerization mixture assumed the appearance of a smooth gel. The cold bath was removed and the mixture was stirred for 30 min. The polymer was isolated by precipitation with MeOH and dried; yield: 4.6 g (88%); mp 287 °C.

Cyclopolymer 20 from cis-1,3-Diisocyanatocyclohexane (**19**); Typical Procedure:^[30,31]

CAUTION: Cyanide salts can be absorbed through the skin and are extremely toxic.

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

DMF was allowed to stand over KOH overnight, distilled, stored over NaH, and redistilled before use in polymerization. The initiator soln was prepared by distilling DMF (100 mL) directly into a flask containing previously dried NaCN (0.49 g, 10 mmol), and the soln was stored under N₂. A three-necked flask was equipped with a magnetic stirrer, thermometer, dropping funnel, N₂ inlet tube, and CaCl₂ tube. The diisocyanate **19** (1.66 g, 10 mmol)

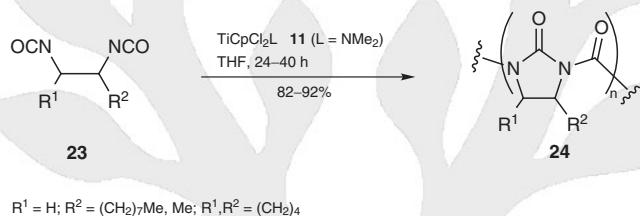
and DMF (9 mL) were added to the flask and heated to 25 °C. The initiator soln (1 mL, 0.1 mmol) was added all at once from the dropping funnel with vigorous stirring. The reaction proceeded exothermically. After the mixture had stirred for 2 h, Et₂O was added to precipitate the polymer **20**, which was collected by filtration, washed with Et₂O, and dried at rt under vacuum. The polymer was soluble in benzene (**CAUTION: carcinogen**); yield: 1.66 g (quant); mp 260 °C (dec).

18.9.1.1.3.1

Variation 1:
Through Organotitanium(IV)-Catalyzed Cyclopolymerization of 1,2-Diisocyanates

The cyclopolymerization of 1,2-diisocyanates by using dichloro(η⁵-cyclopentadienyl)(dimethylamino)titanium(IV) (**11**, L = NMe₂)^[33] (Scheme 5) represents an interesting extension of the organotitanium(IV)-catalyzed polymerization methodology developed for monoisocyanates (see Section 18.9.1.1.2).

Scheme 5 Organotitanium(IV)-Catalyzed Cyclopolymerization of 1,2-Diisocyanates^[33]



The polymerization of 1,2-diisocyanatodecane [**23**, R¹ = H; R² = (CH₂)₇Me] (Scheme 5) in varying monomer-to-initiator ratio ([monomer]₀/[initiator]₀ = 50–500) gives yields of 85–95%.^[33] The resulting polymers show monomodal molecular-weight distributions and polydispersities of 1.2–1.8. In addition, the absolute number-average molecular weight, measured by size-exclusion chromatography and light scattering, increases linearly with the initial monomer-to-initiator ratio, indicating the absence of chain-transfer steps during polymerization. The infrared spectra of the resulting polymers **24** show two absorptions at about 1771–1778 and 1698–1700 cm^{−1}, characteristic of inter-ring and intra-ring carbonyl stretching frequencies, respectively. These results are in good agreement with those obtained for cyclopolymer synthesized by using an anionic procedure.^[27,28] Although infrared, ¹H NMR, and ¹³C NMR spectra of the polymers indicate that the monomer undergoes complete cyclization, the exact microstructure of the repeat units (see Section 18.9.1.1.3) remains unknown. Attempts to polymerize 1,3-diisocyanatopropane and 1,4-diisocyanatobutane lead to insoluble polymers that cannot be fully characterized; however, the infrared spectrum of poly(1,3-diisocyanatopropane), but not that of poly(1,4-diisocyanatopropane), shows two carbonyl absorption at 1718 and 1685 cm^{−1}, consistent with a cyclic repeat unit.

Cyclopolymer 24 [R¹ = H; R² = (CH₂)₇Me] from 1,2-Diisocyanatodecane [23, R¹ = H; R² = (CH₂)₇Me]:^[33]

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

THF was distilled from Na/benzophenone, degassed, and stored under argon. 1,2-Diisocyanatodecane [**23**, R¹ = H; R² = (CH₂)₇Me] was synthesized from maleic anhydride in 30% overall yield^[33] and stored under argon in a drybox. Polymerization was carried out by us

ing standard Schlenk techniques in a drybox. An oven-dried, 25-mL Schlenk tube with a magnetic stirrer bar was charged with titanium complex **11** ($L = \text{NMe}_2$; 2.6 mg, 0.011 mmol). THF (0.5 mL) was added, and the mixture was stirred until the catalyst completely dissolved. 1,2-Diisocyanatodecane [**23**, $R^1 = \text{H}$; $R^2 = (\text{CH}_2)_7\text{Me}$; 0.534 g, 2.38 mmol; monomer/initiator = 209] was added and the color of the soln changed from red–orange to orange. After 40 h (less time was required for lower monomer/initiator ratios), the viscous mixture was dissolved in MeOH/ CHCl_3 (1:9, 20 mL). The soln was poured into vigorously stirred MeOH (150 mL) to form a white precipitate that was isolated by centrifugation. The oily solid was dissolved in benzene (25 mL) (**CAUTION: carcinogen**) and transferred to a 25-mL round-bottomed flask. The flask was attached to a vacuum line and immersed in a liq N_2 bath. After the soln was completely frozen, the flask was placed under vacuum and the liq N_2 bath was removed. When all the benzene had sublimed, a foamy white solid remained; yield: 0.463 g (87%); IR (thin film) $\tilde{\nu}_{\text{max}}$: 1778 (vs), 1698 (vs) cm^{-1} .

18.9.2 Product Subclass 2: Polyisocyanurates

Previously published information on this product subclass can be found in *Houben–Weyl*, Vol. E 20, pp 1739–1751. Isocyanurates are named systematically as 1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-triones, but the isocyanurate nomenclature is retained throughout this section in keeping with usage in polymer chemistry.

Since the pioneering work of A. W. Hoffman in the early 20th century, aromatic and aliphatic monoisocyanates have been known to form six-membered isocyanurates **4** (see Section 18.9.1.1.1, Scheme 1) when treated with suitable catalysts.^[5] Numerous catalysts can be used, including trialkylphosphines,^[34] tertiary amines,^[35] epoxides/pyridine,^[36] quaternary ammonium hydroxides,^[37] Group IV organometallic compounds (e.g., trialkyl-antimony and -arsenic oxides),^[38] and tetrabutylammonium fluoride.^[39]

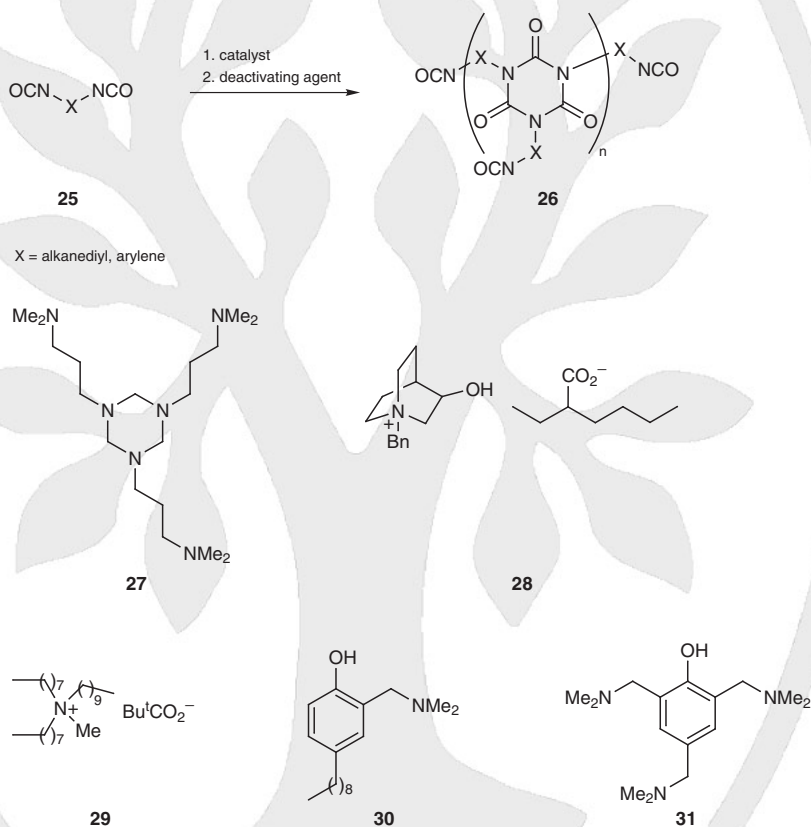
Isocyanurates typically give a single absorption band at 1690–1710 cm^{-1} in their IR spectra and are characterized by their extreme thermal stability; e.g., triphenylisocyanurate [1,3,5-triphenyl-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione] decomposes above 480 °C.^[40] When diisocyanates or polyisocyanates are used, polyisocyanurates are obtained. Reviews are available on the catalytic cyclotrimerization and polytrimerization of isocyanates.^[5,40] The interest in polyisocyanurates (which is evident from the large number of patents filed on such materials) stems from their enhanced properties, for example, their high thermal stability, flame resistance, and thermal insulating capacity. Unmodified isocyanurate polymers are, however, of little commercial value because of their brittleness and friability, which probably result from their high cross-link density. Considerable efforts have therefore been devoted to the modification of polyisocyanurates. Polyisocyanurate structures are used in polyurethane chemistry as cross-linkers in the production of rigid foams and coatings with improved thermal behavior.^[40–42] Several methods are known for introducing the isocyanurate structure into polyurethanes. One is based on the use of partially trimerized isocyanates (i.e., isocyanate-terminated prepolymers) as at least a part of the isocyanate component in the polyurethane formulation.^[43] Alternatively, a quasi-prepolymer containing isocyanate end groups is first prepared by treating an excess of diisocyanate with a polyol and polytrimerizing the product in the presence of additional isocyanate and a trimerization catalyst.^[44] Finally, in a one-step process, the isocyanurate group is introduced simultaneously with the formation of the polyurethane by treating an excess of the diisocyanate with a polyol in one vessel in the presence of a trimerization catalyst.^[45]

18.9.2.1 Synthesis of Product Subclass 2

18.9.2.1.1 Method 1:
Isocyanatoisocyanurates by Partial Trimerization of Polyisocyanates

Unless polymerization is terminated, the polytrimerization of diisocyanates **25** ultimately leads to the formation of insoluble and unusable products.^[36] Premature termination of the polymerization, on the other hand, gives polymers **26** containing isocyanurate groups [trimer ($n = 1$) and higher oligomers ($n = 2, 3$, etc.)], useful as raw materials for coatings and foams. The trimerization reaction is generally terminated by deactivation of the catalyst when the proportion of trimer reaches a desired value (Scheme 6).

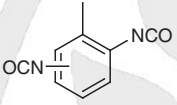
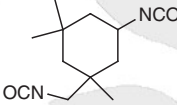
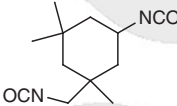
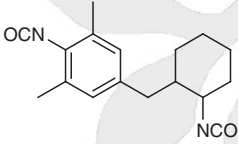

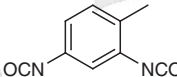
Scheme 6 Catalytic Cyclotrimerization of Diisocyanates; Examples of Catalysts^[43,46–60]



The nature of the catalyst and of the deactivating agent are the keys to the formation of high-quality isocyanatoisocyanurates that are storage-stable, have little odor, are colorless, and have a low free-monomer content. Continual efforts have been made to improve catalysts for the effective polytrimerization of diisocyanates. In addition to the catalysts mentioned in Section 18.9.2, catalysts for polytrimerization of polyisocyanates include 3,3',3''-(1,3,5-triazine-1,3,5-triyl)tris(*N,N*-dimethylpropan-1-amine) (**27**),^[46,47] alkali metal carboxylates (e.g., potassium acetate),^[48,49] quaternary ammonium hydroxides,^[50] quaternary ammonium alkanoates (e.g., **28** and **29**),^[51–53] quaternary hydroxyalkylammonium salts,^[54] quaternary ammonium alkylcarbonates,^[55] guanidines,^[56] aromatic sulfonium zwitterions,^[57] amino silyl catalysts (e.g., hexamethyldisilazane),^[58] and a mixture of a Mannich base (e.g., **30** or **31**) with a carbamic acid ester (generated in situ by reaction of

a secondary alcohol with the isocyanate present):^[43,59,60] various combinations of these catalysts can also be used. Deactivation of the catalyst can be achieved either by thermal decomposition (when Mannich bases are used as the catalysts) or by the addition of a catalyst poison. Catalyst poisons include sulfur for phosphine catalysts, acidic compounds (e.g., phosphoric acid, hydrochloric acid) for basic catalysts, alkylating agents (methyl toluenesulfonate or iodomethane) for Mannich bases, and hydroxy-group-containing compounds (e.g., alcohols or phenols) for aminosilyl catalysts. Various examples of partial polytrimerization of diisocyanates are listed in Table 3.

Table 3 Isocyanatoisocyanurate Oligomers from Diisocyanates^{[47,52,53,58–60]a}

Entry	Diisocyanate 25	Catalyst (catalyst/ 25 ; w/w)	Conditions	NCO Content ^b (wt%)	Deactivating Ref Agent	
1		27 (0.58)	EtOAc, toluene, 50°C, 3 h	3.69 ^c	BzCl	[47]
2		28 (0.5)	rt to 160°C, ca. 60 min	29.2	— ^d	[53]
3		40% (w/v) 29 in MeO(CH ₂ CH ₂ O) ₃ H (2.8 × 10 ^{−4})	85°C, 2 h	29.6 ^e	HCl	[52]
4		30 (3.75) and  (0.05)	AcOCH ₂ CH ₂ OAc 40°C, 72 h	5.9 ^f	MeOTs, 100°C, 1 h	[59]
5		40% (w/v) 31 in xylene (0.002)	40°C, 48 h	8.0 ^g	MeOTs, 80°C, 1 h	[60]
6	OCN(CH ₂) ₆ NCO	Me ₂ NTMS (0.02)	100°C, 90 min	23 ^h	BzCl	[58]

^a See Scheme 6.

^b Of product.

^c Free of monomeric **25**.

^d No deactivating agent used.

^e Trimer content [gel permeation chromatography (GPC)]: 78.3%; η (Brookfield): 0.73 Pa·s.

^f Free **25** content: 1.4%; trimer content (GPC): 37%; η (Brookfield, 25°C): 0.32 Pa·s.

^g Free **25** content: 0.15%; η (Brookfield, 23°C): 1.7 Pa·s.

^h After distillation of residual free **25**; η (Brookfield, 25°C): 1.6 Pa·s.

Oligomeric Polytrimer **26** from Isophorone Diisocyanate (Table 3, Entry 3);

Typical Procedure:^[52]

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

Isophorone diisocyanate (IPDI; 710 g, 3.19 mol) was placed in a 1-L, four-necked flask, equipped with a N₂ inlet, mechanical stirrer, condenser, and thermocouple. The reactor

was heated to 85 °C with vigorous stirring under a N₂ purge. A 40% (w/v) soln of the quaternary ammonium salt **29** in triethylene glycol methyl ether (0.2 g) was added in small portions to maintain the temperature at 85 °C. After about 2 h, FT IR spectroscopy indicated a 43.4% conversion. At this point, the catalyst was quenched by addition of HCl to give a nearly colorless product; yield: 700 g; η 2.2 Pa·s; NCO content: 28.6%.

The NCO content of the product was increased to 29.6% by dilution with the monomer (IPDI): η 0.73 Pa·s; oligomer distribution (SEC): trimer 78.3%; pentamer 16.4%; heptamer and higher oligomers 5.3%.

18.9.2.1.1.1

Variation 1:**Poly(urethane isocyanurate) Foams from Diisocyanates and Polyols**

Urethane-modified polyisocyanurate rigid foams were first prepared in 1961 by the trimerization of an isocyanate-terminated prepolymer in the presence of a combination of triethylamine and propylene oxide as the trimerizing agent.^[61] Poly(urethane isocyanurates) have attracted considerable attention for the production of flame-resistant foams, useful as construction materials and for thermal insulation. In such polymers, the polyol (5–30% by weight) acts essentially as an internal plasticizing agent to reduce the extreme friability resulting from a high isocyanurate content; however, the nature and quantity of the polyol have to be precisely tailored to avoid a decrease in the thermal stability and flammability resistance of the foam.^[40] Isocyanurate foams with enhanced properties (low friability, high flame resistance, and thermal stability), as well as their methods of preparation, have been the subjects of numerous patents. These foams are generally prepared by treating a polyol (diol, triol, or higher polyol) and a polyisocyanate [often polymeric 1,1'-methylenebis(4-isocyanatobenzene) (PMDI), available under such trade names as PAPI and Mondur] with a trimerization catalyst in the presence of a blowing agent (e.g., a chlorofluorocarbon, hydrochlorofluorocarbon, or hydrocarbon) and a silicone surfactant. Initially, the reaction proceeds to give a urethane quasi-prepolymer containing isocyanate groups that further trimerize to give poly(urethane isocyanurates). The urethane bonds also act as cocatalyst in the trimerization reaction.

Rigid Poly(urethane isocyanurate) Foam from Polymeric 1,1'-Methylenebis(4-isocyanatobenzene) and a Polyester Polyol; Typical Procedure:^[62]

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

Polymeric 1,1'-methylenebis(4-isocyanatobenzene) [PMDI; equivalent weight: 138, η (25 °C): 2.0 Pa·s; 464.0 g], FCCL₃ (R-11B; 110.0 g) and L5340 silicone surfactant (Union Carbide) (4.0 g) were blended and cooled to 15.6 °C. Polyester polyol (PS-3152C, Stepan), prepared by the reaction of phthalic anhydride with diethylene glycol [hydroxyl number: 320, η (25 °C): 2.5 Pa·s, 15% free diethylene glycol] was then added to the vessel and all the ingredients were mixed at 3600 rpm for 10 s. Next, a catalyst combination (22 g), prepared from KOAc (1.18 parts), potassium octanoate (1.62 parts by weight), 2,4,6-tris[(dimethylamino)methyl]phenol (**31**; 0.69 parts), and diethylene glycol (6.51 parts), was mixed during 2 s into the contents of the vessel at 25 °C. All the ingredients were mixed at 3600 rpm for an additional 10 s, and then poured into a box to give a rigid polyisocyanurate foam; cream time: 18 s; gel time: 29 s; density: 27.55 kg·m⁻³; closed cells: 89%; K-factor: 0.146 BTU·in·h⁻¹·ft⁻²·°F⁻¹.

18.9.3

**Product Subclass 3:
Polyurylenes, Polysemicarbazides, and Polybiurets**

The polyaddition of aliphatic and aromatic diamines to diisocyanates to form polyureas is an important and well-known reaction (see Section 18.9.8). A few other amino bifunctional nucleophiles, such as hydrazine derivatives, also add to aromatic diisocyanates to form linear polymers that differ significantly from polyureas. Aliphatic primary amines or *O*-benzylhydroxylamine can also behave as bifunctional nucleophiles, and in the presence of appropriate catalysts they react with diisocyanates to form linear polybiurets. In polyurea chemistry, biurets are formed as side products in reactions between unreacted diisocyanate and the urea groups of the polymer chain, resulting in cross-linking.

18.9.3.1

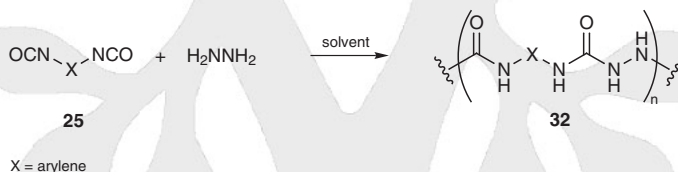
Synthesis of Product Subclass 3

18.9.3.1.1

**Method 1:
Polyurylenes: Reaction of Diisocyanates with Hydrazine**

Aromatic diisocyanates **25** (X = arylene) undergo addition polymerization with hydrazine to give linear, high-melting polyurylenes, e.g. **32** (Scheme 7).^[63] These hard, nonelastic polymers show good resistance to heat, light, and solvents. Similarly, in polyurethane chemistry, the use of hydrazine as a chain extender improves the light resistance of the final polymer.^[64]

Scheme 7 Polyaddition Reaction of Hydrazine and Aromatic Diisocyanates^[63]



Polyureylene 32 [X = 2,4-(1-MeC₆H₃)] from Hydrazine and 2,4-Diisocyanatotoluene [25, X = 2,4-(1-MeC₆H₃)]; Typical Procedure.^[63]

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

A soln of 2,4-diisocyanatotoluene [**25**, X = 2,4-(1-MeC₆H₃); 8.7 g, 0.05 mol] in dioxane (50 mL) was mixed with a soln of H₂NNH₂•H₂SO₄ (6.5 g, 50 mmol), Et₃N (10.1 g, 100 mmol) in dioxane (300 mL), and H₂O (80 mL) with vigorous stirring at rt. The polymer precipitated immediately and the slurry was stirred for 5 min at rt. The polymer was collected by filtration, boiled in H₂O for 15 min, and dried in a vacuum oven at ca. 70 °C; η_{inh} 0.31 dL•g⁻¹ (H₂SO₄); mp 306 °C.

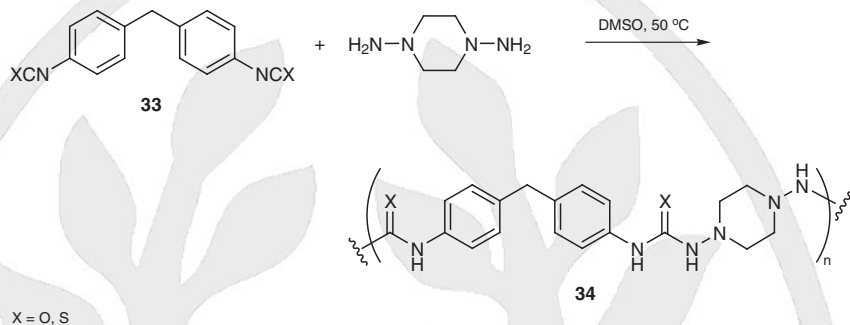
18.9.3.1.1.1

**Variation 1:
Reaction of a Diisocyanate or a Diisothiocyanate with Piperazine-
1,4-diamine: Polysemicarbazides and Polythiosemicarbazides**

Polysemicarbazides (e.g., **34**, X = O) and polythiosemicarbazides (e.g., **34**, X = S) can be synthesized by the reaction of diisocyanates (e.g., **33**, X = O) or diisothiocyanates (e.g., **33**, X = S), respectively, with bishydrazines, such as piperazine-1,4-diamine (Scheme 8).^[65] The polymerization is conducted in dimethyl sulfoxide, in which the polymer is readily soluble, to give a very viscous solution that can be cast to give clear, tough, colorless films

or wet-spun to form fibers. Film samples are completely amorphous. The polythiosemicarbazides, but not the polysemicarbazides, exhibit a high affinity for copper(II) over a wide pH range.

Scheme 8 A Polysemicarbazide and a Polythiosemicarbazide from a Diisocyanate or Diisothiocyanate and Piperazine-1,4-diamine^[65]



Polysemicarbazide 34 (X = O) from Piperazine-1,4-diamine and 1,1'-Methylenebis(4-isocyanatobenzene) (33, X = O); Typical Procedure:^[65]

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

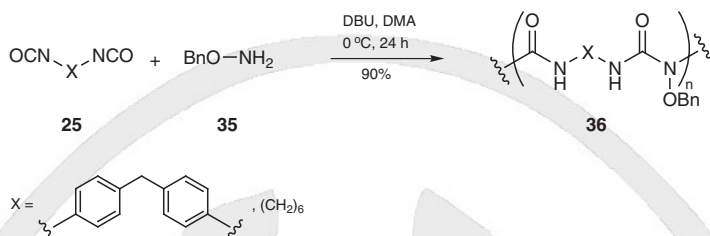
1,1'-Methylenebis(4-isocyanatobenzene) (33, X = O; 37.5 g, 150 mmol) was added to a soln of recrystallized (chlorobenzene) piperazine-1,4-diamine (17.4 g, 150 mmol) in DMSO (500 mL) at ca. 50 °C and the mixture rapidly became viscous. Heating and stirring were stopped after 2 h. The next day, the polymer was precipitated in H_2O , mixed (Waring blender), washed thoroughly in H_2O , and dried; yield: 51 g; η_{inh} 0.49 $\text{dL}\cdot\text{g}^{-1}$ (c 0.5 $\text{g}\cdot\text{dL}^{-1}$, DMSO); mp 320 °C.

18.9.3.1.2

Method 2:

Polybiurets: Reaction of Diisocyanates with Primary Amines or O-Benzylhydroxylamine

There are relatively few examples of the preparation of linear polybiurets through the direct polyaddition of primary amines to diisocyanates. Polyaddition of various primary aliphatic amines with 1,6-diisocyanatohexane or 1,1'-methylenebis(4-isocyanatobenzene) in dimethyl sulfoxide at 100 °C for 20 h gives low-molecular-weight polybiurets in fair to good yields.^[66] Alternatively, linear polybiurets **36** with inherent viscosities of up to 0.52 $\text{dL}\cdot\text{g}^{-1}$ are obtained in high yield by the polymerization of O-benzylhydroxylamine (35) with diisocyanates **25** in dimethylacetamide with 1,8-diazabicyclo[5.4.0]undec-7-ene as the catalyst (Scheme 9).^[67,68] Unlike ordinary polyureas, these polymers are white fibrous materials and exhibit excellent solubility in common solvents such as tetrahydrofuran, dimethyl sulfoxide, 1-methylpyrrolidin-2-one, and dimethylacetamide. Colorless, transparent films can be obtained by casting from tetrahydrofuran solutions on glass plates. Infrared spectra of the biuret-containing polymers display characteristic absorption bands at 3410, 3252 (NH stretching), and 1727 cm^{-1} (C=O stretching). On hydrogenation in the presence of palladium acetate in dimethylacetamide, poly(N-benzyl-oxybiurets) **36** are debenzylated to yield poly(N-hydroxybiurets) in quantitative yields. Both poly(N-benzyl-oxybiurets) **36** and the corresponding poly(hydroxybiurets) adsorb metal cations efficiently, with good selectivity for iron(III) in the case of poly(hydroxybiurets).

Scheme 9 Polybiurets from O-Benzylhydroxylamine and Diisocyanates^[67,68]

Polybiuret 36 (X = 4,4'-C₆H₄CH₂C₆H₄) from O-Benzylhydroxylamine (35) and 1,1'-Methylenebis(4-isocyanatobenzene) (25, X = 4,4'-C₆H₄CH₂C₆H₄); Typical Procedure:^[67,68]

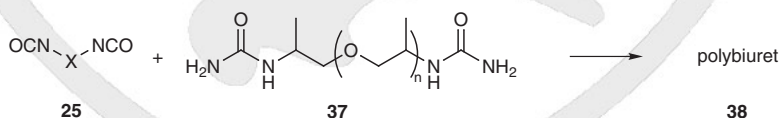
CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

A soln of 1,1'-methylenebis(4-isocyanatobenzene) (25, X = 4,4'-C₆H₄CH₂C₆H₄; 250 mg, 1 mmol) in DMA (0.5 mL) was added dropwise over 5 min to a mixture of BnONH₂ (35; 123 mg, 1 mmol) and DBU (1 drop) in DMA. Additional DMA (0.5 mL) was used to rinse the residue of the diisocyanate. The mixture was stirred for 24 h under N₂ at 0 °C, and the resulting viscous soln was poured into EtOH to precipitate the polybiuret, which was purified by reprecipitation from THF with EtOH; yield: 336 mg (90%); η_{inh} 0.52 dL·g⁻¹ (c 0.25 g·dL⁻¹, DMA, 25 °C); IR (KBr) $\tilde{\nu}_{\text{max}}$: 3410, 3254 (NH), 1726 (C=O), 1593 (Ph) cm⁻¹.

18.9.3.1.2.1

Variation 1:**Reaction of Polyisocyanates with Polyalkylene Polyureas**

Although the formation of biuret (dicarbonimidic diamide) can be considered as a side reaction in polyurea and polyurethane chemistry, there is ongoing interest in developing methods for the controlled incorporation of biurets into foam plastics.^[69] One approach involves the use of low-molecular-weight monomeric polyisocyanates having biuret structures, which can be prepared by heating aromatic or aliphatic polyisocyanates with “biuretizing” agents such as water,^[70] hydrogen disulfide,^[71] primary amines,^[72] tertiary alcohols,^[73] or aldoxime derivatives.^[74] Alternatively, biuret foam products can be prepared by the direct reaction of polyisocyanates 25 with polyoxyalkylene diureide (e.g., 37) at moderate temperatures without addition of a catalyst (Scheme 10).^[75] The reaction proceeds faster in the presence of water, which can function as both the catalyst and the blowing agent. The gel time varies from less than 1 minute to 30 minutes or more.

Scheme 10 Reaction of Poly(propylene oxide)- α,ω -diureide and Diisocyanates^[75]

Polybiuret Foam 38 from Polyoxypropylene Diureide 37 and Polycarbodiimide-Modified 1,1'-Methylenebis(4-isocyanatobenzene) 25; Typical Procedure:^[75]

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

To a small paper cup was added the diureide **37** (weight-average molecular weight 2000; JEFFAMINE BuD-2000, Huntsman Performance Chemicals) (45.5 g, 22.5 mmol), a polycarbodiimide-modified 1,1'-methylenebis(4-isocyanatobenzene) [equivalent weight 138, η (25 °C): 2.0 Pa·s; ISONATE 143L, Dow Chemical] (31.4 g), H₂O (1 g, 55 mmol), and 1,1',1'',1'''-[ethane-1,2-diyl dinitrilo]tetrapropan-2-ol (Quadrol, BASF) (4.6 g, 16 mmol) as a cross-linking agent and catalyst. The mixture was stirred with a tongue depressor, then poured into a larger paper cup to produce a rigid foam; gel time: 50 s.

18.9.4

Product Subclass 4:

Poly[4(5)-iminoimidazolidine-2,5(4)-diones] and Poly(imidazolidine-2,4,5-triones)

Previously published information on the chemistry and synthesis of poly[4(5)-iminoimidazolidine-2,5(4)-diones] can be found in *Houben-Weyl*, Vol. E 20, pp 2191–2192; a review is also available.^[42]

Heterocyclic polymers containing imidazolidine-2,4,5-trione (parabanic acid) linkages were developed in the 1970s, mainly by the Exxon Research and Engineering Company.^[76] Some of these polymers display good thermal stabilities and high glass-transition temperatures, but they undergo slow decomposition when heated at or above their glass-transition temperatures.^[77] Their infrared spectra display two characteristic strong bands at ca. 1735 cm⁻¹, corresponding to the C=O bond stretching frequency, and ca. 1390 cm⁻¹, corresponding to the C–N bond in the five-membered ring. These polymers can be prepared by a variety of methods, including the hydrolysis of the corresponding poly[4(5)-iminoimidazolidine-2,4(5)-diones] [also known as poly(iminohydantoins)].^[76] Poly[4(5)-iminoimidazolidine-2,4(5)-diones] were first prepared by Oku and co-workers from diisocyanates and hydrogen cyanide.^[78] The 4(5)-iminoimidazolidine-2,4(5)-dione ring in all these polymers is characterized by three typical absorption bands in infrared spectra near 1800, 1740, and 1670 cm⁻¹ (C=O bond stretching frequency). Aromatic poly[4(5)-iminoimidazolidine-2,4(5)-diones] are generally infusible below 250 °C, but do not have a high thermal stability.

18.9.4.1

Synthesis of Product Subclass 4

18.9.4.1.1

Method 1:

Poly(iminoimidazolidinediones) and Poly(imidazolidine-2,4,5-triones) from Diisocyanates and Hydrogen Cyanide

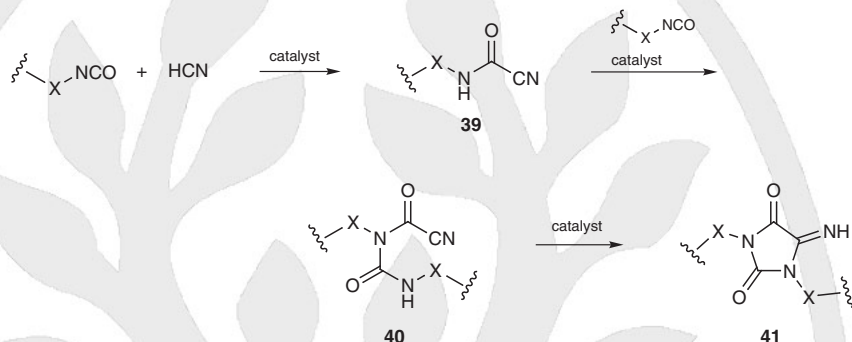
The reaction of phenyl isocyanate with hydrogen cyanide to yield the corresponding *N,N'*-disubstituted 5-iminoimidazolidine-2,4-dione via the corresponding bis[(cyanocarbonyl)-amino] compound was discovered by Dieckmann and co-workers in 1905. By starting from diisocyanates and hydrogen cyanide, poly(imidazolidinediones) are obtained.

SAFETY: Hydrogen cyanide gas is highly toxic by inhalation, ingestion, and skin contact. Proper safety precautions should be taken during its storage, and handling.

Four related procedures have been reported for the preparation of poly(imidazolidinediones).^[76,78] The first of these involves the reaction of hydrogen cyanide with diisocyanates: this is known as the “one-shot” method. The formation of the heterocyclic ring in polymer **41** involves a series of three concerted reactions, via intermediates **39** and **40**,

that can be promoted by various catalysts, such as organic bases (aliphatic tertiary amines or pyridine), organometallic compounds (Scheme 11), or alkali metal cyanides. The isocyanate group is either an unchanged diisocyanate monomer or the isocyanate end group of a polymer chain. Accordingly, the resulting polymer **41** is characterized by repeat units containing 4-iminoimidazolidine-2,5-dione or 5-iminoimidazolidine-2,4-dione ring structures.

Scheme 11 Proposed Mechanism for 5-Iminoimidazolidine-2,4-dione Ring Formation in the Polymerization of Diisocyanates with Hydrogen Cyanide^[76]



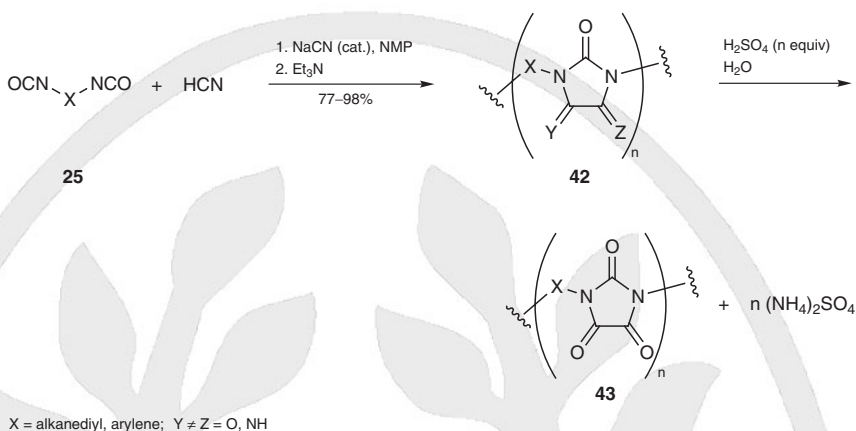
Insoluble cross-linked heterocyclic polymers can be formed when high temperatures ($>80^{\circ}\text{C}$) and tertiary amine bases are used as catalysts in the initiation and propagation steps of the polymerization reaction. Cross-linking is believed to occur by reaction of some imino groups of the heterocyclic rings with isocyanate groups. Conversely, when polymerization is catalyzed by an alkali metal cyanide, soluble polymers are obtained;^[79] however, incomplete cyclization (particularly in the case of aliphatic diisocyanates) can occur in cyanide ion catalyzed polymerization. In such cases, a tertiary amine (which is an efficient catalyst of ring closure) is added to the mixture to ensure complete cyclization within 5 minutes to 2 hours after the addition of all reagents is complete (Scheme 12).^[79] The reaction is generally carried out in 1-methylpyrrolidin-2-one, but other solvents such as dimethylformamide, dimethylacetamide, and dimethyl sulfoxide are equally suitable.

The second method involves the polyaddition of diisocyanates to bis[(cyanocarbonyl)amino] derivatives (see Section 18.9.4.1.1.1).

The third method involves the polycondensation of bis[(cyanocarbonyl)amino] derivatives under heating in the presence of a basic catalyst (e.g., pyridine); however, polyaddition, as conducted in the former procedure, is more satisfactory.^[78]

The fourth method involves the polymerization of (cyanocarbonyl)amino isocyanates, prepared by reaction of 1 equivalent of a diisocyanate with 1 equivalent of hydrogen cyanide. The polymerization can be initiated and propagated in the presence of cyanide ion as a catalyst.^[76] The polymers produced from (cyanocarbonyl)amino isocyanates are characterized by sequential imidazolidine rings with the same orientation of imino and oxo groups.

Solutions of poly(iminoimidazolidinediones) **42** ($\text{Y} \neq \text{Z} = \text{O}, \text{NH}$) are rapidly and quantitatively hydrolyzed to the corresponding poly(imidazolidine-2,4,5-triones) **43** on treatment with, for example, an aqueous solution of hydrochloric acid or sulfuric acid with heating (Scheme 12).^[76,80]

Scheme 12 Poly(iminoimidazolidinediones) by Polymerization of Diisocyanates with Hydrogen Cyanide and Their Conversion into Poly(imidazolidine-2,4,5-triones)^[79]

Poly(iminoimidazolidinedione) 42 from 1,1'-Methylenebis(4-isocyanatobenzene) (25, X = 4,4'-C₆H₄CH₂C₆H₄) and Hydrogen Cyanide; Typical Procedure:^[79]

CAUTION: Hydrogen cyanide can be absorbed through the skin and is extremely toxic.

CAUTION: Cyanide salts can be absorbed through the skin and are extremely toxic.

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

A soln of 1,1'-methylenebis(4-isocyanatobenzene) (25, X = 4,4'-C₆H₄CH₂C₆H₄; 470 g, 1.88 mol) in NMP (1 L) and a soln of HCN (51 g, 1.89 mol) in NMP (184 mL) were added dropwise and simultaneously over 7 min to a soln of NMP (6 L) containing a sat. soln of NaCN (105 mg, 2.1 mmol) in NMP (25 mL). The exothermic reaction raised the temperature to 45 °C and the soln became viscous. After 30 min, Et₃N (20 g, 0.2 mol) was added to the soln; no temperature rise was noted. The mixture was stirred for an additional 30 min, and then MeOH was added to quench unchanged isocyanate groups. The polymer was isolated by precipitation with toluene and dried to give a white powder; yield: 532 g (98%); [η] 1.14 dL·g⁻¹; weight loss (thermogravimetric analysis): 5% at 362 °C.

Poly(imidazolidine-2,4,5-trione) 43 from 1,1'-Methylenebis(4-isocyanatobenzene) (25, X = 4,4'-C₆H₄CH₂C₆H₄) and Hydrogen Cyanide; Typical Procedure:^[76]

A soln of 1,1'-methylenebis(4-isocyanatobenzene) (25, X = 4,4'-C₆H₄CH₂C₆H₄; 470 g, 1.88 mol) in NMP (1 L) and a soln of HCN (51 g, 1.89 mol) in NMP (175 mL) were added simultaneously to a soln of NMP (6 L) containing a sat. soln of NaCN (105 mg, 2.1 mmol) in NMP (25 mL). The exothermic reaction raised the temperature to 52 °C and the addition required about 10 min. After 30 min, Et₃N (20 g, 0.2 mol) was added. The mixture was stirred for an additional 30 min and then 37% aq HCl (200 mL) was added slowly. The exothermic reaction was controlled with an ice bath so that the temperature never exceeded 35 °C during the addition. The solution was stirred for an additional 30 min then poured into MeOH to precipitate the polymer, which was soluble in DMF, NMP, and DMSO; yield: 500 g (92%); [η] 1.46 dL·g⁻¹; mp 293 °C; IR (thin film) $\tilde{\nu}_{\text{max}}$: 1730 (C=O).

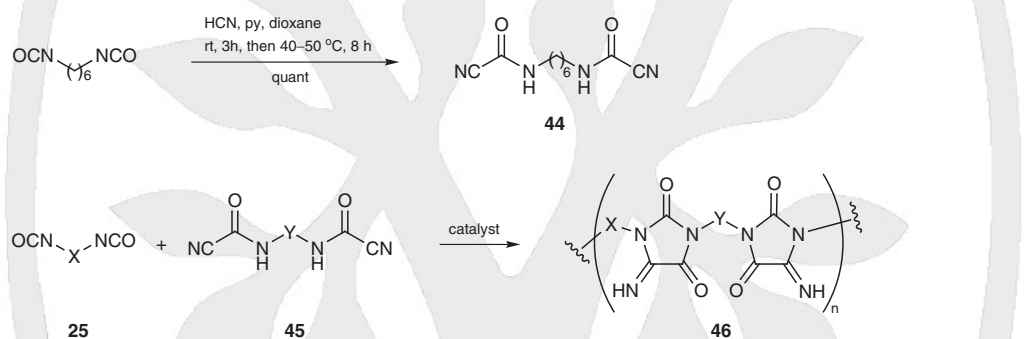
18.9.4.1.1.1

Variation 1:

From Diisocyanates and Bis[(cyanocarbonyl)amino] Derivatives

Ring formation by the reaction of diisocyanates **25** with bis[(cyanocarbonyl)amino] derivatives **44** (Scheme 13) involves only the last two steps shown in Scheme 11 (Section 18.9.4.1.1). The bis[(cyanocarbonyl)amino] compound, e.g. **44**, is first prepared by the reaction of 1 equivalent of a diisocyanate with 2 equivalents of hydrogen cyanide (Scheme 13). Although a catalyst (e.g., pyridine) is typically required for the production of bis[(cyanocarbonyl)amino] compounds **45** from aliphatic diisocyanates, it is not necessary for the addition reaction of aromatic diisocyanates (in fact, pyridine tends to promote polymer formation). The polymerization reaction (Scheme 13) is best conducted by adding the diisocyanate **25** to a solution of the bis[(cyanocarbonyl)amino] compound **45** and the catalyst. This order of addition of reagents allows a better temperature control and limits the extent of cross-linking. The poly(iminoimidazolidinediones) **46** thus formed have a sequential alternation of 4-iminoimidazolidine-2,5-dione and 5-iminoimidazolidine-2,4-dione ring structures as well as of X and Y groups (Scheme 13).^[76,78,79,81]

Scheme 13 Poly(iminoimidazolidinediones) from Bis[(cyanocarbonyl)amino] Compounds, Prepared from Diisocyanates, and Diisocyanates^[76,78,79,81]



X	Y	Catalyst	Conditions	Yield ^a (%)	[η] ^{a,b} (dL·g ⁻¹)	η_{inh} ^{a,c} (dL·g ⁻¹)	Ref
(CH ₂) ₆	(CH ₂) ₆	pyridine	NMP, 120 °C, 10 h	n.r.	0.32 ^d	n.r.	[78]
(CH ₂) ₆	4,4'-C ₆ H ₄ CH ₂ C ₆ H ₄	pyridine	NMP, 120–130 °C, 10 h	>90	0.36 ^d	n.r.	[78]
4,4'-C ₆ H ₄ CH ₂ C ₆ H ₄	(CH ₂) ₆	Et ₃ N	NMP, 25–30 °C, 5 h	94	n.r.	0.70 ^e	[76]
4,4'-C ₆ H ₄ CH ₂ C ₆ H ₄	4,4'-C ₆ H ₄ CH ₂ C ₆ H ₄	sat. NaCN in NMP	NMP, 2 min	54	n.r.	0.29	[79]
2,4-(1-MeC ₆ H ₃)	2,4-(1-MeC ₆ H ₃)	sat. NaCN in DMF	DMF	92	n.r.	0.25	[79]
2,4-(1-MeC ₆ H ₃)	(CH ₂) ₆	Et ₃ N	NMP, 10 min	96	n.r.	0.14 ^f	[81]

^a n.r. = not reported.

^b [η] = intrinsic viscosity.

^c η_{inh} = inherent viscosity.

^d In NMP at 25 °C.

^e In NMP (c 0.3 g·dL⁻¹) at 25 °C.

^f In NMP (c 0.5 g·dL⁻¹) at 25 °C.

1,6-Bis[(cyanocarbonyl)amino]hexane (44); Typical Procedure:^[78]

CAUTION: Hydrogen cyanide can be absorbed through the skin and is extremely toxic.

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

OCN(CH₂)₆NCO (16 g, 95 mmol) was added dropwise to a stirred mixture of pyridine (1 g, 11 mmol) and liq HCN (20 g, 740 mmol) in dioxane (80 mL) cooled to 5 °C. Stirring was continued for 3 h at rt and for 8 h at 40–50 °C. Removal of the solvent and excess HCN under reduced pressure gave a white solid; yield: quant; mp 100–101 °C (acetone/benzene).

Poly(iminoimidazolidinedione) 46 [X = 4,4'-C₆H₄CH₂C₆H₄; Y = (CH₂)₆] from **1,1'-Methylenebis(4-isocyanatobenzene)** (25, X = 4,4'-C₆H₄CH₂C₆H₄) and **1,6-Bis[(cyanocarbonyl)amino]hexane** [45, Y = (CH₂)₆]; **Typical Procedure:**^[79]

A soln of 1,1'-methylenebis(4-isocyanatobenzene) (**25**, X = 4,4'-C₆H₄CH₂C₆H₄; 55 g, 0.2 mol) in NMP (125 mL) was added to a soln of 1,6-bis[(cyanocarbonyl)amino]hexane [**45**, Y = (CH₂)₆; 44.4 g, 0.2 mol] and Et₃N (2 mL) in NMP (150 mL) under dry N₂. Addition required 1 h and the temperature was controlled at 25–30 °C on a water bath. The soln was stirred for 4 h then half was poured into toluene to precipitate the polymer; yield: 47 g (94%); η_{inh} 0.70 dL·g⁻¹ (c 0.3 g·dL⁻¹, NMP, 25 °C).

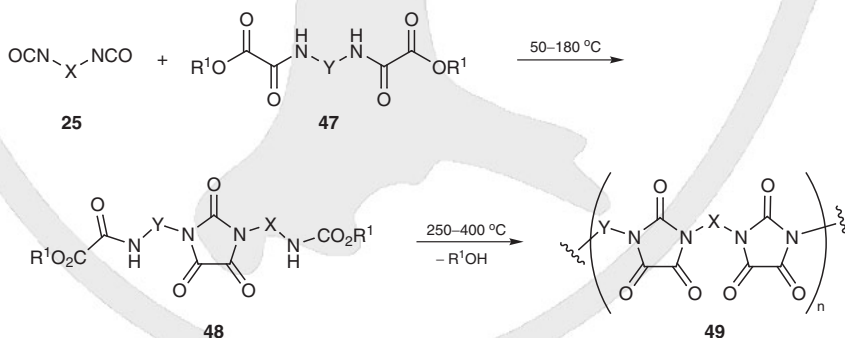
18.9.4.1.2

Method 2:

Poly(imidazolidine-2,4,5-triones) from Diisocyanates and (Arylenediimino)bis(oxoacetate) Diesters

The base-catalyzed reactions of (aryleneimino)oxoacetate esters with isocyanates or diisocyanates give 1,3-disubstituted imidazolidine-2,4,5-triones and bis(1,3-disubstituted imidazolidine-2,4,5-trione) derivatives, respectively, in good to excellent yields.^[82,83] Suitable catalysts include triethylamine, tributylamine, and 1,4-diazabicyclo[2.2.2]octane. In a similar fashion, poly(aryleneimidazolidine-2,4,5-triones) **49** can be obtained by treatment of diisocyanates **25** with (arylenediimino)bis(oxoacetate) diesters **47** (Scheme 14).^[83,84]

Scheme 14 Poly(imidazolidine-2,4,5-triones) from Diisocyanates and (Arylenediimino)-bis(oxoacetate) Diesters^[83]



R¹ = Me, Et, Bu; X = alkanediyl, arylene; Y = arylene

The main advantage of this procedure (Scheme 14) compared with the previous ones (see Section 18.9.4.1.1) is that it does not require the use of highly toxic hydrogen cyanide. (Arylenediimino)bis(oxoacetate) diesters **47** are prepared by heating aromatic diamines (except for benzene-1,2-diamines and -1,3-diamines, which cannot be used) with an ex-

cess of a dialkyl oxalate. Polymerization of diisocyanates **25** with (arylenediimino)bis(oxoacetate) diesters **47** is typically conducted in 1-methylpyrrolidin-2-one or cresol, or in the absence of a solvent at 50–200 °C. Products with a relatively low degree of polymerization (e.g., **48** and its higher homologues) that form viscous solutions in aprotic solvents (e.g., dimethylformamide, 1-methylpyrrolidin-2-one) are initially obtained (Scheme 14).^[83] Upon heating these monomers in solution or in the absence of a solvent at 250–450 °C, the end groups react further to give highly resistant, film-forming polymers **49**, useful in coating applications.^[83,85]

Poly(imidazolidine-2,4,5-trione) Coating 49 {X = 4,4'-C₆H₄OC₆H₄; Y = 4,4'-[3,3'-(MeO)₂C₆H₃C₆H₃]} from 1,1'-Oxybis(4-isocyanatobenzene) and Diethyl 2,2'-[(3,3'-Dimethoxybiphenyl-4,4'-diyl)diimino]bis(oxoacetate); Typical Procedure:^[83]

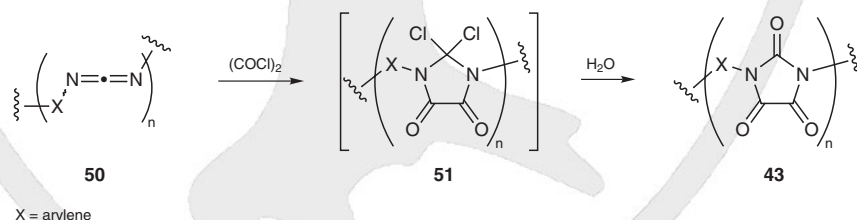
Diiminobis(oxoacetate) **47** {R¹ = Et; Y = 4,4'-[3,3'-(MeO)₂C₆H₃C₆H₃]; 444 g, 1 mol} was dissolved with stirring in *N,N*-dimethylaniline (100 g, 0.82 mol) and DMF (700 g). A soln of 1,1'-oxybis(4-isocyanatobenzene) (**25**, X = 4,4'-C₆H₄OC₆H₄; 252 g, 1 mol) in xylene (1.5 L) was then added at 50 °C. The temperature increased to 140 °C, the initially clear soln turned cloudy, and a yellow substance began to separate. After several hours, the mixture was cooled to rt, and the solid product was isolated by filtration, washed with toluene, and dried under reduced pressure at 70 °C to give a pale yellow powder; yield: 622 g (89%). (The polymeric product was soluble in DMA, DMSO, and NMP. Upon stoving at 320–350 °C on metallic surfaces, the solns gave clear elastic coatings that could only be dissolved in warm, concd H₂SO₄.)

18.9.4.1.3

**Method 3:
From Polycarbodiimides and Oxalyl Chloride**

The addition of oxalyl chloride to both the C=N bonds of carbodiimides gives 1,3-disubstituted 2,2-dichloroimidazolidine-4,5-diones, which are easily hydrolyzed to the corresponding imidazolidine-2,4,5-triones.^[86,87] There is one example of the application of this reaction in a polycondensation. Accordingly, poly(imidazolidine-2,4,5-triones) **43** are obtained by the condensation of polycarbodiimides **50** with oxalyl chloride followed by treatment of the dichlorinated intermediate **51** with water (Scheme 15).^[88] Alternatively, copolymers are obtained when partial condensation takes place.

Scheme 15 Poly(imidazolidine-2,4,5-triones) from Polycarbodiimides and Oxalyl Chloride^[88]



Poly(imidazolidine-2,4,5-trione) 43 [X = 2,4-(1-MeC₆H₃)] from a Polycarbodiimide **50** and Oxalyl Chloride; Typical Procedure:^[88]

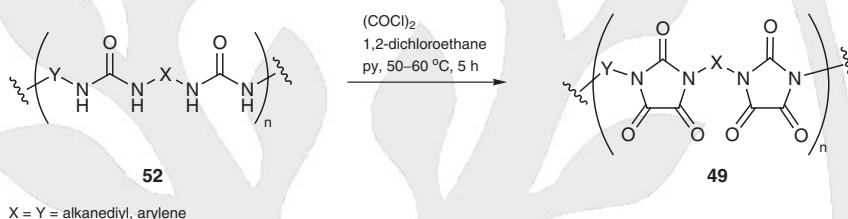
A soln of polycarbodiimide **50** [X = 2,4-(1-MeC₆H₃)] was prepared by treating 2,4-diisocyanatotoluene with 5-methyl-1-phenyl-2,3-dihydro-1*H*-phosphole 1-oxide in Cl₂C=CCl₂ at 120 °C for 4 h.^[89] Oxalyl chloride (1.5 equiv per equiv of carbodiimide group) was added dropwise to this soln and the mixture was stirred for 7 h. The pale yellow precipitate was collected by filtration and washed several times with MeOH. The resulting powder was subsequently dried under reduced pressure at 80 °C for 3 h; imidazolidine-2,4,5-trione conversion: 60%; IR (thin film) $\tilde{\nu}_{\text{max}}$: 2140 (C=N), 1744 (C=O) cm⁻¹.

18.9.4.1.4

Method 4:
From Polyureas and Oxalyl Chloride

N,N'-Disubstituted imidazolidine-2,4,5-triones can be prepared by the reaction of N,N'-disubstituted ureas with oxalyl chloride in refluxing toluene.^[87] Similarly, poly(imidazolidine-2,4,5-triones) **49** can be prepared from polyureas **52** (see Section 18.9.8) and oxalyl chloride (Scheme 16).^[90,91] Cyclization of polyureas is performed in dichloroethane in the presence of pyridine as a catalyst. In the case of aliphatic and aliphatic-aromatic polyureas, the cyclization reaction is complete, as revealed by the complete disappearance of the infrared bands at 1610 and 3300 cm⁻¹ characteristic of the urea group. Only partial cyclization occurs under these conditions for aromatic polyureas. Poly(imidazolidine-2,4,5-triones) **49** prepared from aliphatic and aliphatic-aromatic polyureas have melting points in the range 141–350 °C, whereas those of polymers prepared from aromatic polyureas are in the range 310–360 °C.

Scheme 16 Poly(imidazolidine-2,4,5-triones) from Polyureas and Oxalyl Chloride^[90]



Poly(imidazolidine-2,4,5-trione) **49 [X = Y = (CH₂)₆] from a Polyurea **52** and Oxalyl Chloride: Typical Procedure:**^[90]

Oxalyl chloride (5 mL, 0.06 mol) was added at rt to a stirred suspension of polyurea **52** [X = Y = (CH₂)₆; 1.3 g; η_{inh} 0.34 dL·g⁻¹ (c 1 g·dL⁻¹, DMF/LiCl, 20 °C)], prepared by the reaction of OCN(CH₂)₆NCO with H₂N(CH₂)₆NH₂, in 1,2-dichloroethane (40 mL) containing a few drops of pyridine. The mixture was then heated for 5 h at 50–60 °C. The polymer was precipitated by pouring the soln into rapidly stirred MeOH (400 mL), isolated by filtration, washed with MeOH, and dried at 70 °C; η_{inh} 0.34 dL·g⁻¹ (c 1 g·dL⁻¹, DMF/LiCl, 20 °C); mp 360 °C (dec).

18.9.5

Product Subclass 5:
Polyhydantoins and Poly(iminoimidazolidinones)

Previously published information on the chemistry and synthesis of polyhydantoins can be found in *Houben–Weyl*, Vol. E 20, pp 2190–2191; a review is also available.^[42] Hydantoins are systematically named as imidazolidine-2,4-diones, but the hydantoin nomenclature is retained throughout this section in keeping with usage in polymer chemistry.

Like poly(imidazolidine-2,4,5-triones) (see Section 18.9.4), polymers containing repeating hydantoin groups display high thermal resistance and are useful in coating applications (electrical insulation, wire enameling, temperature-resistant films, and lacquers). As revealed by thermogravimetric analysis, aromatic polyhydantoins start to decompose in air at temperatures above 300 °C. Polyhydantoins containing sulfone groups are high-temperature-resistant plastics that remain stable up to 350 °C. Heat resistance is generally reduced by the introduction of aliphatic components, and mixed aliphatic-aromatic polyhydantoins start to decompose at lower temperatures.^[92]

Several methods are known for the preparation of polymers containing hydantoin groups, including condensation of ethyl chloroacetate with polyureas,^[93] reaction of N-carboxyglycine with amines,^[94] condensation of bishydantoins with formaldehyde,^[95]

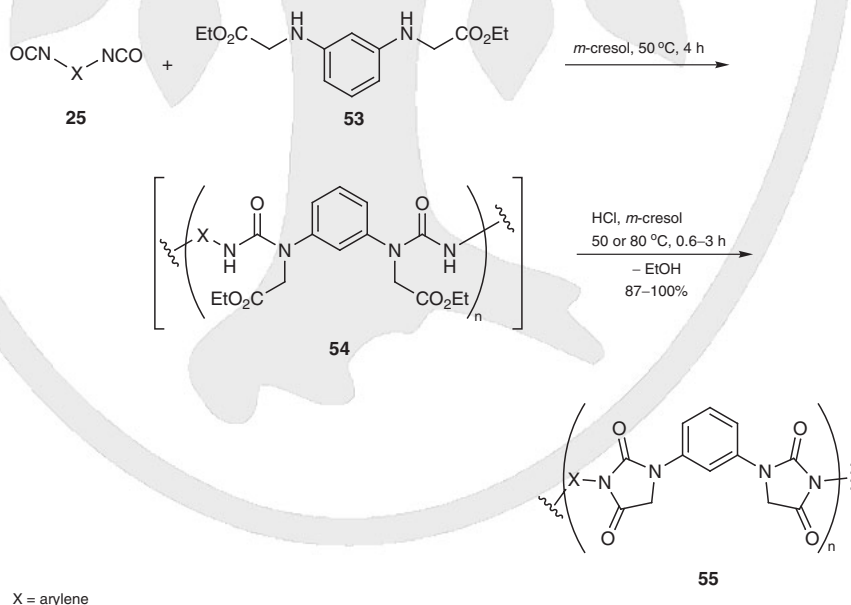
or polymerization of *N*-vinylhydantoins.^[96] The method that has received by far the most attention, however, is the polyaddition/cyclocondensation reaction of bis(alkyl glycinates) with diisocyanates.^[42,92,97,98] Similarly, *N,N'*-bis(1-cyanocycloalkyl)diamines react with diisocyanates, to give poly(iminoimidazolidinones).^[99] Polyhydantoins are typically characterized by infrared spectra showing carbonyl absorptions at ca. 1750–1780 (4-oxo group) and 1700–1720 cm⁻¹ (2-oxo group).

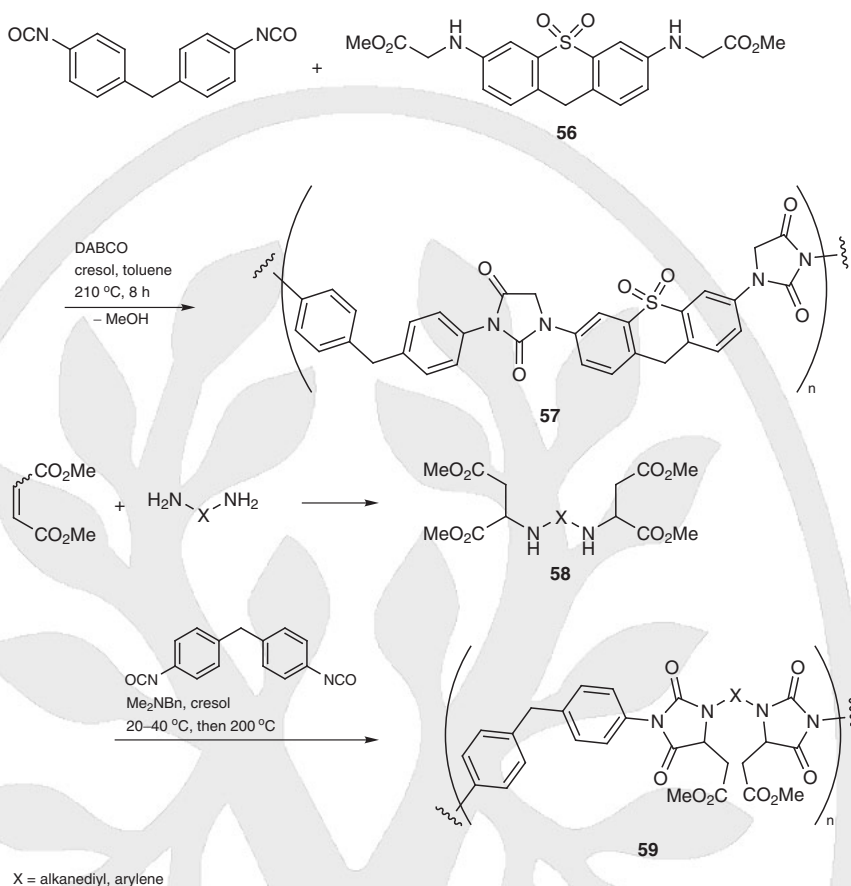
18.9.5.1 Synthesis of Product Subclass 5

18.9.5.1.1 Method 1: From Diisocyanates and Bis(alkyl glycinates)

The polyaddition/cyclocondensation of bis(alkyl glycinates), e.g. **53**, and diisocyanates **25** to yield polyhydantoins, e.g. **55** (Scheme 17), is an extension of the well-known route to substituted hydantoins by the reaction of amino acid esters with monoisocyanates.^[100,101] This route involves the initial formation of an intermediate ureido ester that is converted into the corresponding hydantoin in a high yield at elevated temperature or in the presence of a catalyst. Model studies on bishydantoins undertaken to investigate the reactivity of bis(alkyl glycinates), e.g. **53**, with monoisocyanates and of mono(alkyl glycinates) with diisocyanates reveal that intermediate diureido esters (with the exception of those prepared from 2,4-diisocyanatotoluene) are formed readily after 15 hours at room temperature in toluene, and can be isolated in good to high yields.^[92] The cyclization to the corresponding bishydantoin is more difficult than for the corresponding monoureido esters and requires prolonged heating (15 hours in refluxing acetic acid or 1-methylpyrrolidin-2-one).^[92] The reaction can be applied in polycondensation reactions (Scheme 17) to give both low- and high-molecular-weight polyhydantoins (e.g., **55**). The starting poly(alkyl glycinates) are typically prepared by treating polyamines with α -haloacetic acids derivatives or by Strecker synthesis and subsequent hydrolysis of the intermediate nitrile.

Scheme 17 Polyhydantoins from Diisocyanates and Bis(alkyl glycinates)^[98,102,103]





Oligomers and low-molecular-weight polymers containing functional end groups (e.g., urethane, isocyanate) are formed in the presence of an excess of diisocyanate **25** (1–2 equivalents). Conversely, high-molecular-weight polymers are typically obtained when equimolar amounts of isocyanate and glycinate are used. Because the alcohol liberated during the cyclization can react with free isocyanate to form a urethane, it is necessary to ensure that the polyaddition step is complete before cyclocondensation occurs. In a two-step procedure, a poly(ureido ester) (e.g., **54**) is first formed in *m*-cresol at 50 °C before the cyclocondensation stage, which is conducted at 50 or 80 °C in the presence of a condensation catalyst such as hydrochloric acid (Scheme 17).

Alternatively, the isocyanate and the glycinate (e.g., **56**, **58**) can be condensed at a high temperature, typically 200–250 °C, to give polyhydantoins (e.g., **57**, **59**). Although the reaction can be conducted in the absence of a solvent,^[92] phenolic compounds (phenol, *m*-cresol), which catalyze the formation of ureido esters,^[42] are particularly well suited as solvents. Other acidic or basic catalysts that promote the polycondensation include phosphoric acid,^[98] 1,4-diazabicyclo[2.2.2]octane,^[102] and dimethylbenzylamine.^[103] Solutions of hydantoins in *m*-cresol can be used directly for coating applications. Alternatively, a stable prepolymer (“primary melt”) can be first generated by reacting a poly(alkyl glycinate) with a blocked polyisocyanate (e.g., a cresyl urethane) in the absence of a solvent at 100–120 °C.^[85] After the application of this fluid melt to the desired substrate, condensation is completed by heating to 200–450 °C in a stoving oven. High-temperature-resistant, chemically and physically inert coatings, foils, or shaped products are thereby obtained.

Polyhydantoin 55 ($X = 4,4'\text{-C}_6\text{H}_4\text{CH}_2\text{C}_6\text{H}_4$) from **1,1'-Methylenebis(4-isocyanatobenzene)** (25, $X = 4,4'\text{-C}_6\text{H}_4\text{CH}_2\text{C}_6\text{H}_4$) and **Diethyl 2,2'-(1,3-Phenylenediimino)diacetate** (53);

Typical Procedure:^[98]

A mixture of diethyl 2,2'-(1,3-phenylenediimino)diacetate (**53**; 2.80 g, 10 mmol) and 1,1'-methylenebis(4-isocyanatobenzene) (**25**, $X = 4,4'\text{-C}_6\text{H}_4\text{CH}_2\text{C}_6\text{H}_4$; 2.52 g, 10.08 mmol) was added to *m*-cresol (10 mL) all at once at 50 °C. The mixture was stirred at 50 °C for 4 h and became very viscous as the reaction proceeded. *m*-Cresol (10 mL) and concd HCl (1 mL) were then added and stirring was continued at 50 °C for additional 3 h to give a clear soln of the polyhydantoin. The soln was poured into acetone (700 mL) and the polymer was separated by filtration, washed repeatedly with acetone, and dried under reduced pressure at 120 °C for 4 h; yield: 4.38 g (100%); η_{inh} 0.60 dL·g⁻¹ (*c* 0.5 g·dL⁻¹, H₂SO₄, 30 °C); IR (thin film) $\tilde{\nu}_{\text{max}}$: 1770, 1710 (C=O) cm⁻¹.

18.9.5.1.1.1

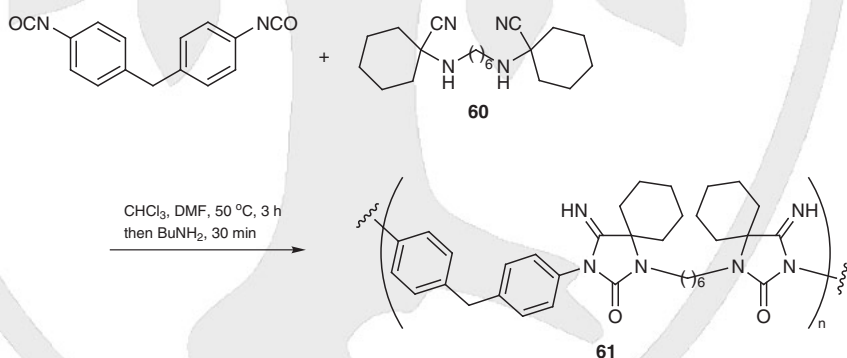
Variation 1:

Poly(iminoimidazolidinones) from *N,N'*-Bis(1-cyanocycloalkyl) Diamines and Diisocyanates

Poly(iminoimidazolidinones) have been studied far less than the corresponding polyhydantoins, and only one account describes their synthesis.^[99] Poly(iminoimidazolidinones) (e.g., **61**) are synthesized by polycondensation of *N,N'*-bis(1-cyanocycloalkyl)arylenediamines and *N,N'*-bis(1-cyanocycloalkyl)alkylenediamines (e.g., **60**) with 1,1'-methylenebis(4-isocyanatobenzene) (Scheme 18) in a manner closely related to the method described in Section 18.9.5.1.1 for the preparation of polyhydantoins: only low-molecular-weight (typically less than 3300) polymers are obtained, however. These polymers are soluble in chloroform, *m*-cresol, and dimethylformamide. The imine groups cannot be hydrolyzed to give the corresponding polyhydantoins.

Poly(iminoimidazolidinones) are characterized by infrared absorption bands at approximately 1745 and 1665 cm⁻¹.

Scheme 18 A Poly(iminoimidazolidinone) from 1,1'-(Hexamethylenediimino)dicyclohexanecarbonitrile and 1,1'-Methylenebis(4-isocyanatobenzene)^[99]



Poly(iminoimidazolidinone) 61 from **1,1'-(Hexane-1,6-diyl-diimino)dicyclohexanecarbonitrile** (**60**) and **1,1'-Methylenebis(4-isocyanatobenzene)**; **Typical Procedure:**^[99]

A soln of the diamino dinitrile **60** (1.30 g, 3.93 mmol) and 1,1'-methylenebis(4-isocyanatobenzene) (1.00 g, 4 mmol) in CHCl₃/DMF (15:8; 23 mL) was heated for 3 h at 50 °C. BuNH₂ (1.5 mL, 15.1 mmol) was then added and the soln was stirred for 30 min. The CHCl₃ was removed in vacuo and the remaining soln was poured into H₂O to precipitate the polymer; yield: 1.75 g (76%); M_n (vapor-pressure osmometry, CHCl₃): 3200; η_{inh} 0.20 dL·g⁻¹ (*c* 0.5 g·dL⁻¹, *m*-cresol, 25 °C); mp 167 °C; IR (thin film) $\tilde{\nu}_{\text{max}}$: 1745, 1665 cm⁻¹.

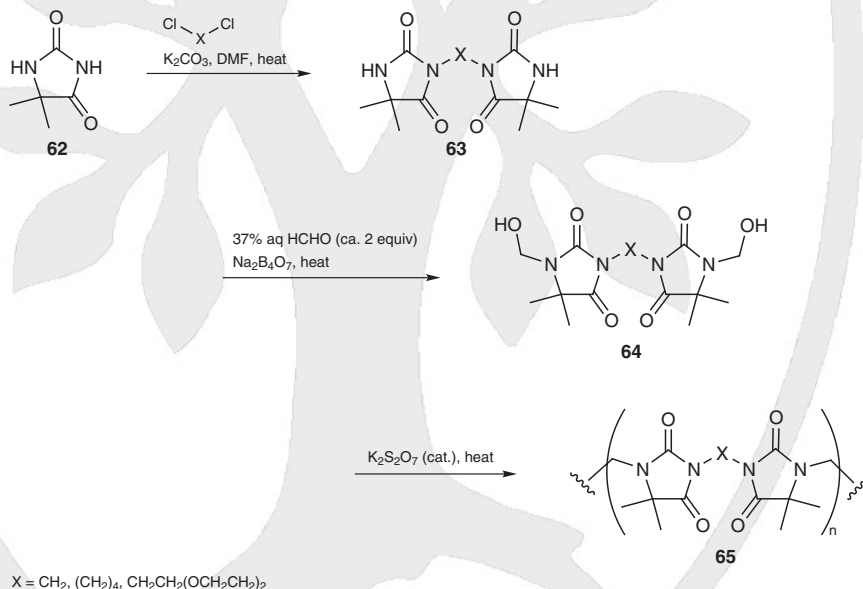
18.9.5.1.2

**Method 2:
From Bishydantoins and Formaldehyde**

Linear polymers containing hydantoin repeating units (e.g., **65**) can be prepared by condensation of about 2 equivalents of formaldehyde with 3,3'-bishydantoins (e.g., **63**), formed by the reaction of 5,5-dimethylimidazolidine-2,4-dione (**62**; 5,5-dimethylhydantoin)^[104] with dihalo compounds (Scheme 19).^[95]

A monohydantoin (e.g., **62**) can also be condensed with a slight excess of formaldehyde to produce water-soluble resins.^[105] This reaction shares some similarities with the condensation of urea and formaldehyde in the production of urea-formaldehyde resins (see Section 18.9.7). The main difference is the absence of cross-linking in hydantoin-formaldehyde resins.

In the case of 3,3'-bishydantoins, the polymerization process initially involves the base-catalyzed (sodium tetraborate is typically employed) formation of a bis(hydroxymethyl) derivative (e.g., **64**), which can then undergo intermolecular condensation at higher temperature to produce oligomers and polymers. Under acidic conditions, methylene bridges are formed predominantly with elimination of formaldehyde and water; suitable acid catalysts include potassium pyrosulfate, sulfuric acid, 4-toluenesulfonic acid, or hydrochloric acid. Alternatively, polymerization can be performed in a one-step process by treating the 3,3'-bishydantoin with formaldehyde in the presence of the acid catalyst.

Scheme 19 Condensation of 3,3'-Bishydantoins with Formaldehyde^[95]

Hydantoin-Formaldehyde Resin 65 [X = (CH₂)₄] from 3,3'-Butane-1,4-diylbis(5,5-dimethylimidazolidine-2,4-dione) [63, X = (CH₂)₄] and Formaldehyde; Typical Procedure:^[95]

The bishydantoin **63** [X = (CH₂)₄; 31 g, 100 mmol] was stirred with 37% aq HCHO (20.8 g, 240 mmol) and Na₂B₄O₇·10H₂O (0.3 g, 0.79 mmol) under heating on a steam bath. Stirring and heating were continued until the mixture had liquefied and resolidified. The solid reaction product was then recrystallized (hot H₂O) to give colorless crystals of the bis(hydroxymethyl)bishydantoin **64**. Bishydantoin **64** was heated in the presence of a trace of K₂S₂O₇ for 3 h under a vacuum at 225 °C to give the polymer; η_{inh} 1.75 dL·g⁻¹.

18.9.6

**Product Subclass 6:
Polyhydrouracils and Poly(quinazolinediones)**

In addition to poly(imidazolidine-2,4,5-triones) (see Section 18.9.4.) and polyhydantoins (see Section 18.9.5), heterocyclic polymers prepared by polyaddition–cyclocondensation reactions of diisocyanates with suitable monomers include polyhydrouracils^[99] and poly(quinazolinediones).^[106] These polymers, which are composed of the heterocyclic hydrouracil and quinazolinedione nuclei as the recurring structural units, are also characterized by good and excellent thermal stability, respectively. Whereas polyhydrouracils start to decompose at about 400 °C,^[99] poly(quinazolinediones) are stable up to 500 °C,^[106] as assessed by thermogravimetric analysis.

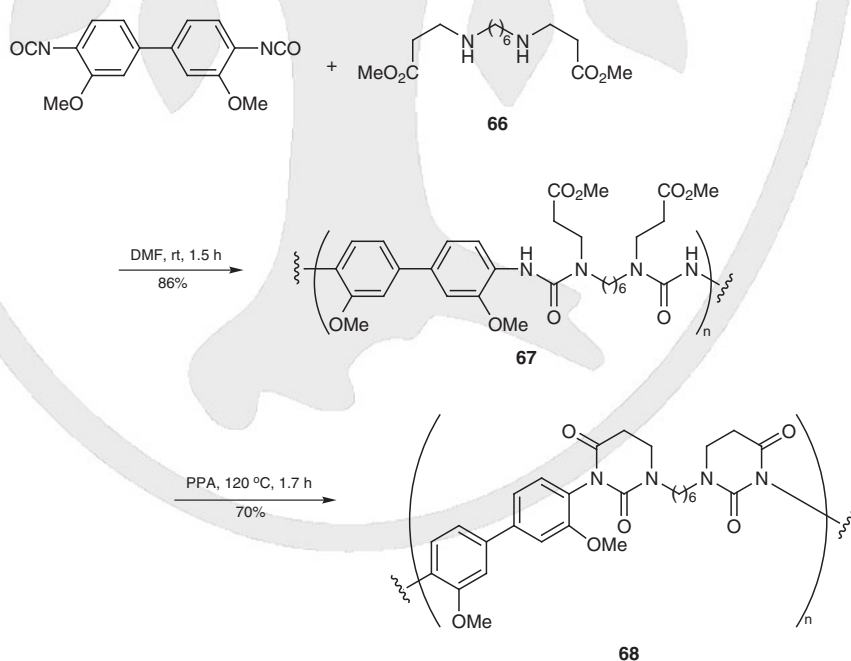
18.9.6.1

Synthesis of Product Subclass 6

18.9.6.1.1

**Method 1:
Polyhydrouracils by Cyclization of 2-(Methoxycarbonyl)ethyl-Substituted
Polyureas**

The acid-catalyzed cyclization of ureidopropanoates yields hydrouracils.^[107] Similarly, polyurea **67**, formed by the reaction of an aromatic diisocyanate with *N,N'*-bis[(2-methoxycarbonyl)ethyl] diamine **66**, cyclize to form polyhydrouracil **68** on heating to about 115–120 °C in the presence of polyphosphoric acid as catalyst (Scheme 20).^[99] Cyclization is complete, as shown by the disappearance of the characteristic urea absorptions at 3400 (amide I) and 1510–1535 cm^{−1} (amide II) and a shift of the carbonyl absorptions. Polyhydrouracils are typically characterized by infrared spectra showing carbonyl absorption at about 1724 (4-oxo group) and 1680 cm^{−1} (2-oxo group). Polyhydrouracils are soluble in chloroform, dimethylformamide, and *m*-cresol. Their melting points are typically 100–150 °C higher than those of their polyurea precursors.

Scheme 20 Preparation of a Polyhydrouracil^[99]

Polyhydrouracil 68 by Cyclization of Polyurea 67, Prepared from Dimethyl 3,3'-(Hexane-1,6-diyl-diimino)bis(propanoate) (66) and 4,4'-Diisocyanato-3,3'-dimethoxybiphenyl:^[99]

The polyurea **67** was prepared by treatment of dimethyl 3,3'-(hexane-1,6-diyl-diimino)-bis(propanoate)^[99] (**66**; 1 equiv) with 4,4'-diisocyanato-3,3'-dimethoxybiphenyl (1 equiv) in DMF at rt; yield: 86%; η_{inh} 0.51 dL·g⁻¹ (*c* 0.5 g·dL⁻¹, *m*-cresol, 25 °C); mp 130 °C.

A mixture of the polyurea **67** (800 mg) in PPA (22 mL), prepared from P₂O₅ (22.5 g, 0.16 mmol) and 85% H₃PO₄ (15 mL, 0.13 mmol), was heated at 120 °C for 1.7 h and then poured into H₂O (150 mL). The solid was washed repeatedly with H₂O and then dissolved in DMF (10 mL). The soln was poured into H₂O (50 mL) and the precipitated polymer was again washed repeatedly with H₂O and dried under reduced pressure at 90 °C for 6 h; yield: 500 mg (70%); η_{inh} 0.52 dL·g⁻¹ (*c* 0.5 g·dL⁻¹, *m*-cresol, 25 °C); mp 280 °C.

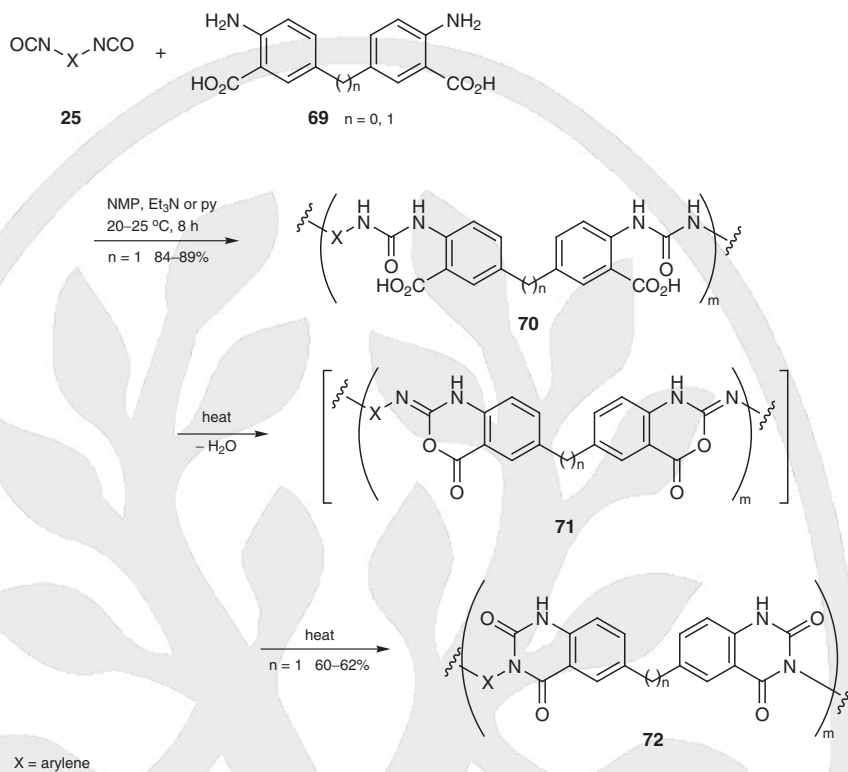
18.9.6.1.2

Method 2:

Poly(quinazolinediones) from Aromatic Diisocyanates and Bisanthranilic Acids

Aromatic poly(quinazolinediones) (e.g., **72**) of high molecular weight are typically obtained through thermal cyclodehydration of aromatic poly(urea acids) (e.g., **70**), prepared by polyaddition reaction of aromatic diamino dicarboxylic acids (e.g., **69**, *n* = 0, 1) with aromatic diisocyanates **25**.^[106,107] The cyclodehydration reaction involves the formation of an intermediate poly(2-imino-1,2-dihydro-4*H*-3,1-benzoxazin-4-one) (e.g., **71**) at about 140–180 °C. On further heating (230–330 °C), this undergoes an intramolecular rearrangement to yield the thermodynamically stable poly(quinazolinedione) **72** (Scheme 21). In the absence of a catalyst, the rate of polymerization of aromatic diaminodicarboxylic acids with aromatic diisocyanates is extremely slow, and the reaction yields only oligomers. Procedures for effective polyaddition include melt polymerization in the bulk state,^[106] interfacial polymerization at room temperature in the presence of aqueous sodium hydroxide,^[106] polymerization in polyphosphoric acid,^[108] and polymerization in 1-methylpyrrolidin-2-one at about 25 °C in the presence of pyridine or triethylamine.^[107,109]

Poly(urea acids) (e.g., **70**) are characterized by infrared absorptions at about 1680–1670 cm⁻¹ (CO₂H and urea carbonyl), whereas the poly(quinazolinediones) (e.g., **72**) show absorptions at about 1740 and 1630 cm⁻¹ (4-oxo and 2-oxo groups, respectively). The formation of the intermediate poly(2-imino-1,2-dihydro-4*H*-3,1-benzoxazin-4-one) (e.g., **71**) during the dehydration process gives rise to an absorption band at about 1775 cm⁻¹, characteristic of the benzoxazinone ring.

Scheme 21 Preparation of Poly(quinazolinediones)^[107,109]

Poly(urea acids) 70 ($n = 1$) from 3,3'-Methylenebis(6-aminobenzoic acid) (69, $n = 1$) and Aryl Diisocyanates 25; General Procedure:^[107]

To a stirred soln containing 3,3'-methylenebis(6-aminobenzoic acid)^[107] (**69**, $n = 1$; 2.84 g, 10 mmol) in dry NMP (15 mL) at 18°C under N_2 was added one drop of pyridine and a soln of a diisocyanate 25 (10 mmol) in dry NMP (15 mL). The soln was stirred for 8 h at 20°C . The resulting poly(urea acid) **70** ($n = 1$) was isolated by pouring the mixture into H_2O , then washed with H_2O and MeOH and dried under a vacuum; yield: 84–89%.

Poly(quinazolinediones) 72 ($n = 1$) by Cyclization of Poly(urea acids) 70 ($n = 1$);

General Procedure:^[107]

A poly(urea acid) **70** (2 g) was mixed with DMA (5 mL), Ac_2O (10 mL), and pyridine (5 mL). The mixture was heated to 140°C for 6 h. The soln was cooled and the solid was collected by filtration and washed with H_2O and acetone. The polymer obtained was heated at 250°C for 2 h and then at 180°C for 2 h under vacuum; yield: 60–62%.

18.9.7

**Product Subclass 7:
Urea-Formaldehyde Resins**

Previously published information on urea-formaldehyde resins can be found in *Houben-Weyl*, Vol. E 20, pp 1811–1890, as well as in several monographs.^[110–113]

Urea-formaldehyde resins are thermosetting polymers formed by the condensation of urea with formaldehyde. They represent the major portion of amino resins (so-called aminoplasts) produced worldwide, the remainder of the production consisting essentially of melamine-formaldehyde resins. Urea-formaldehyde resins are complex mixtures of various condensation products, ranging from simple hydroxymethylated ureas to linear

or branched oligomeric and polymeric molecules. The precise properties of any particular urea–formaldehyde resin will depend on the molar ratio of formaldehyde to urea used in its manufacture, the type and proportion of the various linkages (methylene and oxydimethylene linkages) within the resin structure, and the proportions of high- and low-molecular-weight material. Early attempts to characterize the resinous products resulting from the reaction of urea and formaldehyde go back to the 1880s. Since then, the interest in urea–formaldehyde resins has grown steadily, with a number of patents filed in the 1920s, and the first commercial applications as thermosetting molding materials (British Cyanide) and wood glues (I. G. Farbenindustrie) appearing in the 1930s. The advantages of urea–formaldehyde resins are their water solubility before curing, colorlessness, hardness after curing, and relatively low cost.

Today, the market for urea–formaldehyde resins is mature. The resins are used as adhesives (e.g., for bonding particleboard and plywood), as additives for plastics, as components of paints, as textile-finishing agents (as monomeric hydroxymethylated derivatives of urea), and as paper-finishing agents. Among these applications, adhesives account for over 90% of all the urea–formaldehyde resins consumed. In 2000, the global consumption of urea–formaldehyde resins was about 11 million tons. Urea–formaldehyde resins as adhesives are usually employed as colloidal aqueous solutions with a 60–70% solids content.

The main drawback of urea–formaldehyde resins lies in the lability of the aminomethylene linkage, which decreases their water resistance and results in emission of formaldehyde, which in significant concentrations forms an irritating and toxic vapor. Because of this drawback, products made from urea–formaldehyde resins cannot withstand use outdoors or in places where there is a high humidity. The increasing concerns about health hazards resulting from slow releases of formaldehyde^[114] have led to stringent regulations^[115] and to extensive research and development programs to reduce formaldehyde emission levels, particularly from products bonded with urea–formaldehyde adhesive resins. Methods for reducing emissions of formaldehyde include formulation of resins with a low formaldehyde/urea ratio (<1.15), chemical treatment with formaldehyde-scavenging materials before or after resin application, and resin additives.

18.9.7.1 **Synthesis of Product Subclass 7**

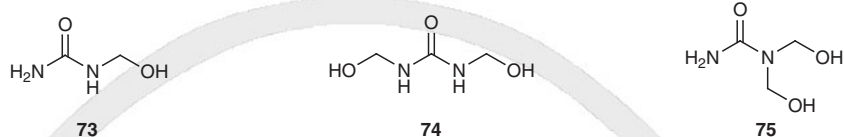
18.9.7.1.1 **Method 1: By Reaction of Urea with Formaldehyde**

Urea–formaldehyde condensation involves two main reactions. The first, the so-called methylation or hydroxymethylation reaction, is the addition of formaldehyde to urea (typically at a formaldehyde/urea ratio of 1.8–2.4); this leads to the formation of various (hydroxymethyl)urea compounds, including mono(hydroxymethyl)urea (**73**), bis(hydroxymethyl)ureas (**74** and **75**), and tris(hydroxymethyl)urea (**76**) (Scheme 22). These species can be isolated by controlling the ratio of the reactants and then characterized by various methods including ¹³C NMR spectroscopy.^[116] Tetrakis(hydroxymethyl)urea has not been isolated because it cyclizes spontaneously to form 3,5-bis(hydroxymethyl)tetrahydro-4H-1,3,5-oxadiazin-4-one (**77**). The hydroxymethylation reaction is reversible and is catalyzed by both acids and bases. This first step is generally conducted by heating in neutral or weakly alkaline aqueous media (pH 7–9), conditions under which hydroxymethyl groups can be stabilized by intramolecular hydrogen bonding. This procedure allows hydroxymethylation reactions to proceed in the absence of condensation reactions.

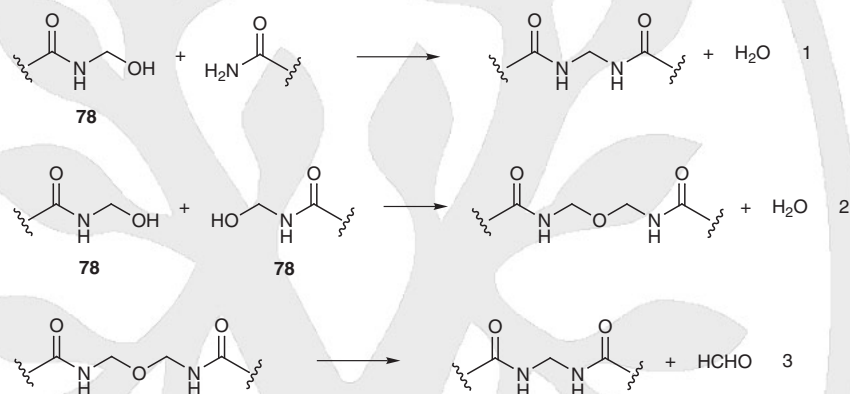
SAFETY: Formaldehyde is a highly toxic gas by inhalation, ingestion, and through skin contact. Proper safety precautions should be taken during its storage and handling.

Scheme 22 Urea-Formaldehyde Resins

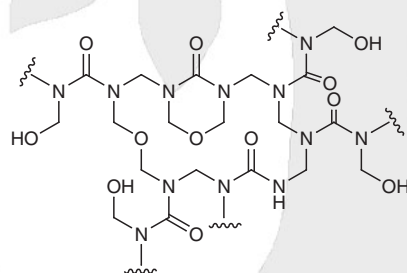
hydroxymethyl urea derivatives



condensation reactions



theoretical three-dimensional UF network (simplified model)



The second step in the formation of urea-formaldehyde resins involves the condensation reactions between the various hydroxymethyl species **78** (Scheme 22). These reactions are mainly acid-catalyzed (i.e., they occur at pH < 6) and lead to a complex mixture of low-molecular-weight urea-formaldehyde adducts (oligomers) that have been extensively studied by liquid-state ^1H and ^{13}C NMR, as well as by Fourier-transform infrared and Raman spectroscopy.^[116,117] Essentially, condensation occurs by two mechanisms (Scheme 22): formation of methylene linkages ($\text{N}-\text{CH}_2-\text{N}$) through the reaction of a hydroxymethyl group with a urea nitrogen, and the formation of oxydimethylene linkages ($\text{N}-\text{CH}_2\text{OCH}_2-\text{N}$) resulting from the reaction of two hydroxymethyl groups. The oxydimethylene bridge, which is less stable than the methylene bridge, can also rearrange to form a methylene linkage with liberation of formaldehyde. When the required viscosity

is reached, the condensation reaction is generally terminated by neutralizing the mixture to a weakly alkaline pH. At this stage, a second and sometimes a third addition of urea can be made to reduce the final formaldehyde/urea ratio to a desired level. This urea–formaldehyde prepolymer cures irreversibly to form an insoluble and infusible cross-linked condensation polymer on heating at low pH values: either acids (e.g., phosphoric acid) or ammonium salts (e.g., ammonium chloride or ammonium sulfate) can be used to lower the pH (Scheme 22). High-resolution solid-state ^{13}C NMR with cross-polarization and magic-angle spinning has proved particularly useful in gaining insight into the complex molecular structures of cured solid urea–formaldehyde resin.^[118,119]

Liquid Urea–Formaldehyde Resin with a Low Formaldehyde/Urea Ratio;

Typical Procedure:^[120]

Throughout the condensation, the mixture was agitated in a reactor fitted with an agitator. Aq HCHO (40% formalin) (2500 kg, 33.3×10^3 mol) was added to the reactor and neutralized with 40% w/v aq NaOH to a pH of 7.4 under constant agitation. Urea (1000 kg, 16.7×10^3 mol) was added, and the mixture (urea/formaldehyde 2:1) was then heated to 82–83 °C and the pH was adjusted to 7.2. Condensation was carried out under these conditions for 30 min before the pH was adjusted to 5.4 with a formic acid soln. The condensation was continued at 82–83 °C until the mixture reached a viscosity of 28 mPa·s (Brookfield viscometer, 65 °C). A second batch of urea (100 kg, 1.7×10^3 mol) was immediately added and the condensation was continued at 82–83 °C until the mixture reached a Brookfield viscosity of about 68 mPa·s (65 °C). The pH of the mixture was then adjusted to 6.1 by the addition of 40% w/v aq NaOH. A third batch of urea (640 kg, 10.7×10^3 mol) was added, so that the final formaldehyde/urea mole ratio was 1.15:1. The heat source was removed and the final stage of the condensation was carried out for 25 min with agitation only. At the end of this time, the temperature of the mixture had dropped to about 60 °C. The mixture was evaporated under a partial vacuum at 54–57 °C to a solid content of 65.8%. It was then cooled to about 38 °C, and the pH adjusted to 7.1 with 40% w/v aq NaOH. The resulting water-soluble product was stored at about 20 °C; η (20 °C): 0.75 Pa·s; free HCHO content: 0.13%.

18.9.8

Product Subclass 8: Polyureas and Copolyureas

Previously published information on polyureas can be found in *Houben–Weyl*, Vol. E 20, pp 1721–1751, as well as in several reviews.^[121–124]

Early work on linear polyureas $(\text{NHCONHX})_n$ and copolyureas $(\text{NHX}^1\text{NHCONHX}^2\text{NHCO})_n$ was conducted at I. G. Farbenindustrie^[125,126] and at Du Pont de Nemours^[127–129] in the 1930s. O. Bayer, G. H. Rinke, and W. Siefken at I. G. Farbenindustrie prepared polyureas by the polyaddition reaction between diisocyanates and diamines in a manner analogous to the synthesis of polyurethanes (see Section 18.7), which were also disclosed for the first time in the same patent.^[125] Chemists at du Pont de Nemours and Co. developed an alternative method for producing polyurea based on the thermal reaction of polyamines with ureas.^[127,128] Since then, many derived methods have appeared in the literature, together with an increasing number of patents on the production and applications of aliphatic and aromatic polyureas and block copolyureas, including poly(urethane–ureas). Like polyurethanes, polyureas show a high tensile strength, good flexibility, and high abrasion and impact resistance, and can be formulated with a wide variety of property ranges. The thermal stability of polyureas is higher than that of the corresponding polyurethanes. The rate of polymer formation is one of the important differences between polyurethane and polyurea technologies. Whereas catalysis is typically required for polyurethane preparation, the formation of polyureas by the reaction of polyamines and polyisocyanates is characterized by high reaction rates and does not require catalysis. Polyureas have found

applications as elastomers, foams, fibers, coatings, and films. Commercial polyureas are elastomeric in nature and are typically produced from an amine-terminated polyether polyol, a diamine chain extender, and a polyisocyanate. In the 1980s, with the advent of reaction injection molding, polyurea and copoly(urethane urea) elastomers found some applications in the automotive industry for the production of body parts.^[130–132] Polyurea elastomers have also been applied successfully to spray-coating technology.^[133,134] Polyurea spray elastomers are characterized by their fast cure, insensitivity to humidity, and thermal and chemical stability. The current market size for polyurea spray coatings is several thousands of tons a year, and the market is growing rapidly.

Polyureas have also been investigated for applications in various fields, including second-order nonlinear optics, medicinal chemistry, catalysis, and microencapsulation. Aromatic and aliphatic polyureas display interesting properties for use in second-order nonlinear optics. In these polymers, the urea moieties, which possess a large dipole moment (4.9 D), can be aligned by poling to produce noncentrosymmetric structures desirable for second-order nonlinear optical effects.^[135] Short-chain anionic polyureas synthesized from 4,4'-diaminobiphenyl-3,3'-disulfonic acid are active as antiviral agents against human immunodeficiency virus, herpes simplex virus, and cytomegalovirus.^[136] Some chiral polyurea-rhodium complexes are catalytically active in asymmetric reduction of ketones by hydride transfer.^[137] Polyurea-encapsulated palladium and palladium acetate^[138] have been proposed as recoverable and reusable catalysts for a variety of reactions, including cross-coupling reactions and hydrogenation.

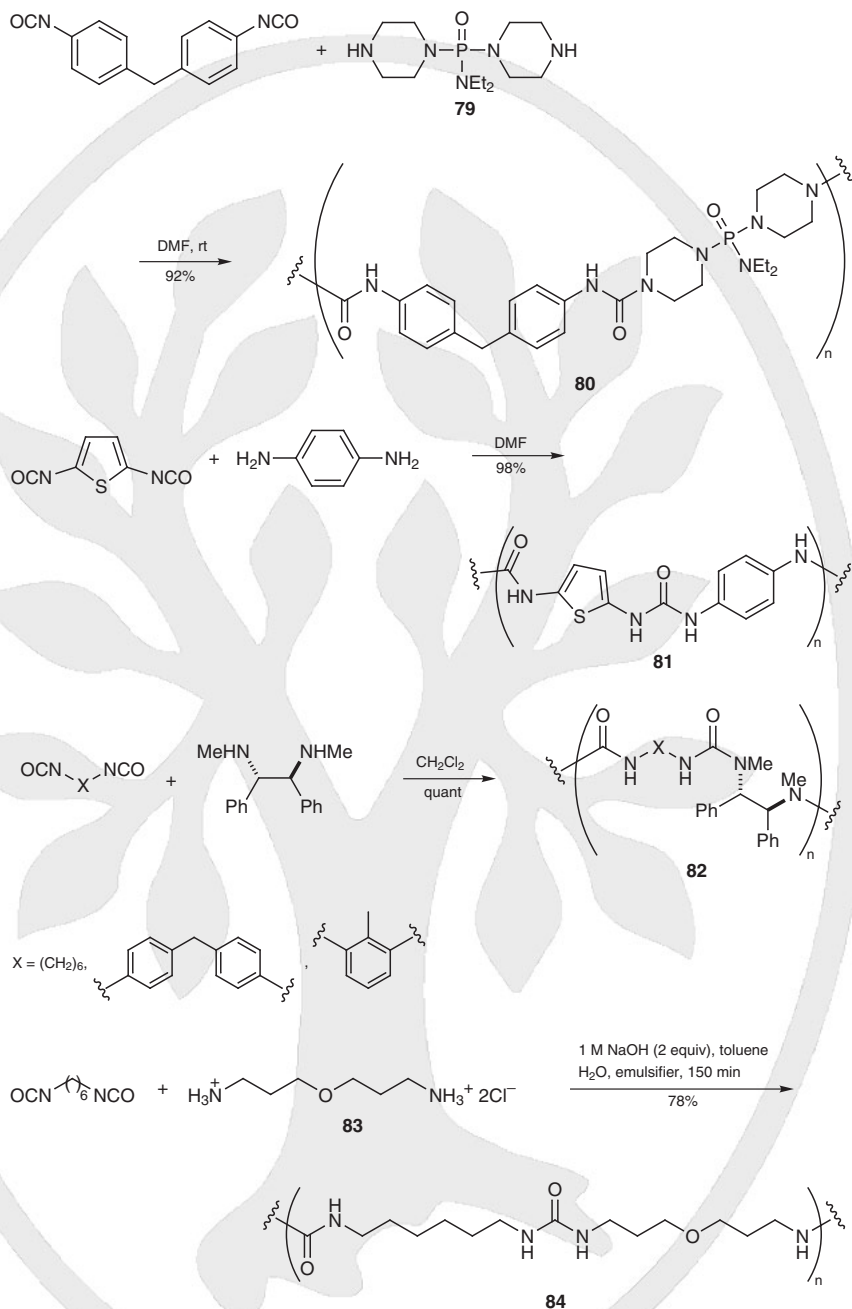
Polyureas are characterized by an absorption band at about 1640 cm⁻¹ in their infrared spectra, corresponding to the C=O bond stretching frequency, as well as by a band in the region 3320–3360 cm⁻¹ corresponding to NH stretching absorption and typical of a hydrogen-bonded vibrator.

18.9.8.1 Synthesis of Product Subclass 8

18.9.8.1.1 Method 1: By Polyaddition of Diamines and Diisocyanates

Polyaddition of diamines and diisocyanates represents the most common method for the production of polyureas that are free of condensation byproducts. It is generally accepted that amines react almost instantaneously with isocyanates. Aliphatic amines usually react faster than aromatic amines with isocyanates, and aromatic isocyanates are much more reactive toward amines than are aliphatic isocyanates. Although the reaction between isocyanates and amines is autocatalytic, tertiary amines, pyridine, weak carboxylic acids, or organotin compounds can be used as catalysts if necessary.

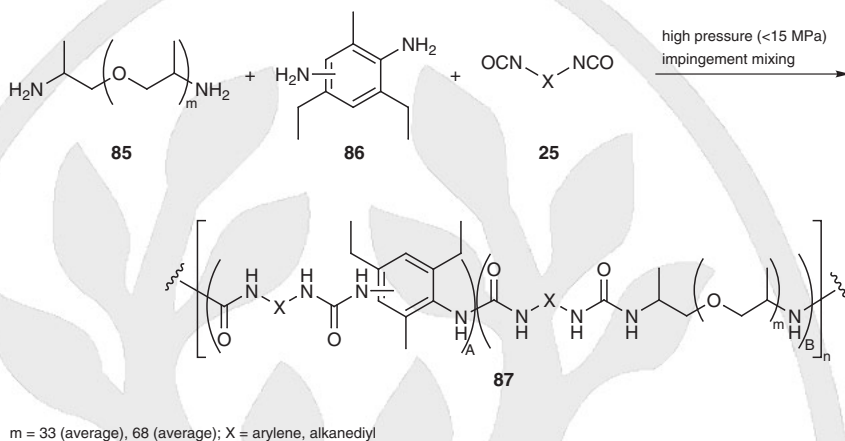
Linear homopolyureas and copolyureas from diisocyanates and diamines (e.g., **79** and **83**) can be prepared by solution polymerization^[137,139–141] (e.g., **80–82**) or interfacial polymerization^[141–144] (e.g., **84**) (Scheme 23). When the reaction of aromatic diisocyanates with aliphatic amines is conducted in the bulk state, biuret formation occurs as a side reaction, causing cross-linking and gel formation. This side reaction is minimized by conducting the polymerization in solvents such as phenols, sulfolane, dimethyl sulfoxide, dimethylacetamide, dimethylformamide or 1-methylpyrrolidin-2-one. Alternatively, in interfacial polycondensation, the polyurea is formed at the interface of an aqueous solution of a diamine and an organic solution of the diisocyanate.^[141–144] The reaction is generally conducted in the presence of an emulsifier to ensure the formation of a homogeneous reactive mixture. Functional polyurea microcapsules containing a variety of active ingredients (e.g., pesticides, cells, inks, or chemicals) for controlled release can be prepared by this technique (see Section 18.9.8.2.2).^[138,145,146]

Scheme 23 Solution and Interfacial Polymerization of Diisocyanates and Diamines^[137,140–142]

Commercial polyurea elastomers are produced by the reaction of a mixture of amine-terminated polyethers **85** and chain extenders (e.g., **86**) with isocyanates **25** [generally 1,1'-methylenebis(4-isocyanatobenzene) (MDI) or its polymeric form (PMDI)]. Compared with polyurethanes, polyurea elastomers are characterized by superior resistance to thermal distortion, and shorter demold times. The distribution and phase separation of hard segments (derived from the reaction of isocyanate with chain extender) and soft segments [derived from the reaction of isocyanate with poly(ether amine)] determine the final properties of the polymer. These block copolymers of the type $-(\text{AB})_n-$ (e.g., **87**) are essen-

tially produced by bulk polymerization at high pressure (<15 MPa) and in impingement mixing equipment (reaction injection molding^[130–132] and spray polyurea elastomer^[133,134] systems) (Scheme 24).

Scheme 24 Polyurea Elastomers by Bulk Polymerization^[147]



These technologies allow the handling of highly reactive precursor materials such as diisocyanates and diamines, which cannot be processed using conventional casting systems. In these two-component systems, one stream generally contains the isocyanate component (component A), while the other stream contains the amine-containing polyether and the amine chain extender (component B). The reaction injection molding process was originally developed for the production of polyurethane and poly(urethane-urea) elastomers, in which the B component comprises a high-molecular-weight polyol, a diol or diamine chain extender, and a catalyst. Whereas polyurethane and poly(urethane-urea) elastomers require the use of organotin catalysts for acceptable processing, amine-terminated polyethers react so rapidly with isocyanates that it is necessary to employ sterically hindered amine chain extenders, such as 2,4,6-trimethyl-1,3-diaminobenzene (**86**), to slow the polymerization reaction and provide enhanced flow before gelation. If polymerization or gelation occurs too rapidly, the elastomer cannot be molded, sprayed, or poured. To overcome the problem of the instability of aromatic polyureas to ultraviolet light, hindered secondary aliphatic diamine chain extenders, such as 1,4-diaminocyclohexane or isophoronediamine, have also been introduced in combination with aliphatic or aralkyl isocyanates [e.g., 1,3-bis(1-isocyanato-1-methylethyl)benzene, generally referred to as *m*-TMXDI] for the production of aliphatic polyurea spray coatings.^[147] High-molecular-weight (molecular weight 2000–5000) primary amine-terminated polyethers used in the production of polyurea elastomers (e.g., **85**) were originally developed by Texaco and are currently manufactured and sold by Huntsman Corporation under the trade name JEFFAMINE. They are essentially polyoxypropylene diols or triols in which the terminal hydroxyl groups are converted into amine groups.

Polyurea 80 from 1,1'-Methylenebis(4-isocyanatobenzene) and Phosphoric Triamide 79 by Solution Polymerization; Typical Procedure:^[140]

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

1,1'-Methylenebis(4-isocyanatobenzene) (1.251 g, 5 mmol) dissolved in DMF (25 mL) was added at rt under N₂ with stirring to phosphoric triamide **79** (1.587 g, 5.5 mmol) dissolved

in DMF (25 mL). A gel-like precipitate was formed at rt and dissolved when the mixture was warmed to 60 °C with stirring. The mixture was concentrated to about 35 mL, filtered warm, and precipitated in acetone (500 mL). The polymer was isolated by filtration and dried; yield: 2.599 g (91.6%); $[\eta]$ 0.15 dL·g⁻¹ (DMF, 25 °C); T_m 230–245 °C (dec 255–270 °C).

Polyurea 84 from 1,6-Diisocyanatohexane and 3,3'-Oxydipropyl-1-amine by Interfacial Polymerization; Typical Procedure:^[142]

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

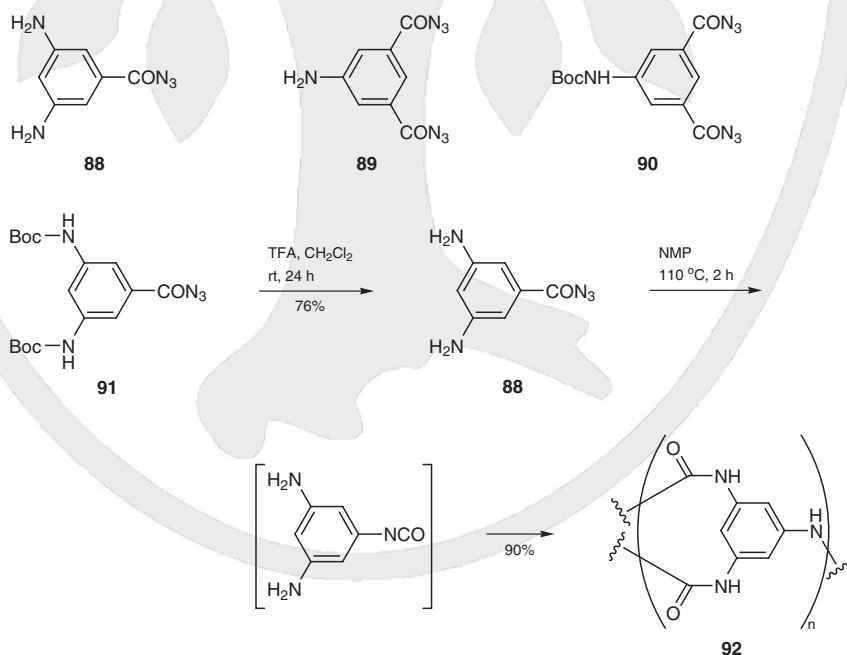
An ice-cold soln of 1 M NaOH (2 L, 2 mol) was added over 30 min with stirring and cooling by ice to a mixture prepared from 1,6-diisocyanatohexane (168 g, 1 mol) in toluene (1 L), a soln of 3,3'-oxydipropyl-1-amine (132 g, 1 mol) in H₂O (1.3 L) and 1 M HCl (2 L), and benzyl-4-hydroxydiphenyl polyglycol ether (18 g) as an emulsifier. The mixture was stirred for 2 h at rt and then the precipitate was collected by filtration, washed several times with H₂O, and dried at 80 °C under reduced pressure; yield: 234 g (78%); η_{red} 95 × 10⁻³ dL·g⁻¹; mp 225–227 °C.

18.9.8.1.1.1

Variation 1:
Hyperbranched Polymers from Diaminophenyl Isocyanate Monomers

Aromatic hyperbranched polymers based on the urea linkage have been synthesized from AB₂- and A₂B-type monomers by a one-pot process involving thermal decomposition (110 °C) of 3,5-diaminobenzoyl azide (**88**) or 5-aminoisophthaloyl diazide (**89**; Scheme 25).^[148,149] Rapid evolution of nitrogen is observed during the initial stages of the reaction, after which the solution is maintained at 110 °C for several hours.

Scheme 25 Preparation of Hyperbranched Polyureas^[148,149]



Whereas the polymerization of the diisocyanate derived from 5-aminoisophthaloyl diazide (**89**) results in the formation of an insoluble product, the hyperbranched polymer **92** prepared by thermal decomposition of 3,5-diaminobenzoyl azide (**88**) is soluble in organic solvents such as dimethyl sulfoxide, 1-methylpyrrolidin-2-one, and dimethylformamide. The Fourier-transform infrared spectrum of polymer **92** indicates the complete disappearance of acyl azide and isocyanate groups and shows strong absorptions at 1656 and 3352 cm^{-1} , indicating the formation of urea linkages.^[148] First- and second-generation dendritic edges can be constructed by a step-by-step growth approach using the *tert*-butoxycarbonyl-protected diisocyanate generated by Curtius rearrangement of the protected diazide **90**.^[149]

3,5-Diaminobenzoyl Azide (**88**):^[149]

3,5-(BocHN)₂C₆H₃CON₃^[149] (**91**; 5 g, 13.3 mmol) was stirred with TFA (9 g, 79.0 mmol) in CH₂Cl₂ (100 mL) at rt for 24 h. A viscous oily layer separated out at the bottom of the flask when the reaction was over. The CH₂Cl₂ was decanted and the residual oily layer was washed with more CH₂Cl₂ and 1 M aq Na₂CO₃. The organic layer was separated, washed with H₂O, and dried (MgSO₄). CH₂Cl₂ was removed under reduced pressure at rt to yield a yellow solid. This was further purified by reprecipitation with petroleum ether from a soln in acetone to give a yellow crystalline material that was dried under reduced pressure at rt; yield: 1.8 g (76%); IR $\tilde{\nu}_{\text{max}}$: 2136 cm^{-1} .

Hyperbranched Polyurea **92** from 3,5-Diaminobenzoyl Azide (**88**):^[148,149]

3,5-Diaminobenzoyl azide (**88**; 1.8 g, 10.2 mmol) was heated to 110 °C in NMP (5 mL) for 2 h. The hyperbranched polymer was precipitated by H₂O, purified by reprecipitation with acetone from NMP soln, and dried under reduced pressure at 90 °C; yield: 1.5 g (90%); M_w (SEC): 19 500; IR $\tilde{\nu}_{\text{max}}$: 3352, 1656 cm^{-1} .

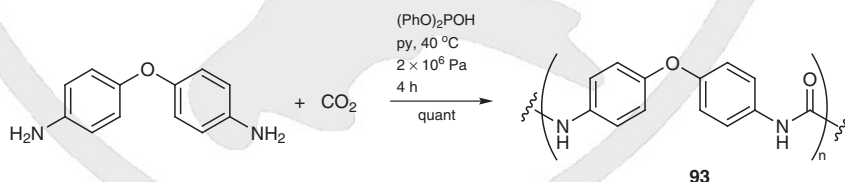
18.9.8.1.2

Method 2:

By Reaction of Diamines with Carbon Dioxide

Primary diamines react with carbon dioxide to give linear polyureas, e.g. **93**, only at high temperatures (ca. 200 °C) and pressures ($\geq 5 \times 10^7$ Pa).^[150] As such, the method is of little practical value, but the reaction temperature and pressure can be lowered considerably (optimal conditions 40 °C and 2×10^6 Pa) when the polycondensation of aromatic diamines with carbon dioxide is conducted in pyridine in the presence of diphenyl phosphite (Scheme 26).^[151] The reaction proceeds via the carbamoyloxy *N*-phosphonium salt of pyridine formed by dephenoxylation of the phosphite.

Scheme 26 Polycondensation of Carbon Dioxide with a Diamine^[151]



Similarly, the polycondensation of diamines with carbon dioxide is promoted by ethylene chlorophosphite in pyridine (ca. 50–60 °C, $2\text{--}2.5 \times 10^6$ Pa)^[152] as well as by triphenyl phosphite and pyridine hydrochloride in 1-methylpyrrolidin-2-one (ca. 60–80 °C, $4\text{--}5 \times 10^6$ Pa).^[153]

Polyurea 93 from Carbon Dioxide and 4,4'-Oxydianiline; Typical Procedure:^[152]

4,4'-Oxydianiline (2 g, 10 mmol) was added to dry pyridine (30 mL) in a 100-mL three-necked flask. 2-Chloro-1,3,2-dioxaphospholane (1.8 mL, 20 mmol) was then added with stirring and cooling. After stirring for 1 h at rt, the mixture was poured into a 300-mL autoclave. The flask was rinsed with dry pyridine (10 mL) and the resulting soln was also added to the autoclave. The reaction was carried out under a CO₂ pressure (2–2.5 × 10⁶ Pa) at 50–60 °C for 6–7 h. At the end of the reaction, the polymer obtained was precipitated with MeOH (300 mL), collected by filtration, and washed with MeOH (30–40 mL). The polyurea was then stirred for 1 h with H₂O, filtered, washed with H₂O (30–40 mL), and dried under vacuum at 60–80 °C; yield: 2.26 g (100% based on the amine); η_{inh} 1.10 dL·g⁻¹ (NMP, 20 °C).

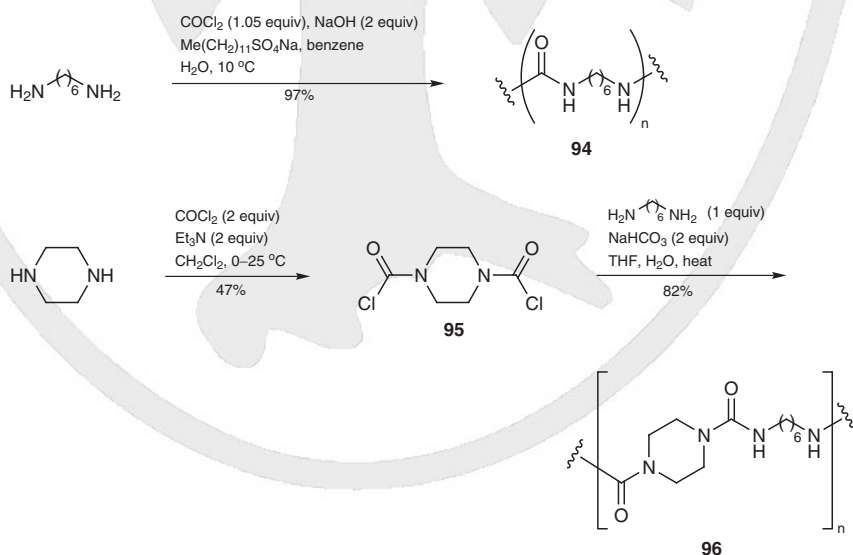
18.9.8.1.2.1

**Variation 1:
By Reaction of Diamines with Phosgene**

Aliphatic polyureas (e.g., **94**) can also be prepared by the polycondensation of diamines with phosgene (Scheme 27).^[154,155] Polymerization is typically conducted at the interface between an organic solution containing phosgene and an aqueous solution of a diamine with sodium hydroxide or sodium bicarbonate to neutralize the hydrogen chloride formed during the reaction. The temperature has a strong influence on both the yield and the molecular weight of the polymer, and low temperatures (<10 °C) are recommended.^[155]

SAFETY: Phosgene is known to be a highly toxic gas. Trichloromethyl chloroformate (diphosgene) and bis(trichloromethyl) carbonate (triphosgene) are safer alternatives, but decompose to liberate phosgene. Proper safety precautions should be taken during the preparation, storage, and handling of phosgene.

Alternatively, secondary diamines can be treated with 2 equivalents of phosgene to give the corresponding biscarbamoyl chloride (e.g., **95**), which can further react with primary or secondary diamines under interfacial conditions to yield homopolyureas and copolyureas (e.g., **96**) (Scheme 27).^[156,157]

Scheme 27 Reactions of Diamines with Phosgene^[154,157]

Polyurea 94 from Phosgene and Hexane-1,6-diamine by Interfacial Polycondensation; Typical Procedure:^[154]

CAUTION: Phosgene is a severe respiratory irritant and very toxic by inhalation.

Benzene (152 mL) (**CAUTION:** carcinogen), H₂O (150 mL), NaOH (4 g, 100 mmol), Me(CH₂)₁₁-SO₄Na (Duponol ME, DuPont) (1.5 g, 5.2 mmol), and H₂N(CH₂)₆NH₂ (5.8 g, 49.9 mmol) were emulsified in a Waring blender with high-speed stirring. The emulsion was cooled to 10 °C and maintained at this temperature during the addition of a soln of COCl₂ (5.2 g, 53.1 mmol) in benzene (23 mL) over 1–2 min. The mixture was stirred for a further 10–15 min. After the stirring was stopped, the polymer and benzene separated from the mixture as a curd-like material. The mixture was boiled until all the benzene was removed. The polymer was then collected by filtration, washed with H₂O, dried in air overnight, and finally dried in a vacuum oven for 1 h at 80 °C; yield: 7 g (97%); η_{inh} 0.55 dL·g⁻¹ (c 0.5 g·dL⁻¹, *m*-cresol, 25 °C).

Piperazine-1,4-dicarbonyl Dichloride (95):^[157]

CAUTION: Phosgene is a severe respiratory irritant and very toxic by inhalation.

A soln of piperazine (51.6 g, 0.6 mol) and Et₃N (203 g, 2 mol) in CH₂Cl₂ (200 mL) was added dropwise to a soln of COCl₂ (150 g, 1.5 mol) in CH₂Cl₂ (900 mL) in a heat-resistant glass flask, equipped with a stirrer, dropping funnel, and thermometer, while the temperature was maintained at 0–5 °C. When the addition was completed, the mixture was allowed to warm to rt and then filtered. The filtrate was poured into a separating funnel and washed with ice water (3 × 200 mL). The organic layer was separated from the aqueous layers, dried (CaCl₂), and concentrated to leave a solid residue that was recrystallized (toluene); yield: 60 g (47%); mp 151–154 °C.

Polyurea 96 from Piperazine-1,4-dicarbonyl Dichloride (95) and Hexane-1,6-diamine:^[157]

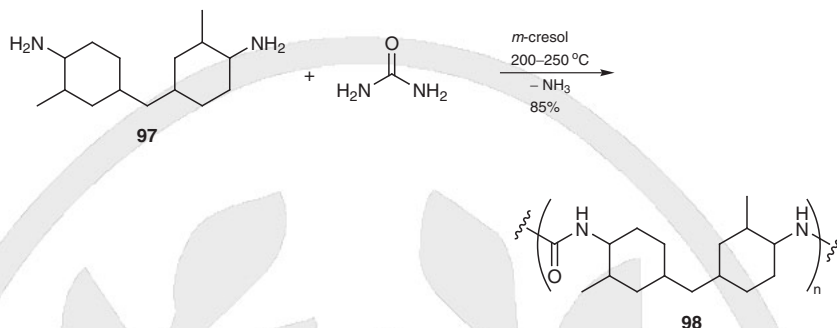
A soln of H₂N(CH₂)₆NH₂ (1.16 g, 10 mmol) and NaHCO₃ (2.23 g, 27 mmol) in H₂O (15 mL) was added to a soln of piperazine-1,4-dicarbonyl dichloride (**95**; 2.11 g, 10 mmol) in THF (35 mL) in a heat-resistant glass flask equipped with a stirrer, dropping funnel, thermometer, and reflux condenser. The mixture was refluxed for 90 min with continuous stirring and then poured into a mechanical blender containing H₂O (300 mL). The precipitate that formed was washed in the blender with H₂O (3 × 300 mL) and then dried by heating at 100 °C for 24 h under reduced pressure (5 Torr); yield: 2.1 g (82%); η_{red} 0.85 dL·g⁻¹ (c 0.2 g·dL⁻¹, 4-chlorophenol, 25 °C); mp 230 °C.

18.9.8.1.2.2

Variation 2:

By Reaction of Diamines with Urea

One of the earliest and simplest methods for the preparation of polyureas, e.g. **98**, consists of the reaction of stoichiometrically equal amounts of urea and an aliphatic amine, e.g. **97**, by heating, typically at 130–250 °C, in an oxygen-free atmosphere (Scheme 28).^[127,128] The polycondensation proceeds in two steps with liberation of ammonia and the initial formation of an ω -aminoalkyl urea at below 180 °C.^[123] Polymerization is then achieved by increasing the temperature to approximately 250 °C. The course of the reaction can be monitored by the quantitative determination of the liberated ammonia. The polymerization can be conducted in the melt^[127] or in various solvents (phenol, *m*-cresol,^[158] or 1-methylpyrrolidin-2-one^[159]).

Scheme 28 Reaction of a Diamine with Urea^[158]

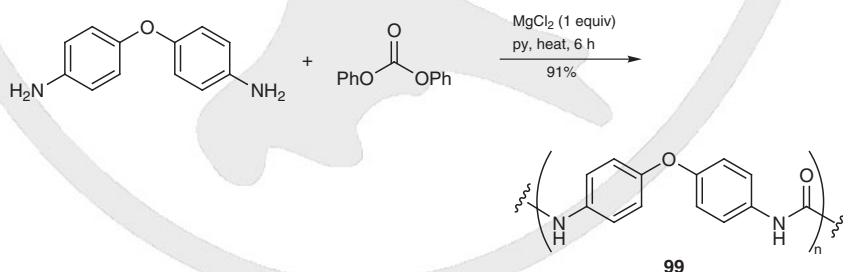
Polyurea 98 from 4,4'-Methylenebis(2-methylcyclohexanamine) (97**) and Urea; Typical Procedure:**^[158]

4,4'-Methylenebis(2-methylcyclohexanamine) (**97**; 238 g, 1 mol) and urea (60 g, 1 mol) were added to *m*-cresol (2500 g) in a stainless-steel reaction vessel provided with a stirrer. The mixture was heated gradually to 200 °C under N_2 . After 3 h, the temperature was raised to 250 °C and the reaction was continued for another 2 h. During this time, *m*-cresol (2000 g) and liberated NH_3 were distilled off. The residual viscous soln was cooled, and then poured with stirring into MeOH (12.6 L). The polyurea deposited in the form of flakes, which were collected by filtration, washed several times with boiling MeOH, and dried; yield: 225 g (85%); relative viscosity (η_r) 1.40 g·dL⁻¹ (c 1 g·dL⁻¹, *m*-cresol, 20 °C); mp 260–270 °C.

18.9.8.1.2.3

**Variation 3:
By Reaction of Diamines with Dicarbonates**

Aliphatic diamines and carbonic esters, such as dibutyl carbonate or diphenyl carbonate, react at high temperatures to give polyureas. Various conditions can be used, including reaction in the melt at 200–240 °C,^[160] in *m*-cresol at 215 °C,^[161] or in dimethylacetamide at 150 °C.^[162] Metal chlorides (e.g., MgCl_2) promote the polycondensation of diphenyl carbonate with aromatic and aliphatic diamines under milder conditions, i.e. in refluxing pyridine, to give polyureas (e.g., **99**) in good yields (Scheme 29).^[163] 4,4'-Oxydianiline also undergoes a polycondensation with alkali metal carbonates (e.g., lithium carbonate) in the presence of triphenylphosphine and polyhalo compounds (e.g., hexachloroethane) in pyridine at 80 °C.^[164]

Scheme 29 Polycondensation of Diphenyl Carbonate with a Diamine^[163]

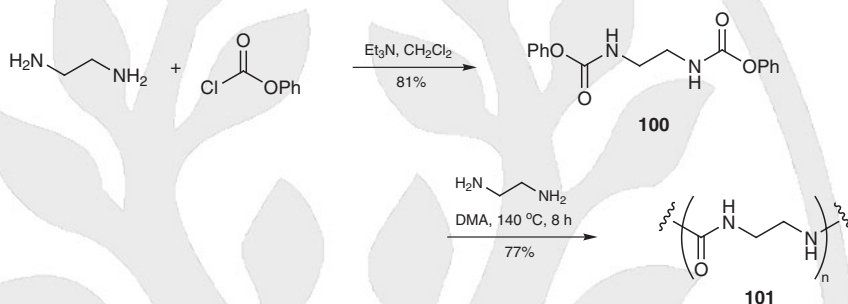
Polyurea 99 from Diphenyl Carbonate and 4,4'-Oxydianiline; Typical Procedure:^[163]

An equimolar mixture of $(\text{PhO})_2\text{CO}$ (2.14 g, 10 mmol) and $(4-\text{H}_2\text{NC}_6\text{H}_4)_2\text{O}$ (2.00 g, 10 mmol) was refluxed for 6 h in pyridine (40 mL) containing MgCl_2 (952 mg, 10 mmol). The mixture was poured into MeOH and the polymer that precipitated was collected by filtration, washed with boiling MeOH, and dried; yield: 2.08 g (91%); η_{inh} 0.44 dL·g⁻¹ (HMPA, 30 °C).

18.9.8.1.2.4

Variation 4:**By Reaction of Diamines with Diurethanes**

An alternative procedure for the preparation of polyureas (e.g., **101**) involves the reaction of diamines with preformed diethyl or diphenyl diurethanes, e.g. **100** (Scheme 30).^[162,165,166] The reaction conditions (temperature and solvents) are similar to those reported for the polycondensation of dicarbonates with diamines (Section 18.9.8.1.2.3). Diurethanes are generally prepared by treatment of a diamine with 2 equivalents or more of the corresponding chloroformate.

Scheme 30 Polycondensation of a Diamine with a Diurethane^[162]**Diphenyl Ethylenebiscarbamate (100); Typical Procedure:**^[162]

An ice-cold mixture of ethylenediamine (18 g, 0.3 mol) and Et_3N (85 mL, 0.6 mol) dissolved in CH_2Cl_2 (200 mL) was added dropwise to a soln of ClCO_2Ph (95 g, 0.609 mol) in CH_2Cl_2 . When the addition was complete, the mixture was diluted with CH_2Cl_2 (200 mL) and THF (200 mL) and washed with 1 M HCl (2×300 mL). The organic phase was dried (Na_2SO_4). The soln was concentrated under reduced pressure and the product was crystallized by addition of CCl_4 (**CAUTION: toxic**) and cooling in ice; yield: 73 g (81%); mp 199–201 °C.

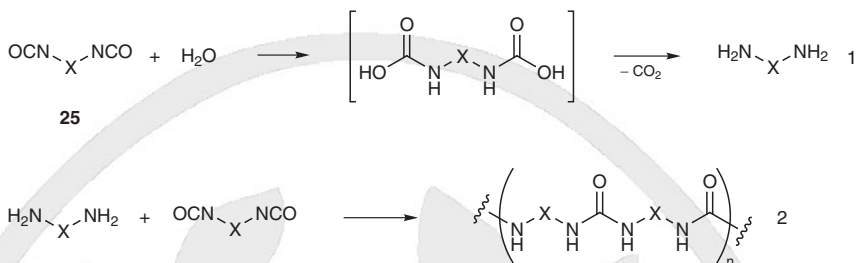
Polyurea 101 from Diphenyl Ethylenebiscarbamate (100) and Ethylenediamine;**Typical Procedure:**^[162]

Diphenyl ethylenebiscarbamate (**100**; 30 g, 0.1 mol) and ethylenediamine (6.0 g, 0.1 mol) were heated with stirring in DMA (150 mL) at 140 °C for 8 h. The mixture was then poured into EtOH (1 L) and the precipitated polymer was collected by filtration. The isolated polyurea **101** was refluxed under stirring with dioxane (500 mL), filtered again, and dried at 80 °C (0.075 Torr); yield: 13.55 g (78%); ^{13}C NMR (TFA, δ): 160.89 (CO), 41.00 (CH_2).

18.9.8.1.3

Method 3:**By Reaction of Polyisocyanates with Water**

Polyurea foams of relatively low density can be prepared by the reaction of polyfunctional isocyanates with water; the carbon dioxide that is evolved during the reaction acts as a foaming agent (Scheme 31).^[167,168] Reactions (1) and (2) correspond to the foaming and polymerization steps, respectively. The reaction of the isocyanate with water is complex, and can involve two possible mechanisms, depending on the stability of the intermediate carbamic acid.^[169] The isocyanate–water reaction is catalyzed by 2-methylimidazole,^[168] by tertiary amines,^[170] by a combination of tertiary amines,^[171] and by copper(II) or zinc(II) salts, as well as by tin catalysts. The use of a cosolvent (dioxane, dimethylformamide, 1-methylpyrrolidin-2-one) improves the homogeneity of the reaction medium and has a favorable effect on the catalysis.^[170] Tris(2-chloroethyl) phosphate is generally incorporated into the formulation to improve the flame resistance of the polyurea foam.^[168,170]

Scheme 31 Reaction of Diisocyanates with Water^[170]**Polyurea Foam from Crude 1,1'-Methylenebis(4-isocyanatobenzene) and Water;****Typical Procedure:**^[168]

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

Crude 1,1'-Methylenebis(4-isocyanatobenzene) (MDI; 100 g) containing approximately 55% of methylenebis(4-isocyanatobenzene) isomers and having an NCO content of 29.2% was mixed with $[\text{Cl}(\text{CH}_2)_2\text{O}]_3\text{P}=\text{O}$ (45 g, 0.157 mol). A soln of imidazole (6 g, 88 mmol) in H_2O (20 mL, 1.11 mol) was added with stirring. The cream time was 12 s. The foam rose completely in 60 s and the product was an open-celled, scorch-free foam with a satisfactory texture and a density of $7\text{--}8\text{ kg}\cdot\text{m}^{-3}$. The amount of H_2O used was approximately 3.2 equiv per equiv of isocyanate.

A similar result was obtained when imidazole was replaced by 2-methylimidazole (4 g, 49 mmol) or by 1,2-dimethylimidazole (2 g, 20 mmol).

18.9.8.1.4

Method 4:**By Cationic Ring-Opening Polymerization of Polycyclic Pseudoureas**

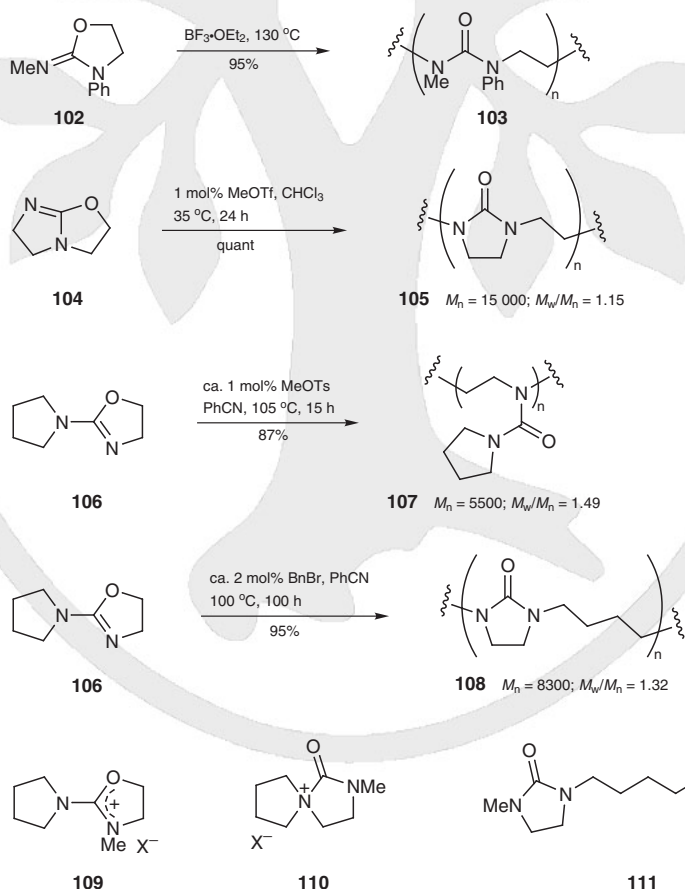
Cyclic compounds containing a 1,3-oxaza group, such as endocyclic imino ethers (e.g., dihydro-1,3-oxazoles) and compounds with *exo*-imino bonds, undergo cationic ring-opening isomerization and polymerization in the presence of a variety of initiators, including Lewis acids, protic acids (sulfuric acid), sulfonate esters, or alkyl halides.^[172,173] Urea-based polymers are produced by the ring-opening polymerization of such cyclic pseudoureas (Scheme 32).^[173–175] Cationic polymerization of *exo*-cyclic pseudoureas (e.g., **102** and **104**) yields polyethyleneureas, e.g. **103** and **105**.^[174,176] Polycyclic pseudoureas (e.g., **104**) are much more reactive toward ring-opening polymerization, owing to the additional ring strain. In the presence of an alkyl sulfonate initiator, the polymerization of 2,3,5,6-tetrahydroimidazo[2,1-*b*][1,3]oxazole (**104**) proceeds even at 0°C in a nonpolar solvent to give polyurea **105** quantitatively. The agreement between the measured and calculated number-average molecular weight, the narrow molecular-weight distributions, and postpolymerization experiments suggest that polymerization has a living character when it is conducted in the presence of methyl trifluoromethanesulfonate in chloroform. Polymer **105**, which is highly crystalline, is thermally stable up to 405°C in air (5% weight loss in thermogravimetric analysis) and is soluble in both chloroform and water.^[177]

Similarly, *endo*-cyclic pseudoureas (e.g., **106**) undergo isomerization polymerization (also known as “single isomerization polymerization” or SIP) at 80°C in benzonitrile and in the presence of an alkyl sulfonate initiator, a trifluoromethanesulfonate, or methyl 4-toluenesulfonate, to produce pendent-type polymers such as **107** (Scheme 32).^[175] The number-average molecular weights of the products are in the range 730–5500. The preparation of high-molecular-weight polymer is hindered by steric disturbance from the 2-sub-

stituent during the polymerization. Interestingly, when the initiator is an alkyl halide (iodomethane, benzyl bromide, or benzyl chloride), an alternative mode of cationic ring-opening polymerization occurs. This process, termed “double isomerization polymerization” (DIP), yields a polymer consisting of 1,3-imidazolidinone recurring units (e.g., **108**) (Scheme 32).^[175] Polymers **107** and **108** are characterized by different carbonyl absorptions in their infrared spectra, the carbonyl stretching frequency of the five-membered imidazolidin-2-one structure in **108** appearing at a higher wavenumber than that of the linear urea in **107** (1676 versus 1622 cm⁻¹, respectively). The mechanisms of polymerization leading to polyureas **107** and **108** initially involve the formation of a 3-methyl-2-pyrrolidino-2-oxazolinium salt **109**. The ring-opening reaction of the oxazolinium through the nucleophilic attack of pyrrolidinooxazolinium salt **109** produces the propagating species. With the sulfonate initiator, the nucleophilicity of the sulfonate counterion is too weak to interfere with propagation; however, when the initiator is an alkyl halide, the oxazolinium ring is opened by the nucleophilic attack of the halide counteranion and rearranges to a spiro-ammonium-type compound **110** that can undergo an attack by the counterion or by the monomer at the pyrrolidine ring to generate the oxazolinium propagating species **111** (Scheme 32).^[175]

Related six-membered cyclic pseudoureas (2-amino-5,6-dihydro-4*H*-1,3-oxazines) display a similar reactivity in both SIP and DIP;^[178] however, cationic polymerization of the corresponding seven-membered ring, 2-amino-4,5,6,7-tetrahydro-4*H*-1,3-oxazepine, is limited to conventional isomerization ring-opening polymerization.^[178]

Scheme 32 Cationic Ring-Opening Polymerization of Polycyclic Pseudoureas^[174,175]



2,3,5,6-Tetrahydroimidazo[2,1-*b*][1,3]oxazole (104):^[177]

All operations were carried out under N₂. A stirrer bar and 60% NaH/mineral oil suspension (0.88 g, 15 mmol) was placed in a 50-mL three-necked flask equipped with a dropping funnel, a three-way stopcock, and a thermometer. The flask was immersed in an ice bath, and DME (15 mL) was added with stirring. 1-(2-Chloroethyl)-2-imidazolidinone (1 g, 6.73 mmol) dissolved in DME (10 mL) was added dropwise to the suspension and the mixture was stirred for 2 h while the temperature was maintained below 5 °C. The mixture was stirred at 30 °C for an additional 14 h and then the supernatant layer was decanted and concentrated under reduced pressure. Vacuum distillation of the residue in the presence of CaH₂ gave a white waxy solid; yield: 0.48 g (63%); mp 56.1 °C; bp 60 °C/1.9 Torr (Kugelrohr).

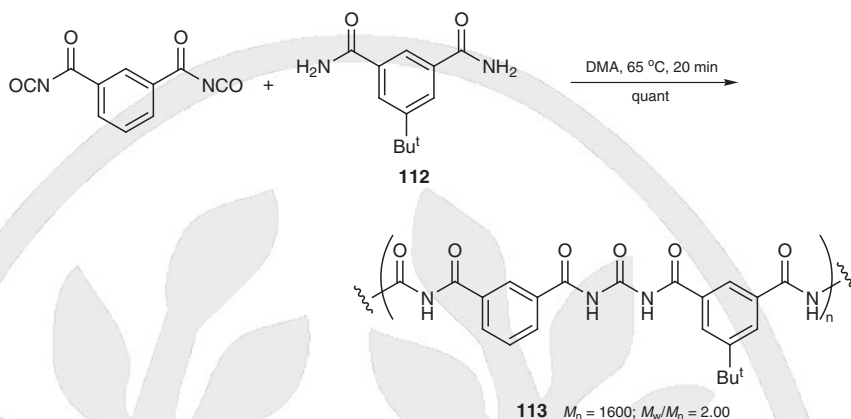
Polyurea 105 from 2,3,5,6-Tetrahydroimidazo[2,1-*b*][1,3]oxazole (104);**Typical Procedure:**^[176]

A test tube equipped with a three-way stopcock and a stirrer bar was dried in vacuum and charged with N₂. The monomer **104** (0.112 g, 1 mmol) dissolved in CHCl₃ (0.9 mL) was introduced into the tube under N₂ by means of a syringe. The soln was cooled at 0 °C, and MeOTf (0.012 mL, 0.10 mmol) dissolved in CHCl₃ (0.1 mL) was added under N₂ from a micro-syringe with stirring. The mixture was allowed to react at 35 °C for 24 h with stirring, then poured into Et₂O (25 mL) to obtain the polymer, which was purified further by reprecipitation from CHCl₃ (2 mL) in Et₂O (25 mL). The polymer was isolated by decantation, washed with Et₂O (10 mL), and dried in a desiccator under reduced pressure for 2 d; yield: 0.114 g (quant); *M_n* 15 000; polydispersity index: 1.15 (gel-permeation chromatography).

18.9.8.1.5

Method 5:**Poly(*N,N'*-diacylureas) by Polyaddition of Diamides to
Bis(*N*-acyl isocyanates)**

Isocyanates such as *N*-acyl isocyanates that bear electron-withdrawing groups on the nitrogen atom are much more reactive than other isocyanates towards nucleophiles. *N*-Acyl isocyanates can react with primary and secondary amides. For example, *N*-benzoyl isocyanate reacts with benzamide at room temperature to give *N,N'*-dibenzoylurea in 30% yield. Alternatively, the reaction of *N*-benzoyl isocyanate with 4-*tert*-butylbenzamide at 65 °C in tetrahydrofuran affords the corresponding diacylurea in quantitative yield after 20 minutes.^[179] By extension, polyaddition of bis(*N*-acyl isocyanates) with diamides (e.g., **112**) results in the formation of ether-insoluble poly(*N,N'*-diacylureas) having —CONHCONHCO— repeating units (e.g., **113**) (Scheme 33).^[179] The polymerization reaction is typically conducted in dimethylacetamide at 65 °C or in refluxing tetrahydrofuran. Number-average molecular weights (*M_n*) are in the range 1600–4700, the higher *M_n* values being obtained for poly(*N,N'*-diacylureas) from aliphatic diamides. The infrared spectra of the resulting polymers typically show carbonyl absorptions at 1674 (*N*-acyl group) and 1771 cm^{−1} (central carbonyl of the urea group).

Scheme 33 Preparation of a Poly(*N,N'*-diacylurea)^[179]

Poly(*N,N'*-diacylurea) 113 from Isophthaloyl Diisocyanide and 5-*tert*-Butylisophthalamide (112):^[179]

Isophthaloyl diisocyanate (108 mg, 0.5 mmol), 5-*tert*-butylisophthalamide (**112**; 110 mg, 0.5 mmol) and dried DMA (1 mL) were added under argon to a 20-mL, round-bottomed flask containing a magnetic stirring bar. The mixture was heated at 65 °C for 20 min with stirring, then poured into Et₂O (20 mL) to precipitate the polymer, which was isolated by filtration and dried under reduced pressure; yield: 228 mg (quant); M_n 1600; polydispersity index: 2.00.

18.9.8.2

Applications of Product Subclass 8 in Organic Synthesis

18.9.8.2.1

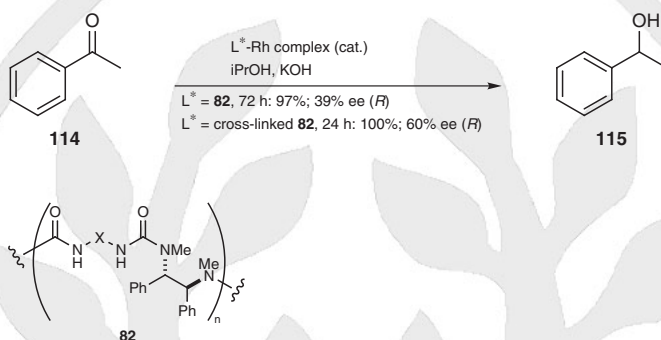
Method 1:**Hydrogenation and Hydrogen-Transfer Reduction**

Insoluble chiral polyurea–rhodium complexes can be used as catalysts in the reduction of acetophenone (**114**) by hydrogen transfer, e.g. to give phenylethanol **115** (Scheme 34).^[137] Chiral polyureas [e.g., **82** (X = 4,4'-diphenylmethyl)] are synthesized in solution by polyaddition of aliphatic or aromatic diisocyanates to C₂-symmetric chiral diamine units, including (1*R*,2*R*)-(+)-*N,N'*-dimethyl-1,2-diphenylethylenediamine, (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine, and (1*S*,2*S*)-(+)-1,2-diaminocyclohexane. The rhodium complexes are prepared by treating a slurry of the polymer with bis(1,5-cyclooctadiene)dirhodium(I) dichloride in propan-2-ol. The best results are obtained with a cross-linked analogue of **82** (X = 4,4'-diphenylmethyl), obtained by using an excess of crude 1,1'-methylenebis(4-isocyanatobenzene) (MDI), which consists of a mixture of diisocyanates and various triisocyanates. The rigidity of the active site therefore appears to be crucial for the selectivity of the catalytic system. The polyurea–rhodium complex derived from cross-linked polyurea **82** is readily separated by filtration at the end of the reaction and can be reused twice without a loss of selectivity or activity. Elemental analysis of the polymer reveals no leaching of the metal content of the catalyst.

Polyureas of pseudo C₂ symmetry incorporating 1,1'-binaphthalene-2,2'-diylbis(diphenylphosphine) (BINAP) group in the main chain can be prepared by the reaction of [2,2'-bis(diphenylphosphino)-1,1'-binaphthalene-6,6'-diyl]dimethanamine [6,6'-bis(amino-methyl)-BINAP] with various diisocyanates, including 1,1'-methylenebis(4-isocyanatobenzene) and 2,6-diisocyanatotoluene.^[180,181] The corresponding ruthenium complexes can be used in the asymmetric hydrogenation of various compounds, including methyl acetoacetate in methanol at 50 °C with a hydrogen pressure of 4 MPa and a substrate/catalyst ratio of 1000.^[180,181] The polyurea–ruthenium complex derived from 2,6-diisocyanatotoluene

gives the best results, with a 100% conversion and 99% ee after recycling four times. When used in ruthenium-catalyzed hydrogenation of alkenic substrates, these polyurea-based ligands give results similar to those obtained with a monomeric BINAP complex equivalent.^[181]

Scheme 34 Hydride-Transfer Reduction of Acetophenone Catalyzed by Chiral Polyurea–Rhodium Complexes^[137]



(*R*)-1-Phenylethanol (115) by Reduction of Acetophenone (114); Typical Procedure:^[137]

A slurry of the cross-linked polyurea **82** [$X = 4,4'-(C_6H_4)_2CH_2$; 0.0127 mmol equiv diamine], $\{Rh(cod)Cl\}_2$ (0.00127 mmol), and KOH (0.0762 mmol) in *i*PrOH (4 mL) was stirred overnight at rt. Acetophenone (**114**; 30.5 mg, 0.254 mmol) was then added and the mixture was heated at 70 °C for 24 h. The polymer was separated by simple filtration; yield: 31 mg (100%); 60% ee.

18.9.8.2.2

Method 2:

Polyurea-Encapsulated Palladium as a Catalyst

Microencapsulation is an attractive strategy for the immobilization of transition-metal-based catalysts, as it may allow effective recovery and reuse of the catalyst. Polyurea microcapsules (see Section 18.9.8.1.1) are suitable for ligating and thus retaining metal species such as palladium(II) acetate.^[138] Microcapsules with sizes ranging from 20 to 250 μm can be prepared by the in situ interfacial polymerization of the polymeric form of 1,1'-methylenebis(4-isocyanatobenzene) (PMDI) in the presence of palladium(II) acetate and a mixture of emulsifiers. The average palladium content in these polyurea microcapsules is 0.4 mmol/gram. Energy-dispersive X-ray analysis along a cross section of a sliced microcapsule shows an even distribution of palladium. Palladium(II) acetate microencapsulated in polyurea is an economical and versatile heterogeneous catalyst for a range of phosphine-free cross-coupling reactions (Heck reactions, Suzuki reactions, and Stille couplings),^[138,182] as well as for the hydrogenation of primary alkenes.^[183] The catalyst can be recovered by simple filtration and recycled up to four times. Similarly, a polyurea-encapsulated palladium(0) catalyst prepared by ligand exchange with formic acid is a highly efficient transfer hydrogenation catalyst for chemoselective reduction of a wide range of aryl ketones to the corresponding benzyl alcohols.^[184]

Polyurea-Microencapsulated Palladium(II) Acetate:^[138]

A mixture of $Pd(OAc)_2$ (5 g) and polymeric 1,1'-methylenebis(4-isocyanatobenzene) (PMDI; SUPRASEC 5025, average functionality 2.7, Huntsman ICI Polyurethane) (2.5 g) in 1,2-dichloroethane (70 mL) was stirred for 1 h at rt. The resulting dark soln was added at a constant rate to an aqueous mixture containing sodium lignosulfonate (Reax 100 M, Westvaco) (10 g), poly(oxypropylene-*co*-oxyethylene) butyl ether (Tergitol XD, Union Carbide) (2.5 g) and poly(vinyl alcohol) (Goshenol GL03, British Traders and Shippers) (5 g) in deion-

ized H₂O (250 mL) under shear from a Heidolph radial-flow impeller (50 mm, 800 rpm) for 2 min. The resulting oil-in-water emulsion was paddle-stirred at rt for 16 h. The polyurea microcapsules obtained were filtered through a polyethylene frit (20- μ m porosity), washed with deionized H₂O, acetone, EtOH, and Et₂O, and dried; particle size: 20–250 μ m; average Pd content (inductively coupled plasma analysis): 0.4 mmol·g⁻¹.

18.9.9 Product Subclass 9: Short-Chain Oligomers

Short-chain monodisperse oligomers are known as peptidomimetics. They are synthesized by a step-by-step approach using solution-phase, liquid-phase, or solid-phase methodologies. The elongation of the chain one monomer at a time allows a high degree of sequence control at the price of slow chain growth. By far the most studied oligomers are N,N'-linked oligoureas in which urea units are connected through ethylene bridges.^[185] Interestingly, enantiopure N,N'-linked oligoureas of general formula [NH—CHR—CH₂—NH—CO]_n bearing side chains of natural amino acids form well-defined helical secondary structures in solution.^[186] There are several approaches for the synthesis of these oligomers, all of which involve cycles of sequential acylation and amine deprotection of appropriately protected carbonyl synthons. The preparation of the activated monomers generally involves the reaction of a monoprotected diamine with carbonylating agents such as phosgene or 4-nitrophenyl chloroformate. The Curtius rearrangement of N-protected β -amino acyl azides is an alternative approach.^[187] Although elongation can be performed in solution, most of the synthetic procedures are elaborated on solid supports starting from {4-[(2,4-dimethoxyphenyl)aminomethyl]phenoxyethyl}polystyrene (Rink's amide resin).^[188] Azapeptides of general formula [NH—NR¹—CO]_n, also termed "azatides" can also be used as peptide backbone mimetics.^[189] They consist exclusively of α -azaamino acids and thus contain consecutive urea bonds. Activated monomers for stepwise elongation of the chain are prepared from N-protected N-alkylhydrazines and a carbonylating agent.

18.9.9.1 Synthesis of Product Subclass 9

18.9.9.1.1 Method 1: N,N'-Linked Oligoureas: Sequential Reaction of 1-Substituted 2-Phthalimidoethyl Isocyanates

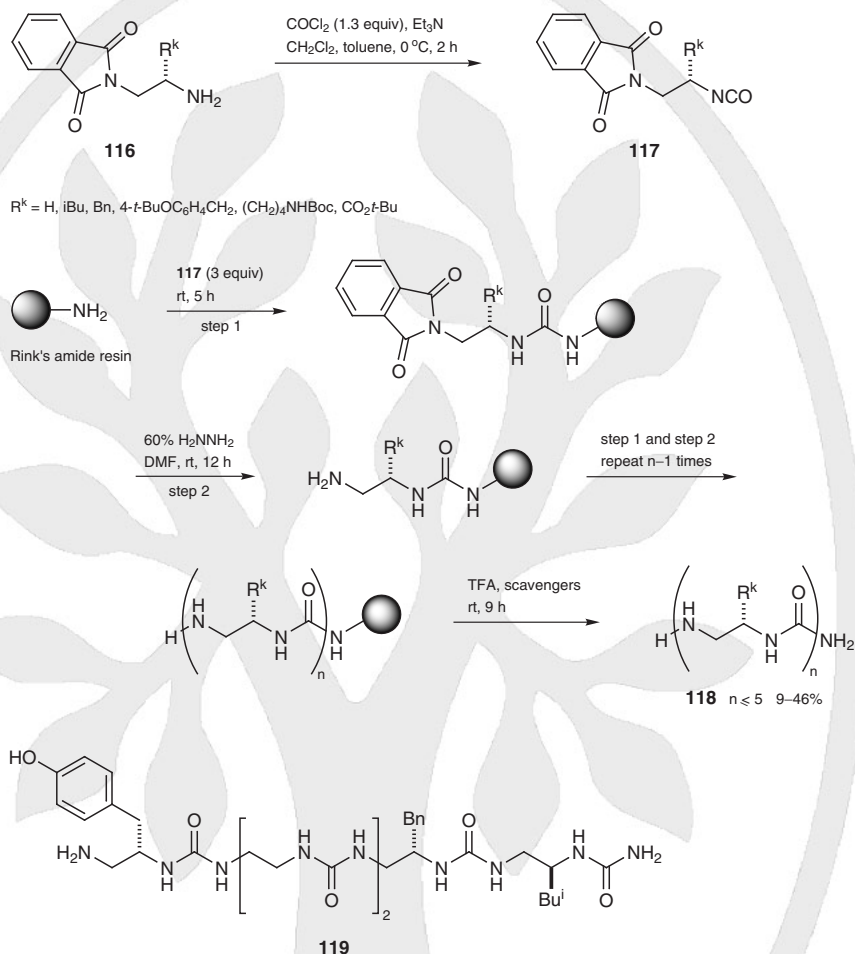
Burgess and co-workers' original synthetic route to N,N'-linked oligoureas is based on the use of 1-substituted 2-phthalimidoethyl isocyanates **117** as activated monomers (Scheme 35).^[185,190] The monophthalimido-protected diamine precursors **116** are readily prepared from N-butoxycarbonyl- or 9-fluorenylmethoxycarbonyl-protected β -amino alcohols in two steps (53–76% yield).^[190] Treatment of the monoprotected amines **116** with phosgene as the carbonylating reagent gives the isocyanates **117**, which can be used in the urea-formation reaction without further purification.

SAFETY: Phosgene is a highly toxic gas. Trichloromethyl chloroformate (diphosgene) and bis(trichloromethyl) carbonate (triphosgene) are safer alternatives, but decompose and liberate phosgene. Proper safety precautions should be taken during the preparation, storage, and handling of phosgene.

This procedure is sufficiently mild to be compatible with functionalized side chains of natural amino acids. Several repetitions of the urea formation/phthaloyl deprotection cycle followed by acidic cleavage of the resin affords oligomers **118** up to the pentamer (n = 5), e.g. **119**, in yields of 9–46% after purification by high-performance liquid chromatography. The main drawbacks of this methodology are the use of phosgene for the preparation of isocyanates **117**, the instability of activated monomers, which precludes stor-

age, and the long reaction times (>5 hours) required for optimal urea formation on the solid support.

Scheme 35 N,N'-Linked Oligoureas from 1-Substituted 2-Phthalimidoethyl Isocyanates^[185,190]



N,N'-Linked Oligourea Pentamer 119; Typical Procedure:^[185,190]

CAUTION: Phosgene is a severe respiratory irritant and very toxic by inhalation.

CAUTION: Hydrazine is flammable and its reaction with oxidants is violent. It is a severe skin and mucous membrane irritant and a possible human carcinogen.

The isocyanate **117** ($\text{R}^k = \text{iBu}$; $k = 1$) was prepared by treating a mixture of the amine **116** ($\text{R}^k = \text{iBu}$; $k = 1$; 0.6 mmol) and Et_3N (0.67 mL, 4.8 mmol) in CH_2Cl_2 (10 mL) with a 2 M soln of COCl_2 in toluene (0.39 mL) at 0°C for 2 h.

The remainder of the synthesis was carried out in a 30-mL vessel fitted with a coarse glass frit. Rink's amide resin^[188] (0.161 g, $0.62 \text{ mmol} \cdot \text{g}^{-1}$) was first swollen in DMF (10 mL) for 2 h and then treated with a soln of the isocyanate **117** ($\text{R}^k = \text{iBu}$, 6 equiv). The mixture was then shaken for 5 h and washed with DMF ($5 \times 10 \text{ mL}$, 1 min) and CH_2Cl_2 ($5 \times 10 \text{ mL}$, 1 min). The phthaloyl group was removed by shaking the resin with 60% $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$ /DMF (5 mL) for 12 h and the resin was washed again using the same washing cycle.

Cycles of urea formation with **117** [$R^k = \text{Bn, H, H, and } 4\text{-}t\text{-BuOC}_6\text{H}_4\text{CH}_2$, sequentially] with intervening phthaloyl deprotection cycles were then performed in the same manner. After removal of the final phthaloyl protecting group, the resin was washed thoroughly with DMF and CH_2Cl_2 and dried under a high vacuum. The oligourea was cleaved from the resin by treatment with 5:2.5:1.5:81.5 (by volume) $\text{PhOH/HS(CH}_2)_2\text{SH/PhSMe/H}_2\text{O/TFA}$ (5 mL) at 25°C for 9 h. The resin was filtered and washed with TFA (5 mL) and the filtrate was concentrated and diluted with H_2O . The resulting aqueous soln was washed with Et_2O ($2 \times 5\text{ mL}$) and lyophilized. The crude product was purified by reverse-phase HPLC (C_{18} ; $10\text{ }\mu\text{m}$; $22 \times 250\text{ mm}$; linear gradient 30–35% B; A = 0.1% aq TFA, B = 0.08% TFA/MeCN; $1.2\text{ mL}\cdot\text{min}^{-1}$). The peak with an elution time of 19.3 min was collected and lyophilized to afford the product as a white powder; yield: 15 mg (21%); MS (MALDI-TOF) m/z 700.4268 ($\text{M} + \text{H}^+$).

18.9.1.1.1

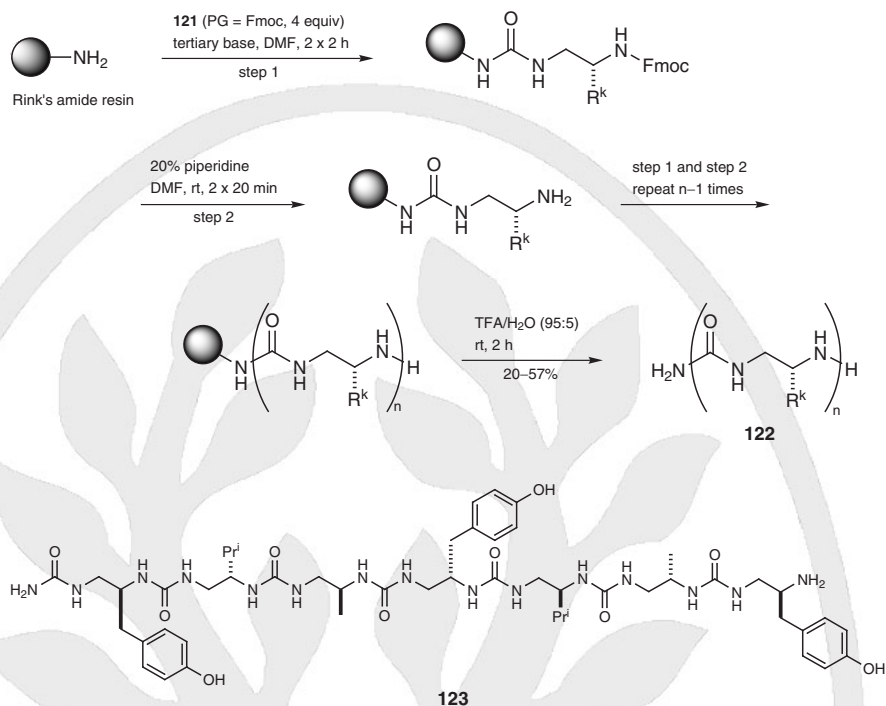
Variation 1:**Sequential Reaction of Activated Carbamates Derived from Monoprotected Diamines**

Reactive carbamate intermediates, including 4-nitrophenyl^[191,192] and succinimidyl^[187,193] carbamates, represent more appropriate building blocks for semi-automated and automated solid-phase syntheses. These activated derivatives react readily with primary and secondary amines to form substituted ureas, yet are stable enough to permit prolonged storage at 4°C for several months. The amino function of the monomer can be conveniently protected by a *tert*-butoxycarbonyl (Boc) or a 9-fluorenylmethoxycarbonyl (Fmoc) group, or masked as an azide. 4-Nitrophenylcarbamate derivatives **120** (Scheme 36) are obtained as solids from the corresponding amine by treatment with 4-nitrophenyl chloroformate. Alternatively, succinimidyl carbamate derivatives **121** (Scheme 36) are synthesized from the corresponding *N*-Boc- and *N*-Fmoc-protected β -amino acyl azides. The intermediate isocyanates generated by the Curtius rearrangement of the acyl azides are trapped with *N*-hydroxysuccinimide in the presence of pyridine to afford the expected carbamates as solids in moderate to good yields. Although attractive, this method requires the preparation of *N*-protected β -amino acids as starting materials. Solid-phase synthesis of oligoureas **122**, (e.g., **123**) up to the nonamer ($n = 9$) can be achieved when **121** (PG = Fmoc) is used (Scheme 36).^[193] Urea formation on a solid support proceeds with an excess of carbamate (3–5 equivalents) in the presence of *N,N*-diisopropylamine. When **121** (PG = Fmoc) is the reactive intermediate, the use of a weaker base such as *N*-methylmorpholine consistently gives better result (Scheme 36).

Scheme 36 Synthesis of *N,N'*-Linked Oligoureas from Activated Carbamate Derivatives^[187,191]



$R^k = \text{H, Me iPr, iBu, s-Bu, Bn, } 4\text{-}t\text{-BuOC}_6\text{H}_4\text{CH}_2, \text{CH}_2\text{O}t\text{-Bu, (CH}_2)_4\text{NHBoc, CO}_2t\text{-Bu}$; PG = Boc, Fmoc



N,N'-Linked Oligourea Heptamer 123; Typical Procedure:^[193]

The oligomeric chain was assembled in a multichannel automated peptide synthesizer on Rink's amide resin^[188] (0.6 mmol·g⁻¹, 60-μmol scale) by using *N*-Fmoc-protected monomers **121** ($R^k = 4\text{-}t\text{-BuOC}_6\text{H}_4\text{CH}_2$, Me, *i*Pr; PG = Fmoc). The monomer (4 equiv) was dissolved in DMF (1 mL) and added to the resin. *N*-methylmorpholine (6.6 μL, 1 equiv) was then added and the mixture was stirred by bubbling N₂ through it for 120 min. A double coupling was performed systematically. The reaction was monitored by using 2,4,6-trinitrobenzenesulfonic acid.^[194] The Fmoc group was removed with 20% piperidine/DMF. After the removal of the last Fmoc protecting group, the resin was washed with DMF (6 × 2 mL, 1 min), CH₂Cl₂ (3 × 2 mL, 1 min), and Et₂O (3 × 2 mL, 1 min), and then dried before cleavage with TFA/H₂O (95:5) for 2 h. After concentration under reduced pressure, the crude material was diluted with aq MeCN, lyophilized, and purified by reverse-phase HPLC (C₁₈, 5 μm, 3.9 × 150 mm; retention time 14.70 min; linear gradient of 5–65% B in 20 min, A = 0.1% aq TFA/H₂O, B = 0.08% TFA/MeCN; flow rate 1.2 mL·min⁻¹) to give a white powder; yield: 42 mg (60%); MS (MALDI-TOF) *m/z* 1051.48 (M+H)⁺, 1073.32 (M+Na)⁺.

18.9.9.1.1.2

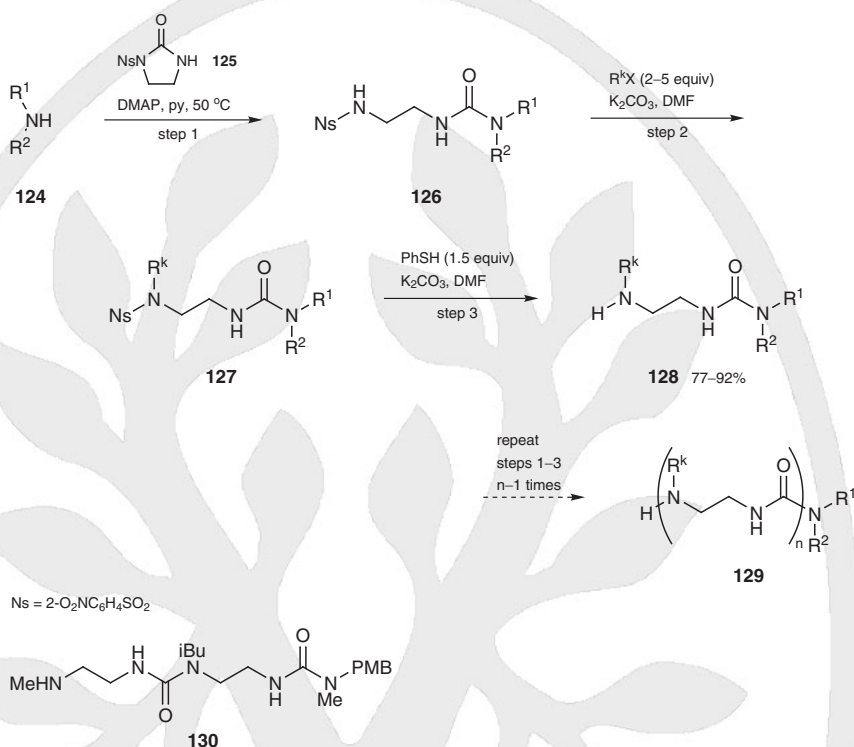
Variation 2:

Sequential Reaction of *N*-(2-Nitrobenzenesulfonyl)imidazolidinone

Alternatively, the oligourea main chain can be extended by ring-opening of 1-(2-nitrobenzenesulfonyl)imidazolidin-2-one (**125**) with a primary or a secondary amine **124** (Scheme 37).^[195] This process allows access to *N*-alkyl *N*,*N*'-linked oligoureas **129** of general formula [NR^kCH₂CH₂NHCO]_n, e.g. **130**. The overall synthesis is iterative and utilizes only two building blocks, the imidazolidone **125** and commercially available alkyl halides (R^kX), for the construction of each repeat unit ("the submonomer approach"). The method involves the repetition of three steps: main-chain extension, side-chain attachment, and deprotection. The side chain is constructed on the resulting sulfonamide **126** by Fukuyama's *N*-alkylation procedure, and the 2-nitrobenzenesulfonyl group in **127** is removed to reveal a secondary amine that is used in the next iteration to give *N*-alkyl *N*,*N*'-linked oligoureas **128**.

All chemical transformations proceed in high yields and the method should be readily adaptable to the solid phase.

Scheme 37 Sequential Reaction of *N*-(2-Nitrobenzenesulfonyl)imidazolidone^[195]



N-Alkyl N,N'-Linked Oligoureas 128; General Procedure:^[195]

A 0.4 M soln of a secondary amine **124**, 1-(2-nitrobenzenesulfonyl)imidazolidin-2-one (**125**; 1.2 equiv), and DMAP (0.5 equiv) in dry pyridine was stirred at 50 °C under N_2 for 4–6 h. The solvent was removed by rotary evaporation and the residue was dissolved in CH_2Cl_2 . The resulting soln was washed with 0.5 M aq HCl and dried (Na_2SO_4). The crude sulfonamide **126** was purified by column chromatography (silica gel). Alkylation was performed by treating a 0.4 M soln of the sulfonamide **126** in DMF with anhyd K_2CO_3 (2 equiv) and an alkyl halide R^kX (2–5 equiv) for between 1 h and 5 d. The solvent was removed and the residue was dissolved in CH_2Cl_2 . The resulting soln was washed with H_2O , dried (Na_2SO_4), and concentrated to afford the crude alkylated product **127**, which was purified by column chromatography (silica gel). The 2-nitrobenzenesulfonyl group was removed by treating a deoxygenated soln of the sulfonamide **127** in DMF containing K_2CO_3 (3 equiv) with PhSH (3 equiv) for 3–6 h. The soln was concentrated and the residue was dissolved in CH_2Cl_2 ; the resulting soln was washed with 1 M aq $NaHCO_3$ and dried (Na_2SO_4). The crude secondary amine was purified by column chromatography on silica gel. The chain was further elongated by repetition of this three-step sequence as often as was necessary.

18.9.9.1.2

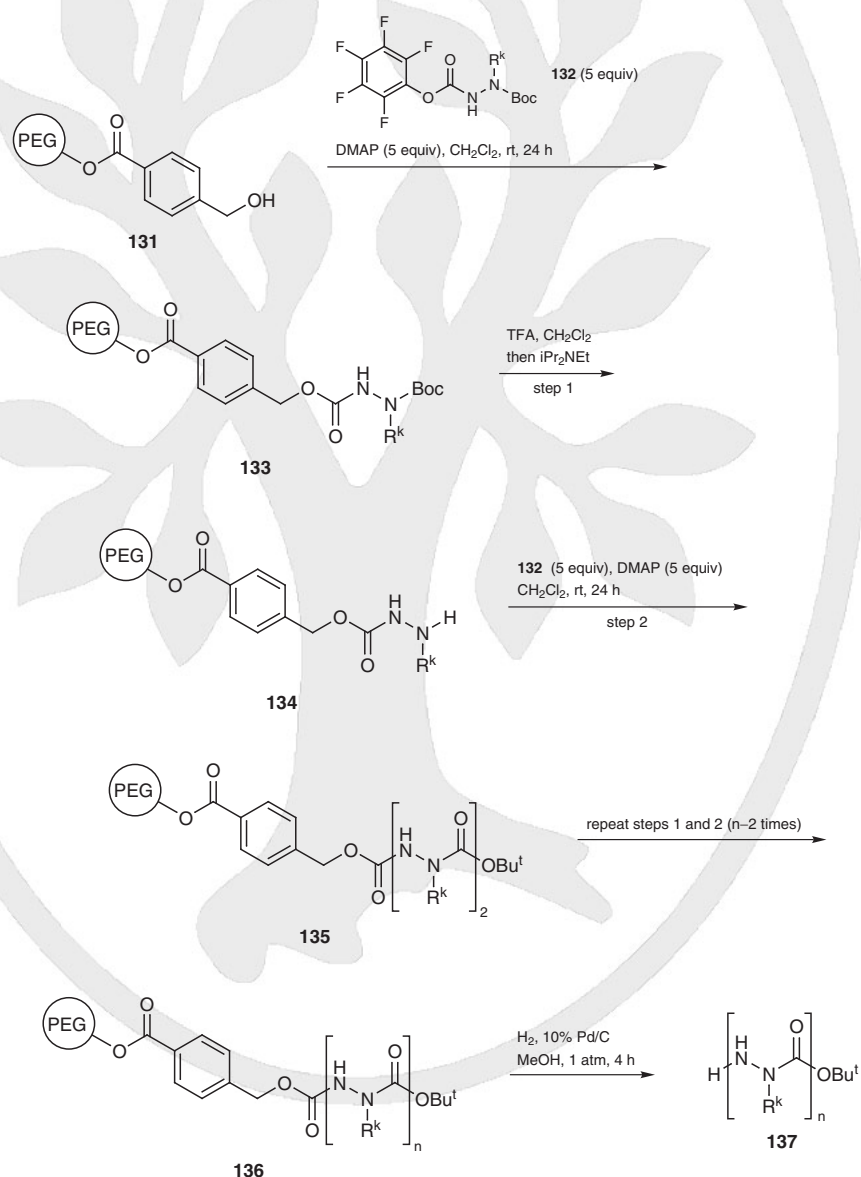
Method 2:

Azatides: Sequential Reaction of Activated N-Protected N-Alkylhydrazines

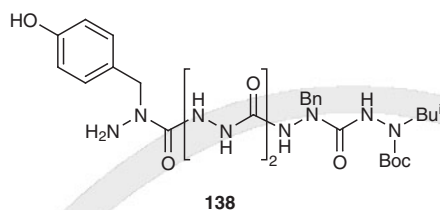
Oligomers of general formula $[NR^kNHCO]_n$ (**137**; azatides) are obtained by chain extension with reactive carbamates derived from N-protected N-alkylhydrazines (Scheme 38).^[189] Activation of hydrazine is challenging, as N-protected N-alkylhydrazines are poorer nucleo-

philes than simple amines. Coupling reactions with carbamates prepared with 4-nitrophenylchloroformate, 1,1'-carbonylbis-1*H*-imidazole, bis(2,4-dinitrophenyl) carbonate, or trichloromethyl chloroformate suffer from complicated side reactions, poor yields, and prolonged reaction times. Activation of *N*-protected *N*-alkylhydrazines as the corresponding carbamates **132** by treatment with bis(pentafluorophenyl) carbonate^[196] gives good results, whereas coupling through the corresponding activated *N*-protected *N*'-alkylhydrazines is not successful. The coupling reaction is believed to proceed via the corresponding isocyanate as a reactive intermediate. Iterative elongation of the chain up to the pentamer, e.g. **138**, is possible by polymer-supported liquid-phase synthesis with poly(ethylene glycol) monomethyl ether as the soluble linear homopolymer (Scheme 38).

Scheme 38 Iterative Synthesis of Azatides^[189]



PEG = polyethylene glycol; n = iteration number; R^k = H, iBu, Bn, 4-BnOC₆H₄CH₂

**Azatide Pentamer 138; Typical Procedure:**^[189]

A mixture of the polymer-supported ester **131** (195 mg, 38 mmol), the pentafluorophenyl carbamate **132** ($R^k = 4\text{-BnOC}_6\text{H}_4\text{CH}_2$, 102 mg, 5 equiv), and DMAP (23.2 mg, 5 equiv) in CH_2Cl_2 (5 mL) was stirred at rt for 24 h. Et_2O was slowly added to this mixture to precipitate the Boc-protected product **133**. This was washed with EtOH and Et_2O then dried over P_2O_5 under a vacuum. The Boc protecting group was removed by treatment of **133** with TFA/ CH_2Cl_2 for 30 min. The trifluoroacetate salt of the hydrazide **134** was precipitated with Et_2O , washed with EtOH and Et_2O , and dried (P_2O_5) under a vacuum. After neutralization of the hydrazide **134** with $i\text{Pr}_2\text{NEt}$ (1 equiv), pentafluorophenyl carbamate **132** ($R^1 = \text{H}$; 5 equiv) and DMAP (5 equiv) were added and the mixture was stirred for 4 h. The polymeric product **135** was precipitated with Et_2O , washed with EtOH and Et_2O , and dried (P_2O_5) under a vacuum. Repetition of this cycle of deprotection, neutralization, and coupling with **132** ($R^1 = \text{H}$, Bn, and $i\text{Bu}$, sequentially) gave the polymer-linked azatide **136**; yield: 137 mg (32.4% from **131**). The polymer-linked azatide **136** was subjected to hydrogenolysis over 10% Pd/C (100 mg) in MeOH (5 mL) for 4 h. The residue was extracted with EtOH and purified by preparative TLC; yield: 13.25 mg (90.7%); MS (ESI⁺) m/z : 617 ($\text{M} + \text{H}$)⁺, 139 ($\text{M} + \text{Na}$)⁺.

18.9.10

**Product Subclass 10:
Organophosphorus Polymers**

Previously published information on organophosphorus polymers can be found in *Houben-Weyl*, Vol. E 20, pp 1758–1771, as well as in a monograph.^[197]

18.9.10.1


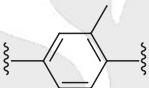
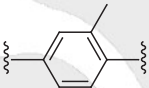
Synthesis of Product Subclass 10

18.9.10.1.1

**Method 1:
Condensation Reaction between Diisocyanates and
Substituted Phosphines and Phosphine Oxides**

Polymers containing $\text{P}-\text{C}(=\text{O})-\text{N}$ or $\text{P}-\text{C}(=\text{O})-\text{P}$ linkages are rarely encountered in the literature. Linear polymeric organophosphorus compounds **140** are obtained in high yields by condensation of tertiary phosphines or phosphine oxides **139** with aromatic or aliphatic diisocyanates **25** (Table 4).^[198] The reaction is catalyzed by tertiary amines such as triethylenediamine, trimethylamine, tributylamine, and *N*-ethylmorpholine. Among other possible catalysts are dibutyltin diacetate and dibutyltin dilaurate. The polymers obtained have intrinsic viscosities ranging from 0.1 to about 3.0 at 30 °C and molecular weights in the range 1600–1 000 000, based on viscosity measurements. These polymers are potentially useful in textiles as burning or charring retardants.

Table 4 Preparation of Condensation Polymers of Tertiary Phosphines and Phosphine Oxides^[198]

$\text{R}^1\text{P}(\text{O})_n\text{H}_2 + \text{OCN}-\text{X}-\text{NCO} \longrightarrow \left[\text{NH}-\text{C}(=\text{O})-\text{P}(\text{O})_n-\text{C}(=\text{O})-\text{NH}-\text{X} \right]_m$							
139	25		140				
R ¹	n	X	Conditions	Ratio (139/25)	Yield ^a (%)	[η] (dL·g ⁻¹) ^{a,b}	Ref
(CH ₂) ₇ Me	0		DABCO (cat.), benzene, 80 °C	1:1	94	0.10	[198]
(CH ₂) ₇ Me	1		DABCO (cat.), benzene, 50 °C	1:1	80	n.r.	[198]
s-Bu	0		DABCO (cat.), benzene, rt	1:1	96	n.r.	[198]
Bn	1	(CH ₂) ₄	DABCO (cat.), DMF, 130 °C	1:2	n.r.	1.5	[198]
(CH ₂) ₇ Me	1	(CH ₂) ₅	Bu ₃ N (cat.), DMF, 165 °C	1:1	n.r.	1.8	[198]
Ph	0	(CH ₂) ₆	DABCO (cat.), THF, 60 °C	1:1	n.r.	0.5	[198]

^a n.r. = not reported.^b In DMF at 30 °C.

Polymer 140 [$n = 0$; $\text{R}^1 = (\text{CH}_2)_7\text{Me}$; $\text{X} = 1,4\text{-(2-MeC}_6\text{H}_3\text{)}$] from Octylphosphine and 2,4-Diisocyanatotoluene; Typical Example:^[198]

CAUTION: Isocyanates are highly toxic upon inhalation and ingestion. Long-term exposure to low levels of isocyanates causes respiratory irritation that can develop into permanent asthmatic-type symptoms.

2,4-Diisocyanatotoluene [**25**, $\text{X} = 1,4\text{-(2-MeC}_6\text{H}_3\text{)}$; 10.4 g, 60 mmol] was added dropwise with stirring to a soln of octylphosphine [**139**, $n = 0$; $\text{R}^1 = (\text{CH}_2)_7\text{Me}$; 8.7 g, 60 mmol] and DABCO (0.5 g, 4.46 mmol) in anhyd benzene (40 mL) (**CAUTION:** carcinogen) purged with N₂. A slightly exothermic reaction occurred and the soln began to thicken and form a viscous gummy solid. The soln was then refluxed for 5 h and the mixture was filtered; yield: 17.9 g (94%); mp 160–165 °C; [η] 0.10 dL·g⁻¹ (DMF, 30 °C).

References

- [1] Ulrich, H., *Chemistry and Technology of Isocyanates*, Wiley: Chichester, UK, (1996).
- [2] National Institute for Occupational Safety and Health, *Criteria for a Recommended Standard: Occupational Exposure to Diisocyanates: DHEW (NIOSH) Publication No. 78-215*, U.S. Department of Health, Education, and Welfare: Washington, DC, (1978); pp 1–139.
- [3] Bur, J.; Fetters, L. J., *Chem. Rev.*, (1976) **76**, 727.
- [4] Parodi, F., In *Comprehensive Polymer Science: The Synthesis, Characterization, Reactions & Applications of Polymers*, Allen, G.; Bevington, J. C., Eds; Pergamon: Oxford, (1989); Vol. 5, p 387.
- [5] Zhitinkina, A. K.; Shibanova, N. A.; Tarakanov, O. G., *Russ. Chem. Rev.*, (1985) **54**, 1104.
- [6] Shashoua, V. E., *J. Am. Chem. Soc.*, (1959) **81**, 3156.
- [7] Sobue, H.; Tabata, Y.; Hiraoka, M.; Oshima, K., *J. Polym. Sci., Part C: Polym. Symp.*, (1964), No. 4, 943.
- [8] Natta, G.; DiPietro, J.; Cambini, M., *Makromol. Chem.*, (1962) **56**, 200.
- [9] Tidswell, B. M.; Gilchrist, S. C., *Polymer*, (1980) **21**, 805.
- [10] Green, M. M.; Cheon, K.-S.; Yang, S.-Y.; Park, J.-W.; Swansburg, S.; Liu, W., *Acc. Chem. Res.*, (2001) **34**, 672.
- [11] Aharoni, S. M., *Macromolecules*, (1979) **12**, 94.
- [12] Mayer, S.; Zentel, R., *Prog. Polym. Sci.*, (2001) **26**, 1973.
- [13] Green, M. M.; Peterson, N.; Sato, T.; Teramoto, A.; Cook, R.; Lifson, S., *Science*, (1995) **268**, 1860.
- [14] Liou, K.; Khemani, K. C.; Wudl, F., *Macromolecules*, (1991) **24**, 2217.
- [15] Okamoto, Y.; Nagamura, Y.; Hatada, K.; Khatri, C.; Green, M. M., *Macromolecules*, (1992) **25**, 5536.
- [16] Lee, J.-S.; Ryu, S.-W., *Macromolecules*, (1999) **32**, 2085.
- [17] Shin, Y.-D.; Kim, S.-Y.; Ahn, J.-H.; Lee, J.-S., *Macromolecules*, (2001) **34**, 2408.
- [18] Gu, H.; Nakamura, Y.; Sato, T.; Teramoto, A.; Green, M. M.; Andreola, C.; Reidy, M. P.; Jha, S. K., *Macromolecules*, (1998) **31**, 6362.
- [19] Shin, Y.-D.; Kim, S.-Y.; Ahn, J.-H.; Lee, J.-S., *Macromolecules*, (2001) **34**, 5071.
- [20] Patten, T. E.; Novak, B. M., *J. Am. Chem. Soc.*, (1991) **113**, 5065.
- [21] Patten, T. E.; Novak, B. M., *Macromolecules*, (1993) **26**, 436.
- [22] Patten, T. E.; Novak, B. M., *J. Am. Chem. Soc.*, (1996) **118**, 1906.
- [23] Hoff, S.; Novak, B. M., *Macromolecules*, (1993) **26**, 4067.
- [24] Goodson, S. H.; Novak, B. M., *Macromolecules*, (2001) **34**, 3849.
- [25] Butler, G. B., In *Encyclopedia of Polymer Science and Engineering*, Mark, H. F.; Kroschwitz, J. I., Eds.; Wiley: New York, (1986); Vol. 4, p 543.
- [26] Beaman, R. G., US 3 048 566, (1962); *Chem. Abstr.*, (1963) **59**, 3968.
- [27] King, C., *J. Am. Chem. Soc.*, (1964) **86**, 437.
- [28] Iwakura, Y.; Uno, K.; Ichikawa, K., *J. Polym. Sci., Part A: Gen. Pap.*, (1964) **2**, 3387.
- [29] Oku, A.; Shono, T.; Oda, R., *Makromol. Chem.*, (1967) **100**, 224.
- [30] Corfield, G. C.; Crawshaw, A., *Chem. Commun.*, (1966), 86.
- [31] Corfield, G. C.; Crawshaw, A., *J. Macromol. Sci., Chem.*, (1971) **A5**, 3.
- [32] Butler, G. B.; Corfield, G. C., *J. Macromol. Sci., Chem.*, (1971) **A5**, 37.
- [33] Patten, T. E.; Novak, B. M., *Macromolecules*, (1996) **29**, 5882.
- [34] Juenge, E. J.; Francis, W. C., *J. Org. Chem.*, (1961) **26**, 3334.
- [35] Kogon, I. C., *J. Am. Chem. Soc.*, (1956) **78**, 4911.
- [36] Jones, I. J.; Savill, N. G., *J. Chem. Soc.*, (1957), 4392.
- [37] Tate, F. E. G.; Wild, J. H., GB 837 120, (1960); *Chem. Abstr.*, (1960) **54**, 122 732.
- [38] Herbstman, S., *J. Org. Chem.*, (1965) **30**, 1259.
- [39] Nambu, Y.; Endo, T., *J. Org. Chem.*, (1993) **58**, 1932.
- [40] Reymore, H. E.; Carleton, P. S.; Kolakowski, R. A.; Sayigh, A. A. R., *J. Cell. Plast.*, (1975) **11**, 328.
- [41] Samborska-Skowron, R.; Balas, A., *Polym. Adv. Technol.*, (2002) **13**, 653.
- [42] Merten, R., *Angew. Chem.*, (1971) **83**, 339; *Angew. Chem. Int. Ed. Engl.*, (1971) **10**, 294.
- [43] Gupta, P.; Nast, R.; Windemuth, E., US 3 996 223, (1976); *Chem. Abstr.*, (1976) **85**, 78 923.
- [44] Sandler, S. R., *J. Appl. Polym. Sci.*, (1967) **11**, 811.
- [45] Haggis, G. A., GB 1 146 661, (1966); *Chem. Abstr.*, (1970) **73**, 56 803.
- [46] Burkus, J., US 2 993 870, (1961); *Chem. Abstr.*, (1962) **56**, 25 153.
- [47] Patton, J. T.; Narayan, T., US 4 386 167, (1983); *Chem. Abstr.*, (1983) **99**, 39 295.
- [48] Haseyama, R.; Hayashi, K.; Kuroda, K.; Kano, T.; Sekido, T.; Nomura, H.; Shikai, K., US 5 159 045, (1992); *Chem. Abstr.*, (1992) **116**, 131 297.

- [49] Slack, W. E.; Kemp, H. T., II, US 5 905 151, (1999); *Chem. Abstr.*, (1995) **123**, 144 879.
- [50] Matsui, Y.; Goto, J., US 3 487 080, (1969); *Chem. Abstr.*, (1969) **71**, 126 091.
- [51] Farrissey, W. J., Jr.; Nashu, A.-M., US 3 954 684, (1976); *Chem. Abstr.*, (1976) **84**, 151 470.
- [52] Katz, L. E.; Barsa, A.; Tucker, B. W.; Grosso, P. V., US 5 691 440, (1997); *Chem. Abstr.*, (1998) **128**, 35 138.
- [53] Ewald, M.; Lomoelder, R.; Kohlstruck, S., US 6 452 003, (2002); *Chem. Abstr.*, (2002) **136**, 86 614.
- [54] Bock, M.; Pedain, J.; Slawyk, W., US 4 288 586, (1981); *Chem. Abstr.*, (1979) **91**, 158 505.
- [55] Brandt, P.; Bruchmann, B.; Laqua, G.; Merger, F.; Otterbach, A.; Stiefenhöffer, K.; Witzel, T.; Wolff, S.; Becker, R., US 5 489 663, (1996); *Chem. Abstr.*, (1995) **123**, 314 850.
- [56] Jackson, R.; Wehner, J. F., US 3 652 424, (1972); *Chem. Abstr.*, (1972) **75**, 152 290.
- [57] Kresta, J.; Shen, C. S., US 4 111 914, (1978); *Chem. Abstr.*, (1978) **88**, 106 017.
- [58] Robin, J., US 4 412 073, (1983); *Chem. Abstr.*, (1983) **98**, 17 199.
- [59] Engbert, T.; Knöfel, H.; Wegener, G.; US 4 698 424, (1987); *Chem. Abstr.*, (1985) **103**, 125 108.
- [60] Schmalstieg, L.; Dieris, C.-G.; Kremer, W.; Riberi, B., US 5 723 564, (1998); *Chem. Abstr.*, (1997) **126**, 158 842.
- [61] Burkus, J., US 2 979 485, (1961); *Chem. Abstr.*, (1963) **59**, 55 107.
- [62] Snider, S. C., US 5 109 031, (1992); *Chem. Abstr.*, (1991) **114**, 208 829.
- [63] Farago, J., US 2 980 651, (1961); *Chem. Abstr.*, (1962) **56**, 61 271.
- [64] Hirai, K.; Shirano, K.; Hara, K.; Okamura, T., US 4 367 307, (1983); *Chem. Abstr.*, (1982) **96**, 53 572.
- [65] Tomic, E. A.; Campbell, T. W.; Foldi, V. S., *J. Polym. Sci.*, (1962) **62**, 387.
- [66] Purgett, M. D.; Deits, W.; Vogl, O., *J. Polym. Sci., Polym. Chem. Ed.*, (1982) **20**, 2477.
- [67] Ishii, S.; Watabe, S.-I.; Nishimura, S.-I.; Kurita, K., *J. Polym. Sci., Part A: Polym. Chem.*, (1994) **32**, 575.
- [68] Kurita, K.; Watabe, S.-I.; Nishimura, S.-I.; Ishii, S., *J. Polym. Sci., Part A: Polym. Chem.*, (1996) **34**, 429.
- [69] Wagner, K., US 3 201 372, (1965); *Chem. Abstr.*, (1965) **63**, 64 072.
- [70] Wagner, K., US 3 124 605, (1964); *Chem. Abstr.*, (1962) **56**, 25 803.
- [71] Schmelzer, H.-G.; Wagner, K., GB 1 043 672, (1964); *Chem. Abstr.*, (1964) **60**, 90 545.
- [72] Windemuth, E.; Bayer, O.; Wagner, K.; Bunge, W., DE 1 174 759, (1964); *Chem. Abstr.*, (1964) **61**, 77 231.
- [73] Britain, J. W., US 3 358 010, (1967); *Chem. Abstr.*, (1964) **66**, 2239.
- [74] Schwindt, J.; Meyborg, H.; Reiff, H.; König, K., US 4 320 068, (1982); *Chem. Abstr.*, (1981) **95**, 188 079.
- [75] Speranza, G.; Su, W.-Y., US 5 013 812, (1991); *Chem. Abstr.*, (1991) **115**, 234 405.
- [76] Patton, T. L., US 3 661 859, (1972); *Chem. Abstr.*, (1972) **77**, 75 784.
- [77] Luongo, J. P.; Schonhorn, H., *J. Polym. Sci., Polym. Chem. Ed.*, (1975) **13**, 1363.
- [78] Oku, A.; Okano, M.; Oda, R., *Makromol. Chem.*, (1964) **78**, 186.
- [79] Patton, T. L., US 3 635 905, (1972); *Chem. Abstr.*, (1972) **76**, 127 782.
- [80] Patton, T. L., US 4 028 311, (1977); *Chem. Abstr.*, (1977) **87**, 40 087.
- [81] Patton, T. L., US 3 591 562, (1971); *Chem. Abstr.*, (1970) **73**, 99 411.
- [82] Kraft, K.; Reese, J., *Angew. Chem.*, (1973) **85**, 982; *Angew. Chem. Int. Ed. Engl.*, (1973) **12**, 919.
- [83] Kraft, K.; Reese, J., US 4 099 007, (1978); *Chem. Abstr.*, (1973) **78**, 44 448.
- [84] Schade, G.; Blaschke, F., US 3 609 113, (1971); *Chem. Abstr.*, (1970) **73**, 5045.
- [85] Dünwald, W.; Lewalter, J.; Merten, R., US 4 005 056, (1977); *Chem. Abstr.*, (1976) **84**, 6659.
- [86] Stachel, H. D., *Angew. Chem.*, (1959) **71**, 246.
- [87] Ulrich, H.; Sayigh, A. A. R., *J. Org. Chem.*, (1965) **30**, 2781.
- [88] Imashiro, Y.; Amano, S., US 4 939 210, (1990); *Chem. Abstr.*, (1990) **112**, 99 559.
- [89] Campbell, T. W.; Smeltz, K. C., *J. Org. Chem.*, (1963) **28**, 2069.
- [90] Caraculacu, G.; Scortanu, E.; Caraculacu, A. A., *Eur. Polym. J.*, (1983) **19**, 143.
- [91] Scortanu, E.; Caraculacu, A. A.; Caraculacu, G.; Agherghinei, I., *Eur. Polym. J.*, (1993) **29**, 999.
- [92] Sallé, R.; Sillion, B.; de Gaudemaris, G., *Bull. Soc. Chim. Fr.*, (1968), 3378.
- [93] Schmidt, K.; Wille, D., GB 1 187 003, (1970); *Chem. Abstr.*, (1970) **72**, 4063.
- [94] Merten, R.; Dünwald, W.; Mielke, K.-H.; Reese, E., DE 1 230 568, (1966); *Chem. Abstr.*, (1967) **66**, 38 958.
- [95] Rogers, A. O., US 3 296 208, (1967); *Chem. Abstr.*, (1965) **63**, 55 099.
- [96] Kelley, E. J., US 3 369 010, (1968); *Chem. Abstr.*, (1968) **68**, 105 675.
- [97] Merten, R.; Dünwald, W.; Mielke, K.-H.; Reese, E., US 3 397 253, (1968); *Chem. Abstr.*, (1967) **66**, 30 088.
- [98] Imai, Y., *J. Polym. Sci., Polym. Chem. Ed.*, (1967) **5**, 2289.

- [99] Dyer, E.; Hartzler, J., *J. Polym. Sci., Polym. Chem. Ed.*, (1969) **7**, 833.
- [100] Wheeler, H. L.; Hoffman, C., *Am. Chem. J.*, (1911) **45**, 568; *Chem. Abstr.*, (1911) **5**, 2072.
- [101] Ware, E., *Chem. Rev.*, (1950) **46**, 403.
- [102] Heywang, G.; Jonas, F.; Merten, R.; Schmidtberg, W., US 4 849 492, (1989); *Chem. Abstr.*, (1990) **112**, 22471.
- [103] Merten, R., US 3 549 599, (1970); *Chem. Abstr.*, (1976) **84**, 5663.
- [104] Allen, B. B.; Henze, H. R., *J. Am. Chem. Soc.*, (1938) **60**, 1796.
- [105] Chadwick, A. F., US 2 532 278, (1950); *Chem. Abstr.*, (1951) **45**, 10 196.
- [106] Yoda, N.; Nakanishi, R.; Kurihara, M.; Bamba, Y.; Toyama, S.; Ikeda, K., *J. Polym. Sci., Part B: Polym. Lett.*, (1966) **4**, 11.
- [107] Padma, S.; Mahadevan, V.; Srinivasan, M., *J. Polym. Sci., Part A: Polym. Chem.*, (1988) **26**, 1253.
- [108] Kurihara, M.; Yoda, N., *J. Polym. Sci., Polym. Chem. Ed.*, (1967) **5**, 1765.
- [109] Tohyama, S.; Kurihara, M.; Ikeda, K.; Yoda, N., *J. Polym. Sci., Polym. Chem. Ed.*, (1967) **5**, 2523.
- [110] Widmer, G., In *Encyclopedia of Polymer Science and Engineering*, Mark, H. F.; Gaylord, N. G.; Bikales, N. M., Eds.; Wiley: New York, (1965); Vol. 2, p 1.
- [111] Diem, H.; Matthias, G., In *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed, electronic release: Wiley-VCH: Weinheim, (2002); DOI: 10.1002/14356007.a02_115.
- [112] Braun, D.; Ritzet, H.-J., In *Comprehensive Polymer Science: The Synthesis, Characterization, Reactions & Applications of Polymers*, Allen, G.; Bevington, J. C., Eds; Pergamon: Oxford, (1989); Vol. 5, p 649.
- [113] Corner, A. H., In *Polymeric Materials Encyclopedia*, Salamone, J.; Salamone, J. C., Ed.; CRC: Boca Raton, FL, (1996); Vol. 10, p 7364.
- [114] Hoey, J. R.; Turcotte, F.; Couet, S.; L'Abbe, K. A., *Can. Med. Assoc. J.*, (1984) **130**, 115.
- [115] Kelly, T. J.; Smith, D. L.; Satola, J., *Environ. Sci. Technol.*, (1999) **33**, 81.
- [116] de Breet, A. J. J.; Dankelmann, W.; Huysmans, W. G. B.; de Witt, J., *Angew. Makromol. Chem.*, (1977) **62**, 7.
- [117] Jada, S. S., *J. Appl. Polym. Sci.*, (1998) **35**, 1573.
- [118] Chuang, I.-S.; Maciel, G. E., *Macromolecules*, (1992) **25**, 3204.
- [119] Kim, M. G.; Amos, L. W., *Ind. Eng. Chem. Res.*, (1990) **29**, 208.
- [120] Kong, H. C., US 4 603 191, (1986); *Chem. Abstr.*, (1985) **103**, 142 862.
- [121] Ryan, A. J.; Stanford, J. L., In *Comprehensive Polymer Science: The Synthesis, Characterization, Reactions & Applications of Polymers*, Allen, G.; Bevington, J. C., Eds; Pergamon: Oxford, (1989); Vol. 5, p 427.
- [122] Chiriac, C. I., In *Encyclopedia of Polymer Science and Engineering*, 2nd ed., Mark, H. F.; Kroschwitz, J. I., Eds.; Wiley: New York, (1988); Vol. 13, p 212.
- [123] Overmars, H. G. J., In *Encyclopedia of Polymer Science and Engineering*, Mark, H. F.; Gaylord, N. G.; Bikales, N. M., Eds.; Wiley: New York, (1969); Vol. 11, p 464.
- [124] Chiriac, C. I.; Tanasă, F., In *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed, electronic release: Wiley-VCH; Weinheim, (2002); DOI: 10.1002/14356007.d21_d01.
- [125] I. G. Farbenindustrie AG, FR 845 917, (1939); *Chem. Abstr.*, (1941) **38**, 1152.
- [126] Bayer, O., *Angew. Chem.*, (1947) **59**, 275.
- [127] Arnold, H. F., US 2 145 242, (1939); *Chem. Abstr.*, (1939) **33**, 23 541.
- [128] E. I. Du Pont de Nemours and Co., GB 530 267, (1940); *Chem. Abstr.*, (1941) **35**, 52 779.
- [129] Hanford, W. E.; Holmes, D. F., US 2 284 896, (1942); *Chem. Abstr.*, (1942) **36**, 42 249.
- [130] Manzione, L. T., In *Encyclopedia of Polymer Science and Engineering*, 2nd ed., Mark, H. F.; Kroschwitz, J. I., Eds.; Wiley: New York, (1988); Vol. 14, p 72.
- [131] Hrymak, A. N., In *Polymeric Materials Encyclopedia*, Salamone, J. C., Ed.; CRC: Boca Raton, (1996); Vol. 10, p 7364.
- [132] Hepburn, C., *Polyurethane Elastomers*, 2nd ed., Elsevier Applied Science: London, (1992); pp 174–198.
- [133] Primeaux, D. J., II; Anglin, K. C., *Polyurethanes '92: Proceedings of the SPI 34th Annual Polyurethane Technical/Marketing Conference, October 21–24*, Technomic: Lancaster, PA, (1992); p 598; *Chem. Abstr.*, (1994) **121**, 207 409.
- [134] Primeaux, D. J., II; Hillman, K. M., *Polyurethane Expo '98 Proceedings, Dallas, September 17–20*, Society of Plastics Industry: Washington, DC, (1998); pp 543–550; *Chem. Abstr.*, (2000) **132**, 109 183.
- [135] Nalwa, H. S., In *Polymeric Materials Encyclopedia*, Salamone, J. C., Ed.; CRC: Boca Raton, FL, (1996); Vol. 9, p 6937.

- [136] Cardin, A. D.; Fordyce, W. A.; Mullins, M. J.; Chamberlin, T. A.; Fazio, M. J., US 6 013 251, (2000); *Chem. Abstr.*, (1993) **119**, 262496.
- [137] Dunjic, P.; Gamez, P.; Fache, F.; Lemaire, M., *J. Appl. Polym. Sci.*, (1996) **59**, 1255.
- [138] Ramarao, C.; Ley, S. V.; Smith, S. C.; Shirley, I. M.; DeAlmeida, N., *Chem. Commun. (Cambridge)*, (2002), 1132.
- [139] Katz, M., US 2 888 438, (1959); *Chem. Abstr.*, (1959) **53**, 97594.
- [140] Hermans, J., GB 1 514 511, (1978); *Chem. Abstr.*, (1979) **90**, 55671.
- [141] Kwon, S.-K.; Choi, K.-L.; Choi, S.-K., *J. Polym. Sci., Part A: Polym. Chem.*, (1987) **25**, 1781.
- [142] Lehman, W.; Rinke, H., US 2 852 494, (1958); *Chem. Abstr.*, (1959) **53**, 9797.
- [143] Yasuzawa, T.; Yamaguchi, H.; Minoura, Y., *J. Polym. Sci., Polym. Chem. Ed.*, (1979) **17**, 3387.
- [144] Yadav, S. K.; Ron, N.; Chandrakham, D.; Khilar, K. C.; Suresh, A. K.; Nadkarni, V. M., *J. Macromol. Sci., Phys.*, (1996) **B35**, 807.
- [145] Hässlin, H. W.; EP 611 253, (1994); *Chem. Abstr.*, (1995) **122**, 162893.
- [146] Hong, K.; Park, S., *J. Appl. Polym. Sci.*, (2000) **78**, 894.
- [147] Primeaux, D. J., II, US 5 162 388, (1992); *Chem. Abstr.*, (1993) **118**, 104575.
- [148] Kumar, A.; Meijer, A. W., *Chem. Commun. (Cambridge)*, (1998), 1629.
- [149] Ambade, A. V.; Kumar, A., *J. Polym. Sci., Part A: Polym. Chem.*, (2001) **39**, 1295.
- [150] Buckley, G. D.; Ray, N. H., US 2 550 767, (1951); *Chem. Abstr.*, (1951) **45**, 46056.
- [151] Yamazaki, N.; Igushi, T.; Higashi, F., *J. Polym. Sci., Polym. Chem. Ed.*, (1975) **13**, 785.
- [152] Higashi, F.; Murakami, T.; Tagushi, Y., *J. Polym. Sci., Polym. Chem. Ed.*, (1982) **20**, 103.
- [153] Chiriac, C. I., *Polym. Bull. (Heidelberg, Ger.)*, (1986) **15**, 65.
- [154] Wittebecker, E. L., US 2 816 879, (1957); *Chem. Abstr.*, (1958) **52**, 53332.
- [155] Alexandru, L.; Dascalu, L., *J. Polym. Sci.*, (1961) **52**, 331.
- [156] Lyman, D. J.; Jung, S. L., *J. Polym. Sci.*, (1959) **40**, 407.
- [157] Cotter, R. J., GB 902 134, (1962); *Chem. Abstr.*, (1963) **58**, 3553.
- [158] W. R. Grace and Co, GB 863 297, (1961); *Chem. Abstr.*, (1961) **55**, 96728.
- [159] Gabler, R.; Müller, H., US 3 185 656, (1965); *Chem. Abstr.*, (1965) **63**, 72852.
- [160] Borner, P.; Gugel, W.; Pasedag, R., *Makromol. Chem.*, (1967) **101**, 1.
- [161] I. G. Farbenindustrie AG, DE 745 684, (1944); *Chem. Abstr.*, (1946) **40**, 4735.
- [162] Kricheldorf, H. R., *J. Macromol. Sci., Chem.*, (1980) **A14**, 959.
- [163] Yamazaki, N.; Igushi, T.; Higashi, F., *J. Polym. Sci., Polym. Chem. Ed.*, (1979) **17**, 835.
- [164] Kosaka, Y.; Watanabe, M.; Sanui, K.; Ogata, N., *J. Polym. Sci., Part A: Polym. Chem.*, (1986) **24**, 1915.
- [165] Martin, A. L., US 2 181 663, (1939); *Chem. Abstr.*, (1940) **34**, 13622.
- [166] Dreyfus, H., US 2 568 885, (1951); *Chem. Abstr.*, (1952) **46**, 10196.
- [167] Saunders, J. H.; Frisch, K. C., *Polyurethanes: Chemistry and Technology, Part I: Chemistry*, Interscience: New York, (1962); pp 76, 180.
- [168] Wooler, A. M., GB 1 548 370, (1975); *Chem. Abstr.*, (1977) **86**, 156462.
- [169] Naegeli, C. A.; Tyabji, L.; Conrad, L.; Litman, F., *Helv. Chim. Acta*, (1938) **21**, 1100.
- [170] Merckaert, P.; Jérôme, R.; Teyssié, P., *J. Appl. Polym. Sci.*, (1982) **27**, 4221.
- [171] Borsus, J. M.; Jérôme, R.; Teyssié, P., *J. Appl. Polym. Sci.*, (1981) **26**, 3027.
- [172] Kobayashi, S., *Prog. Polym. Sci.*, (1990) **15**, 751.
- [173] Mukaiyama, T.; Fujisawa, T.; Nohira, H.; Hyugaji, T., *J. Org. Chem.*, (1962) **27**, 3337.
- [174] Beachell, H. C.; Ngoc Son, C. P.; Tinh, N. H., *J. Polym. Sci., Part B: Polym. Lett.*, (1971) **9**, 735.
- [175] Miyamoto, M.; Shimakura, M.; Tsutsui, K.; Hasegawa, K.; Aoi, K.; Yamaga, S.; Saegusa, T., *Macromolecules*, (1993) **26**, 7116.
- [176] Miyamoto, M.; Watanabe, T.; Kimura, Y., *Macromol. Chem. Phys.*, (1998) **199**, 2237.
- [177] Miyamoto, M.; Watanabe, T.; Kimura, Y., *Macromol. Rapid. Commun.*, (1997) **18**, 897.
- [178] Miyamoto, M.; Aoi, K.; Saegusa, T., *J. Polym. Sci., Part A: Polym. Chem.*, (1997) **35**, 933.
- [179] Kanamaru, M.; Takata, T.; Endo, T., *Macromolecules*, (1994) **27**, 7492.
- [180] ter Halle, R.; Colasson, B.; Schulz, E.; Spagnol, M.; Lemaire, M., *Tetrahedron Lett.*, (2000) **41**, 643.
- [181] Saluzzo, C.; Lamouille, T.; Hérault, D.; Lemaire, M., *Bioorg. Med. Chem. Lett.*, (2002) **12**, 1841.
- [182] Ley, S. V.; Ramarao, C.; Gordon, R. S.; Homes, A. B.; Morrison, A. J.; McConvey, I. A.; Shirley, I. M.; Smith, S. C.; Smith, M. D., *Chem. Commun. (Cambridge)*, (2002), 1134.
- [183] Bremeyer, N.; Ley, S. V.; Ramarao, C.; Shirley, I. M.; Smith, S. C., *Synlett*, (2002) **11**, 1843.
- [184] Yu, J.-Q.; Wu, H.-C.; Ramarao, C.; Spencer, J. B.; Ley, S. V., *Chem. Commun. (Cambridge)*, (2003), 678.
- [185] Burgess, K.; Shin, H.; Linthicum, D. S., *Angew. Chem.*, (1995) **107**, 975; *Angew. Chem. Int. Ed. Engl.*, (1995) **34**, 907.

- [186] Semetey, V.; Rognan, D.; Hemmerlin, C.; Graff, R.; Briand, J.-P.; Marraud, M.; Guichard, G., *Angew. Chem.*, (2002) **115**, 1973; *Angew. Chem. Int. Ed.*, (2002) **41**, 1893.
- [187] Guichard, G.; Semetey, V.; Didierjean, C.; Aubry, A.; Briand, J.-P.; Rodriguez, M., *J. Org. Chem.*, (1999) **64**, 8702.
- [188] Rink, H., *Tetrahedron Lett.*, (1987) **28**, 3787.
- [189] Han, H.; Janda, K. D., *J. Am. Chem. Soc.*, (1996) **118**, 2539.
- [190] Burgess, K.; Ibarzo, J.; Linthicum, D. S.; Russell, D. H.; Shin, H.; Shitangkoon, A.; Totani, R.; Zhang, A. J., *J. Am. Chem. Soc.*, (1997) **119**, 1556.
- [191] Kim, J. M.; Bi, Y.; Paikoff, S. J.; Schultz, P. G., *Tetrahedron Lett.*, (1996) **37**, 5305.
- [192] Boeijen, A.; van Ameijde, J.; Liskamp, R. M. J., *J. Org. Chem.*, (2001) **66**, 8454.
- [193] Guichard, G.; Semetey, V.; Rodriguez, M.; Briand, J.-P., *Tetrahedron Lett.*, (2000) **41**, 1553.
- [194] Hancock, W. S.; Battersby, J. E., *Anal. Biochem.*, (1976) **71**, 260.
- [195] Wilson, M. E.; Nowick, J. S., *Tetrahedron Lett.*, (1998) **39**, 6613.
- [196] Efimov, V.A.; Kalinkina, A. L.; Chakhmakhcheva, O. G., *Nucleic Acids Res.*, (1993) **21**, 5337.
- [197] Sandler, S. R.; Karo, W., In *Polymer Syntheses*, 2nd ed., Sandler, S. R.; Karo, W., Eds.; Academic: New York, (1992); p 460.
- [198] Buckler, S. A.; Epstein, M., US 3 213 042, (1965); *Chem. Abstr.*, (1966) **64**, 11 844.

Product Class 10: Thiocarbonic Acids and Derivatives

S. Sato and N. Furukawa

Product Subclass 1: Thiocarbonyl Dihalides

This class of compounds $X_2C=S$ ($X = F, Cl, Br, I$) is described in *Houben–Weyl*, Vol. 9/4, p 786, and E 4, p 407, and is reviewed elsewhere.^[1]

Of the thiocarbonyl dihalides, the difluoride, dichloride, and dibromide derivatives have been isolated while the diiodide derivatives have been prepared but only the mass spectroscopic and IR data were reported.

In addition to these thiocarbonyl dihalides with two like halides, the compounds bearing two unlike halides have been prepared and their properties are available in the literature.^[2]

The stability of thiocarbonyl dihalides is in the order of $F > Cl \gg Br > I$; this trend is considered to be due to resonance stabilization of the thiocarbonyl double bond by the halogen atom.

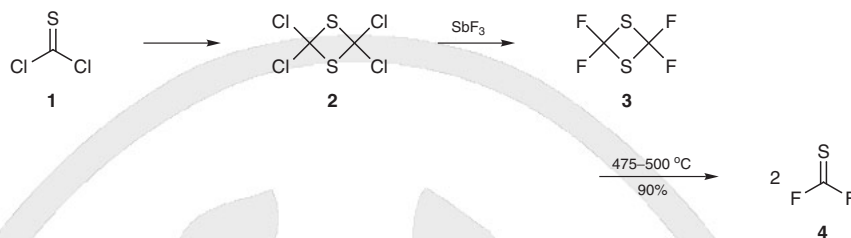
Thiophosgene (thiocarbonyl dichloride) is the most frequently utilized of the thiocarbonyl dihalides and it is used for the synthesis of many thiocarbonic acid derivatives upon treatment with oxygen, sulfur, or nitrogen nucleophiles, which readily substitute the chlorine atoms. Many of the thiocarbonyl derivatives prepared from thiophosgene are described in Sections 18.10.1.1.1, 18.10.2.1.2, 18.10.3.1.1, 18.10.4.1.2, 18.10.5.1.1, 18.10.6.1.3, 18.10.7.1.3, 18.10.8.1.2, 18.10.10.1.2, and 18.10.13.1.1. The thiocarbonyl double bond also acts as an ene-analogous partner for the Diels–Alder reaction and thus reacts with dienes to afford the corresponding [2+4] cycloadducts containing a sulfur atom.^[3–5]

Thiocarbonyl halides also undergo oxidation with oxidants, e.g. 3-chloroperoxybenzoic acid, to give the corresponding sulfoxines (see Section 18.10.2).^[6]

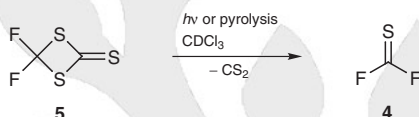
Synthesis of Product Subclass 1

Method 1: Synthesis of Thiocarbonyl Difluoride

Several methods for the synthesis of thiocarbonyl difluoride (**4**) are available. Difluoride **4** is prepared as a colorless gaseous compound by a three-step procedure starting from thiophosgene (**1**). This procedure proceeds by conversion of **1** into the dimer, 2,2,4,4-tetrachloro-1,3-dithietane (**2**), which is fluorinated with antimony(III) fluoride to give 2,2,4,4-tetrafluoro-1,3-dithietane (**3**). The tetrafluoro-substituted compound **3** is then pyrolyzed at 475–500 °C to give thiocarbonyl difluoride (**4**) with a boiling point of –54 °C in high yield (Scheme 1).^[7,8] A costly platinum apparatus is used for the pyrolysis to avoid the photolysis of thiophosgene (**1**), which leads to dissociation to a CSCI radical, and a chlorine radical.^[9]

Scheme 1 Preparation of Thiocarbonyl Difluoride from Thiophosgene^[7]

There are several other procedures for the preparation of thiocarbonyl difluoride (**4**). One useful procedure is the pyrolysis or photolysis of 4,4-difluoro-1,3-dithietane-2-thione (**5**) (Scheme 2).^[10]

Scheme 2 Pyrolysis or Photolysis of 4,4-Difluoro-1,3-dithietane-2-thione^[10]

Alternately, thiocarbonyl difluoride (**4**) is prepared as a byproduct from the reaction of bis(trifluoromethyl) trisulfide with Grignard reagents R^1MgX ($R^1 = Et, iPr$).^[11,12]

Alkali or alkali earth metal salts of trifluoromethanethiol prepared from the metal chlorides [MCl_n , $M = Na, K, Cs$ ($n = 1$); $M = Ca, Ba$, ($n = 2$)] and ammonium salts of trifluoromethanethiosulfate [$n(NH_4^+)(CF_3SSO_3^-)$] are unstable, and decompose to thiocarbonyl difluoride (**4**) and trifluorothioacetyl fluoride.^[13]

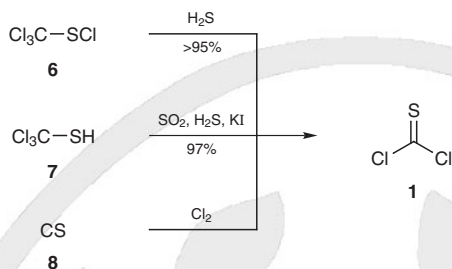
Thiocarbonyl Difluoride (**4**) by Pyrolysis of 2,2,4,4-Tetrafluoro-1,3-dithietane (**3**):^[7,8]

2,2,4,4-Tetrafluoro-1,3-dithietane (**3**; 40 g, 0.24 mol) was added dropwise over a period of 2 h through a Pt tube (1.25×64 cm, inclined at an angle of 30° and heated to $475\text{--}500^\circ\text{C}$ over a length of 30 cm). A slow stream of He ($20\text{ mL}\cdot\text{min}^{-1}$) was passed through the tube during pyrolysis. The effluent gases were condensed in successive traps and cooled by a mixture of acetone and CO_2 and liq N_2 , respectively. The material in the trap was combined and distilled through a 41-cm column packed with Hastelloy helices. The product **4** was obtained as a colorless liquid; yield: 36 g (90%); bp -54°C ; ^{19}F NMR (339 MHz, $CDCl_3$, δ): -107.8 (s).

18.10.1.1.2

Method 2: Synthesis of Thiophosgene

Although thiophosgene (thiocarbonyl dichloride, **1**) is commercially available, in general, three procedures are employed for its preparation as shown in Scheme 3. Among these methods two are recommended: the reduction of trichloromethanesulfonyl chloride (**6**) with hydrogen sulfide^[14,15] and the reduction of trichloromethanethiol (**7**) with sulfur dioxide in the presence of potassium iodide and hydrogen sulfide. Using these methods, the yield of thiophosgene (**1**) is greater than 95%. In addition to these two procedures, thiophosgene (**1**) can also be produced from carbon monosulfide (**8**), generated from carbon disulfide using a high frequency discharge method at 0.1 Torr and chlorine gas (Scheme 3).^[16,17]

Scheme 3 Synthesis of Thiophosgene^[14–17]

The synthesis and reactions of thiophosgene (**1**) before 1978 has been thoroughly reviewed.^[14–21]

Thiophosgene (1) by the Reduction of Trichloromethanesulfonyl Chloride:^[14,15]

CAUTION: Hydrogen sulfide is extremely flammable and at higher levels causes respiratory paralysis and asphyxia.

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

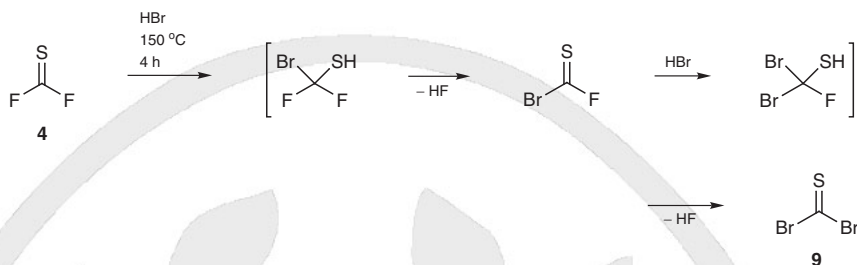
Trichloromethanesulfonyl chloride (**6**; 18.6 g, 100 mmol) and H_2S gas (6.8 g, 200 mmol) were introduced continuously in a glass-column reactor^[14,15,20] packed with silica gel (size 1.5–3 mm, pretreated with HCl in order to remove any trace of iron compounds) and preheated with an electric heater around the glass column tube at 110–140 °C (optimal temperature 115 °C). At this temperature sulfur appeared as was collected in a heated flask and was removed. The gaseous mixture (thiophosgene, HCl gas, and small quantity of CS_2) was removed at the bottom of the column and cooled at –30 °C in a subsequently attached cooler. This procedure afforded thiophosgene containing 4 wt% CS_2 . The analysis was carried out by GC with 15% Voltalef 10 S on Chromosorb T. After an operating time of 24 h, the reactor reached a state of equilibrium, after which thiophosgene (**1**; 11.3 g of condensate per hour) was obtained; bp 73.5 °C.

18.10.1.1.3

Method 3:
Synthesis of Thiocarbonyl Dibromide

Thiocarbonyl dibromide (**9**) is produced by contact of carbon monosulfide (**8**) generated continuously from carbon disulfide at 0.1 Torr by a high frequency discharge process with bromine gas at room temperature as an orange-red liquid having a boiling point of 142–144 °C [$\text{IR } \tilde{\nu}$ 1097 ($\text{C}=\text{S}$) 685 ($\text{C}-\text{Br}$) cm^{-1}].^[7,8,17,21,22]

As an alternative procedure, thiocarbonyl difluoride (**4**) is treated with anhydrous hydrogen bromide at high temperature leading to F–Br exchange to give thiocarbonyl dibromide (**9**). The compound **9** is unstable and decomposes at room temperature over a period of 2 weeks in glassware to result in the formation of bromine (Scheme 4).^[7,8]

Scheme 4 Synthesis of Thiocarbonyl Dibromide^[7,8]**Thiocarbonyl Dibromide (9):**^[7,8]

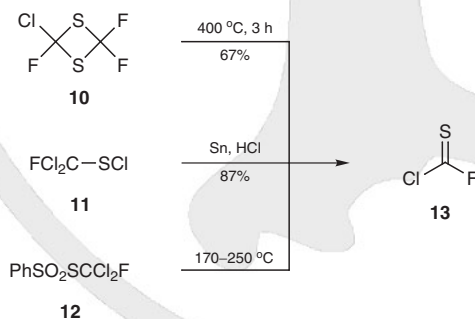
Anhyd HBr (18 g, 0.225 mol) and thiocarbonyl difluoride (**4**; 15 g, 0.184 mol) were condensed in a Hastelloy-lined shaker tube. The tube was then heated at 150 °C for 4 h. After venting, the liquid product recovered from the tube was distilled through a spinning-band column. The mixture was complicated, but a fraction, bp 142–144 °C, n_D^{25} 1.6015, was obtained. This was a heavy orange-red liquid which was found to be thiocarbonyl dibromide (**9**) by its analysis and MS (FW 204).

18.10.1.1.4 Method 4:
Synthesis of Thiocarbonyl Diiodide

Thiocarbonyl diiodide is generated by a similar method to thiocarbonyl dichloride and dibromide from carbon monosulfide and iodine, but it is not isolated. The structure of thiocarbonyl diiodide has been determined by MS and IR spectroscopy [IR $\tilde{\nu}$ 1062 (C=S), 602 (C–I) cm^{-1}].^[17,21,22]

18.10.1.1.5 Method 5:
Synthesis of Thiocarbonyl Chloride Fluoride

Thiocarbonyl chloride fluoride (**13**) is synthesized from the pyrolysis of 2-chloro-2,4,4-trifluoro-1,3-dithietane (**10**) at 400 °C for 3 hours in 67% yield (bp 6–7 °C), together with thiocarbonyl difluoride (**4**) in 91% yield (Scheme 5).^[7,8]

Scheme 5 Synthesis of Thiocarbonyl Chloride Fluoride^[7,8,15,23]

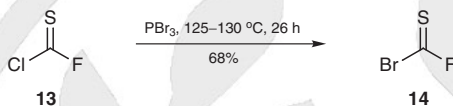
The reduction of dichlorofluoromethanesulfonyl chloride (**11**) with tin and concentrated hydrochloric acid gives **13** in 87% yield.^[23] Alternatively, S-dichlorofluoromethyl benzene-thiosulfonate (**12**) is pyrolyzed at 170–250 °C to give **13** in moderate yield (Scheme 5).^[15]

Compound **13** is also prepared in 54% yield from thiophosgene and antimony(III) fluoride by halogen exchange at 90 °C in sulfolane.^[24]

18.10.1.1.6

Method 6:**Synthesis of Thiocarbonyl Bromide Fluoride**

Thiocarbonyl bromide fluoride (**14**) is obtained by the halogen-exchange reaction of thiocarbonyl chloride fluoride (**13**) with phosphorus tribromide at 125–130 °C in 34% yield (bp 4–8 °C/100 Torr), but it decomposes spontaneously at room temperature (Scheme 6).^[25]

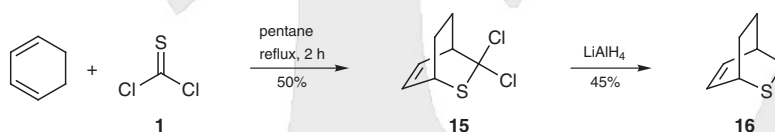
Scheme 6 Synthesis of Thiocarbonyl Bromide Fluoride^[25]**Thiocarbonyl Bromide Fluoride (**14**):**^[25]

In a Carius tube (o.d. 35 mm, length 40 cm), PBr₃ (13.6 g, 50 mmol) and thiocarbonyl chloride fluoride (**13**; 9.85 g, 100 mmol) were condensed at –96 °C. The mixture was heated at 130 °C for 26 h and then cooled at –90 °C and purified by vacuum distillation. The condensate was fractionated by spinning-band column. Thiocarbonyl bromide fluoride (**14**) was distilled at 4–8 °C/100 Torr; both gas and liquid phases were yellow in color; yield: 4.8 g (68%). The compound **14** readily decomposed at 20 °C, but it was characterized by ¹⁹F NMR and mass spectrum analysis.

18.10.1.2

Applications of Product Subclass 1 in Organic Synthesis

2-Thiabicyclo[2.2.2]oct-5-ene (**16**) is synthesized by the Diels–Alder cycloaddition of thiocarbonyl dihalides to cyclohexa-1,3-diene. Thus addition of thiophosgene (**1**) to cyclohexa-1,3-diene gives 3,3-dichloro-2-thiabicyclo[2.2.2]oct-5-ene (**15**), reduction of which with lithium aluminum hydride gives the dechlorinated 2-thiabicyclo[2.2.2]oct-5-ene (**16**) in 45% yield (Scheme 7).^[3] Thiocarbonyl difluoride also undergoes Diels–Alder reaction with cyclohexa-1,3-diene to afford the corresponding [2+4] cycloadduct, 3,3-difluoro-2-thiabicyclo[2.2.2]oct-5-ene, in 79% yield.^[5]

Scheme 7 Synthesis of 2-Thiabicyclo[2.2.2]oct-5-ene^[3]

Anthracene is also used as the dienophile for the addition to thiophosgene (**1**) to afford the [2+4] cycloadduct in 60% yield.^[4]

3,3-Dichloro-2-thiabicyclo[2.2.2]oct-5-ene (15**); Typical Procedure:**^[3]

CAUTION: Thiophosgene (CSCl₂) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

To a soln of cyclohexa-1,3-diene (0.80 g, 10 mmol) in pentane (5 mL) under N₂ was added in one portion thiophosgene (**1**; 0.76 mL, 10 mmol). This mixture was refluxed for 2 h and cooled to dry ice temperature. The orange liquid was decanted and the yellow precipitates were recrystallized four times (pentane, –78 °C) to give a white, waxy, odoriferous, hydrolysis sensitive solid; yield: 0.98 g (50%); mp 98–100 °C.

18.10.2 Product Subclass 2:
Dihalosulfines (Thiocarbonyl Dihalide S-Oxides)

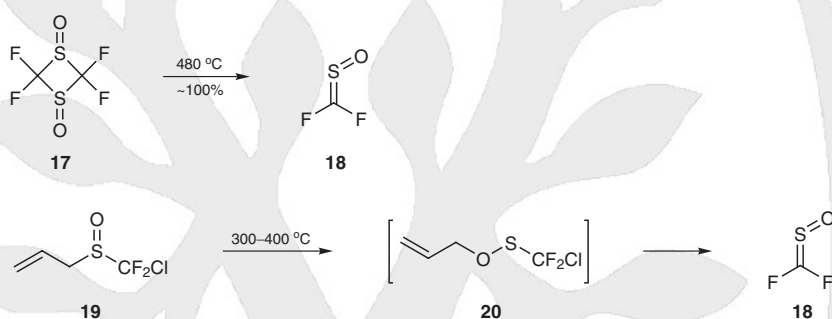
Dihalosulfines are the thiocarbonyl monoxides having the structure $X^1X^2C=S=O$, in which X^1 and X^2 are halogens. Compounds with both two similar ($X^1 = X^2$) and dissimilar ($X^1 \neq X^2$) halogens are known. Sulfines are also discussed in *Science of Synthesis*, Vol. 27 [Heteroatom Analogues of Aldehydes and Ketones (Section 27.4.1.1)].

18.10.2.1 Synthesis of Product Subclass 2

18.10.2.1.1 Method 1:
Synthesis of Difluorosulfine

Difluorosulfine (**18**) is obtained quantitatively by the pyrolysis of 2,2,4,4-tetrafluoro-1,3-dithietane 1,3-dioxide (**17**) at 480 °C under vacuum (0.01 Torr) (Scheme 8).^[26,27]

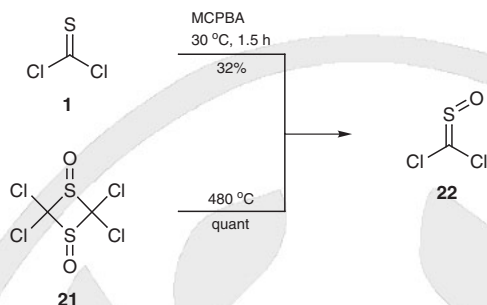
Scheme 8 Synthesis of Difluorosulfine^[26–28]



The pyrolysis of allyl chlorodifluoromethyl sulfoxide (**19**) under vacuum at 300–400 °C gives difluorosulfine (**18**) via intermediate **20**; difluorosulfine (**18**) was identified by mass spectrometry in this case (Scheme 8).^[28]

18.10.2.1.2 Method 2:
Synthesis of Dichlorosulfine

Dichlorosulfine (thiocarbonyl dichloride S-oxide, **22**) was first prepared by oxidation of thiophosgene (**1**) with 3-chloroperoxybenzoic acid in 32% yield (Scheme 9).^[6,29,30] This synthesis opened up sulfine chemistry. See also *Science of Synthesis*, Vol. 27 [Heteroatom Analogues of Aldehydes and Ketones (Section 27.4.1.1.3)].

Scheme 9 Synthesis of Dichlorosulfine^[6,27,29,30]

As an alternative procedure, pyrolysis of allyl trichloromethyl sulfoxide at 300–400 °C gives dichlorosulfine (22) in 49% yield via an initial rearrangement to allyl trichloromethylsulfenate in a analogous process to that in Section 18.10.2.1.1 (Scheme 8).^[28] This procedure is also used in the synthesis of chlorofluorosulfine.

2,2,4,4-Tetrachloro-1,3-thietane 1,3-dioxide (21) is pyrolyzed under vacuum (0.5 Torr) at 480 °C to give dichlorosulfine (22) quantitatively (Scheme 9).^[27]

Dichlorosulfine (22) by Oxidation of Thiophosgene (1):^[6]

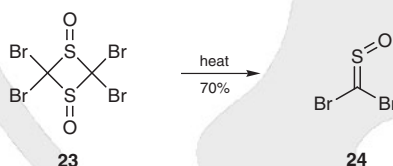
CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

Treatment of thiophosgene (1) in pentane/ Et_2O with MCPBA (slightly less than 1 equiv) at 35 °C for 1.5 h. After removal of 3- $\text{ClC}_6\text{H}_4\text{CO}_2\text{H}$ and solvents, distillation of the remaining oil (bp 34–36 °C/25 Torr) afforded dichlorosulfine (22); yield: 32%.

18.10.2.1.3

Method 3: Synthesis of Dibromosulfine

Dibromosulfine (thiocarbonyl dibromide S-oxide, 24) is synthesized from 2,2,4,4-tetrabromo-1,3-dithietane 1,3-dioxide (23), which is prepared from the corresponding thietane by trifluoroperacetic acid. The pyrolysis of dioxide 23 gives the sulfine 24 in 70% yield (Scheme 10).^[31]

Scheme 10 Synthesis of Dibromosulfine^[31]

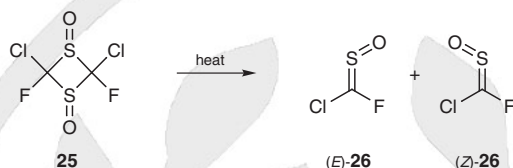
18.10.2.1.4

Method 4: Synthesis of Chlorofluorosulfine

As described in Section 18.10.2.1.1, allyl dichlorofluoromethyl sulfoxide is pyrolyzed to give the chlorofluorosulfine. The formation was identified by using a mass spectrophotometer.^[28]

Pyrolysis of 2,4-dichloro-2,4-difluoro-1,3-dithietane 1,3-dioxide (**25**), synthesized from the corresponding dithietane and hydrogen peroxide, affords chlorofluorosulfine (**26**) as a mixture of *Z*- and *E*-isomers (Scheme 11). The structures of these two isomers of **26** were determined by ^{19}F NMR.^[24]

Scheme 11 Synthesis of Chlorofluorosulfine^[24]

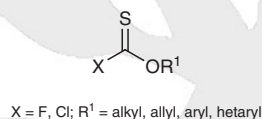


18.10.3

Product Subclass 3:
Halothioformate O-Esters (Carbonohalidothioate O-Esters)

The structure of this subclass of compounds is shown in Scheme 12, where X is a halogen atom (F, Cl) and R¹ is an alkyl or an aryl or hetaryl moiety and is discussed in *Houben–Weyl*, Vol. E 4, p 411. Other review articles and books are also available.^[1]

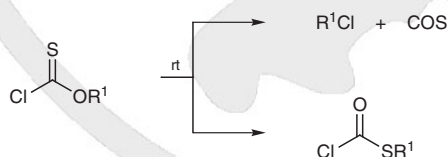
Scheme 12 O-Alkyl, O-Aryl, or O-Hetaryl Chlorothioformates



In general, halothioformate *O*-esters (sometimes named as *O*-alkyl or *O*-aryl halothiocarboxonates, halothionoformates, carbonohalidothioate *O*-esters, or halothiocarboxonate *O*-esters) bearing either a fluorine or a chlorine atom and either an alkoxy or an aryloxy group at the thiocarbonyl group are known. The chloro derivatives are most common and a few fluoro derivatives are known.

In general, halothioformate *O*-esters are thermally stable liquid compounds with a sharp boiling point at atmospheric pressure or reduced pressure. However, *O*-alkyl chlorothioformates can decompose gradually even at room temperature and rapidly at higher temperatures to give one of two different product mixtures (Scheme 13).^[32,33] Therefore, *O*-alkyl chlorothioformates should be stored at low temperature in a refrigerator. The aryl esters are stable and can be stored at room temperature.

Scheme 13 Thermal Decomposition of O-Alkyl Chlorothioformates^[32,33]

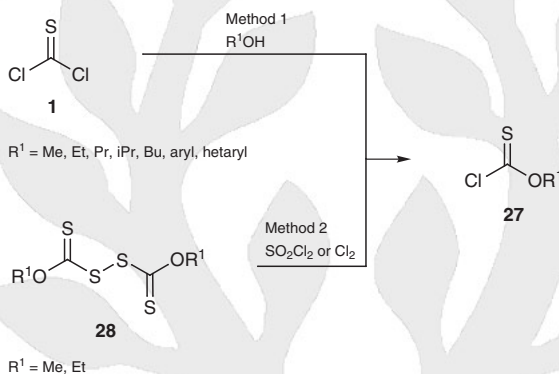


Although *O*-alkyl chlorothioformates are stable at room temperature, they undergo hydrolysis in an S_N1-like fashion as indicated by examining the substituent effect of the alkyl group attached at the alkoxy group. The first-order reaction rate of the hydrolysis of chlorothioformates *O*-esters follows the order, R¹ = *i*Pr > Et > Me and the solvent isotope effect also agrees with the S_N1 mechanism.^[34–36]

In the case of aryl derivatives, the hydrolysis reactions proceed via an addition–elimination process in less-polar solvents and the mechanism shifts to an S_N1 -like processes in polar solvents.^[34–38]

There are two major routes for the synthesis of the chlorothioformate *O*-esters **27** (Scheme 14). The first method discussed in Section 18.10.3.1.1 is the substitution of the chlorine atom of thiophosgene (**1**) with an appropriate alcohol or phenol in the presence of a base such as sodium or potassium hydroxide or amine in chloroform or hydrocarbon as a solvent.^[37,39–42] The yields are relatively high. The second method involves the use of disulfides **28** and chlorinating agents and is discussed in Section 18.10.3.1.2.

Scheme 14 Synthesis of Chlorothioformate *O*-Esters^[37,39–42]



18.10.3.1

Synthesis of Product Subclass 3

18.10.3.1.1

Method 1:

From Thiocarbonyl Dihalides and Alcohols and Phenols

Chlorothioformate *O*-esters **29** can be synthesized by the substitution of the chlorine atom of thiophosgene (**1**) with an appropriate alcohol or phenol in the presence of a base such as sodium or potassium hydroxide or an amine in chloroform or hydrocarbon as a solvent.^[37,39–41] The yields are relatively high (Table 1). *O*-Alkyl chlorothioformates containing a primary alkyl group are relatively stable, while those containing a secondary alkyl group are unstable and thermally decompose, for example, *O*-isopropyl chlorothioformate (**29**, R¹ = iPr) decomposes on standing at room temperature for one day to carbonyl sulfide and 2-chloropropane.^[39] This procedure is best used for primary and secondary *O*-alkyl chlorothioformates.^[37,40–43] *O*-Aryl chlorothioformates **29** are simply prepared according to this procedure from thiophosgene (**1**) and phenols or naphthols in the presence of sodium hydroxide or triethylamine as a base in a solvent such as benzene, toluene, or chloroform in good yields.^[44–48]

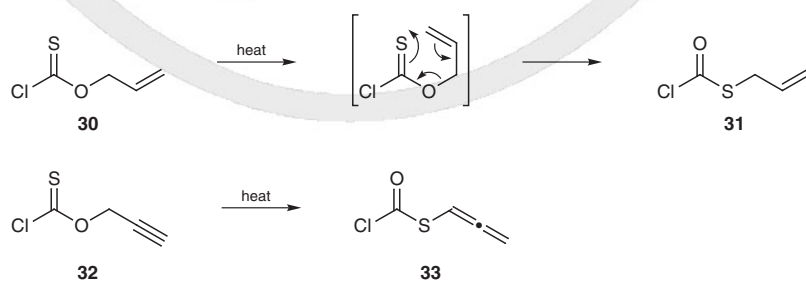
Table 1 Synthesis of Chlorothioformate O-Esters^[39,44–46,49]

$\text{Cl}-\text{C}(=\text{S})-\text{Cl} \xrightarrow{\text{R}'\text{OM}} \text{Cl}-\text{C}(=\text{S})-\text{OR}'$

1 **29**

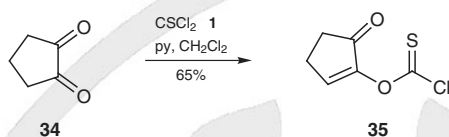
R ¹	M	Conditions	Yield (%)	Ref
Et	K	EtOH, THF, –65 °C, 1 h	81	[39]
Et	K	THF, –65 °C, 1 h	50	[39]
Pr	K	PrOH, THF, –65 °C, 1 h	91	[39]
Pr	K	THF, –65 °C, 1 h	90	[39]
iPr	K	THF, –65 °C, 1 h	88	[39]
Bu	K	THF, –65 °C, 1 h	78	[39]
iBu	K	THF, –65 °C, 1 h	70	[39]
3-ClC ₆ H ₄	Na	CHCl ₃ , 0–10 °C, 1 h	78	[44]
4-ClC ₆ H ₄	Na	CHCl ₃ , 0–10 °C, 1 h	81	[44]
3,4-Cl ₂ C ₆ H ₃	Na	CHCl ₃ , 0–10 °C, 1 h	83	[44]
4- <i>t</i> -BuC ₆ H ₄	Na	CHCl ₃ , 0–10 °C, 1 h	81	[44]
2-Cl-4-O ₂ NC ₆ H ₃	Na	CHCl ₃ , 0–10 °C, 1 h	50	[44]
2,6-Et ₂ C ₆ H ₃	Na	CHCl ₃ , 10–15 °C, 1 h	56	[45,46]
2,6-iPr ₂ C ₆ H ₃	Na	CHCl ₃ , 10–15 °C, 1 h	23	[45,46]
2,6- <i>t</i> -Bu ₂ C ₆ H ₃	Na	CHCl ₃ , 10–15 °C, 1 h	71	[45,46]
4-MeO-2,6- <i>t</i> -Bu ₂ C ₆ H ₂	Na	CHCl ₃ , 10–15 °C, 1 h	66	[45,46]
2-PhC ₆ H ₄	Na	CHCl ₃ , 10–15 °C, 1 h	50	[45,46]
4-PhC ₆ H ₄	Na	CHCl ₃ , 0–10 °C, 1 h	88	[49]
4-PhC ₆ H ₄	Na	CHCl ₃ , 10–15 °C, 1 h	23	[45,46]

Preparation of chlorothioformate *O*-esters bearing an *O*-allyl or an *O*-propargyl group, e.g. **30** and **32**, respectively, does not succeed but instead results in the formation of the corresponding [3,3]-sigmatropic rearrangement products (e.g., **31** and **33**) bearing an allylsulfanyl or propa-1,2-dienylsulfanyl group at room temperature or on heating the chlorothioformate *O*-esters. Unsubstituted allylic **30** or propargylic derivatives **32** can be prepared by treatment of allyl alcohol with thiophosgene (**1**) in the presence of sodium hydride at –78 °C in diethyl ether for 1 hour; on warming to room temperature they rearrange to the corresponding chlorothioformate *S*-esters **31** and **33**, thus supporting the mechanism shown in Scheme 15.^[43,50]

Scheme 15 [3,3]-Sigmatropic Rearrangement of *O*-Allyl and *O*-Prop-2-ynyl Chlorothioformate to *S*-Allyl and *S*-Propa-1,2-dienyl Chlorothioformate^[43,50]

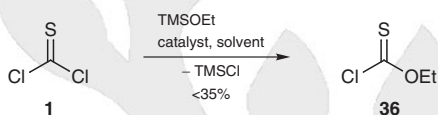
Cyclopentane-1,2-dione (**34**) reacts with thiophosgene (**1**) in the presence of pyridine to give *O*-(2-oxocyclopentyl) chlorothioformate (**35**) in 65% yield (Scheme 16).^[51]

Scheme 16 Synthesis of *O*-(2-Oxocyclopentyl) Chlorothioformate^[51]



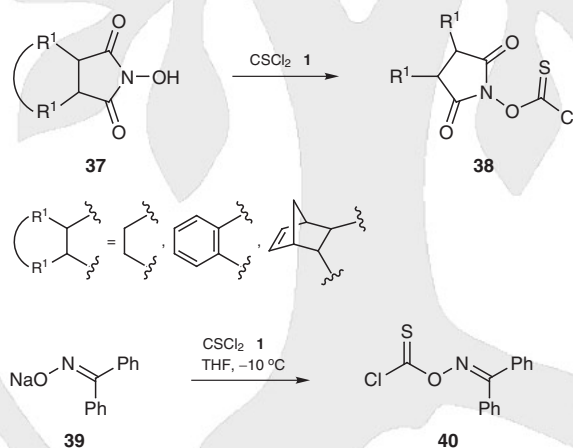
The reaction of ethoxytrimethylsilane and thiophosgene (**1**) in many solvents, such as benzene, dioxane, and tetrahydrofuran, using catalysts such as hydrochloric acid, aluminum chloride, and boron trifluoride is also used for preparation of *O*-ethyl chlorothioformate (**36**) in less than 35% yield as shown in Scheme 17.^[39]

Scheme 17 Synthesis of *O*-Ethyl Chlorothioformate^[39]



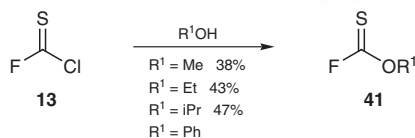
Hydroxylamines **37** also give *O*-amino chlorothioformate derivatives **38** as shown in Scheme 18. Similarly, the sodium salt of benzophenone oxime sodium salt **39** reacts with thiophosgene (**1**) in tetrahydrofuran at below 10°C to give the corresponding chlorothioformate **40** (Scheme 18).^[52]

Scheme 18 Synthesis of *O*-Amino Chlorothioformates^[52]



O-Alkyl and *O*-phenyl fluorothioformates **41** are prepared by the substitution reaction of thiocarbonyl chloride fluoride (**13**) with an alcohol without solvent (Scheme 19). In this reaction, the chlorine atom is substituted selectively.^[23]

Scheme 19 Synthesis of *O*-Alkyl and *O*-Phenyl Fluorothioformate^[23]



O-Alkyl Chlorothioformates 29; General Procedure:^[39]

CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

K (3.9 g, 0.1 mol) was added in small pieces to the respective alcohol (50 mL) with stirring at 25 °C under N_2 . The resultant alkoxide soln could be directly used; if not, the excess of alcohol was removed under N_2 in a rotary evaporator and the residue was dissolved in anhyd THF (20 mL). In a three-necked flask were placed freshly distilled thiophosgene (**1**; 11.5 g, 0.1 mol) and anhyd THF (20 mL). Under stirring, the flask was submerged into a cold bath at –65 °C (dry ice, $\text{CHCl}_3/\text{BuOH}$ 2:1). The soln of the alkoxide in alcohol or THF was added dropwise over 60 min. Then, the mixture was immediately washed with distilled H_2O (2×100 mL) at rt. The organic layer was dried (MgSO_4) and the remaining solvent was removed by distillation (30–36 °C/180 Torr). The crude, light-colored product O-alkyl chlorothioformate **29** was thus obtained; it could be used directly in further reactions.

If the pure product was desired, the crude product was distilled in a pear-shaped flask fitted with a Vigreux column (length 20 cm, 1 cm i.d.) at 10–30 Torr under N_2 . Under these conditions, the froth that impaired the previous distillation was reduced.

O-Biphenyl-4-yl Chlorothioformate (29, $\text{R}^1 = 4\text{-PhC}_6\text{H}_4$):^[49]

CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

Thiophosgene (**1**; 5.1 mL, 67 mmol) in CHCl_3 (40 mL) at 0 °C was treated dropwise with biphenyl-4-ol (11.9 g, 70 mmol) in 5% NaOH (60 mL). The mixture was stirred at 0–10 °C for 1 h, after which time the CHCl_3 layer was washed with dil HCl and H_2O , dried, and concentrated to give the crude product (16 g, 93%). This was recrystallized ($\text{MeOH}/\text{CHCl}_3$ 2:8) to give the desired product; yield: 15.1 g (88%); mp 68–70 °C.

O-2,6-Diethylphenyl Chlorothioformate (29, $\text{R}^1 = 2,6\text{-Et}_2\text{C}_6\text{H}_3$); Typical Procedure:^[45,46]

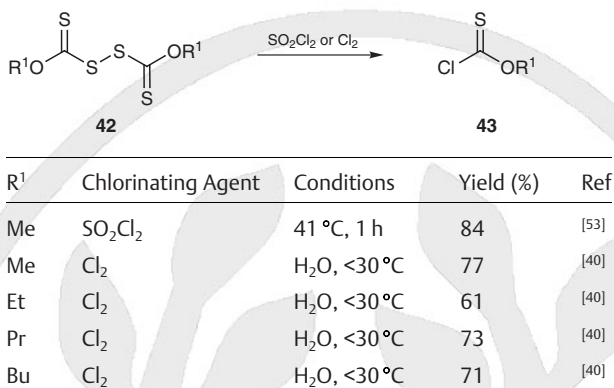
CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

2,6-Diethylphenol (22.6 g, 0.15 mol) in 2 M NaOH (75 mL) was added, with stirring, over 30 min to thiophosgene (**1**; 11.5 mL, 0.15 mol) in CHCl_3 (75 mL). The temperature was kept at 10–15 °C by ice cooling. After addition the soln was stirred for another 60 min. The organic phase was separated, washed with H_2O and dried (Na_2SO_4). The resulting red oil was vacuum distilled, and a yellow oil was obtained; yield: 19.1 g (56%); bp 130–136 °C/13 Torr; n_{D}^{25} 1.5525.

18.10.3.1.2

Method 2:**From Bis(alkoxythiocarbonyl) Disulfide and Sulfuryl Chloride or Chlorine**

O-Alkyl chlorothioformates **43** are produced by the chlorination of bis(alkoxythiocarbonyl) disulfides **42** with sulfuryl chloride^[42,53] or chlorine^[40] (Scheme 20). Previously, this method was not recommended as a preparative method of O-ethyl chlorothioformate because the yield was low when compared to the substitution of thiophosgene with an alcohol (Section 18.10.3.1.1) and also because the starting material was hardly to purify. However, since the procedure has been modified and improvements have been made to the purification method of the starting disulfide, this method can be utilized for preparation.^[37,42,53]

Scheme 20 Synthesis of O-Alkyl Chlorothioformates from Bis(alkoxythiocarbonyl) Disulfide^[40,53]**O-Methyl Chlorothioformate (43, R¹ = Me); Typical Procedure:**^[53]

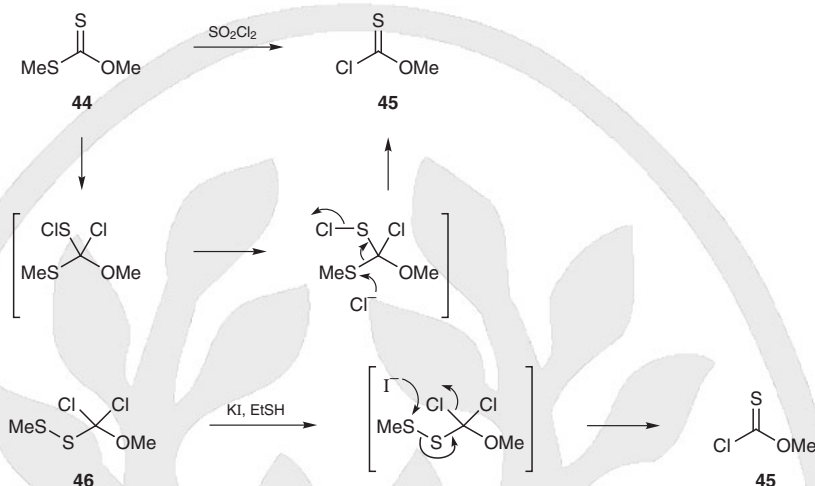
Sulfuryl chloride (80 mL, 1 mol) was added rapidly to a soln of bis(methoxythiocarbonyl) disulfide (214 g, 1 mol) in petroleum ether (bp 30–60 °C) (1 L). The mixture was refluxed (41 °C) for 1 h, and the solvent was then removed over 3 h by an aspirator through a 16-in. Vigreux column. The crude chlorination mixture (274 g, 84% incorporation of Cl₂) was transferred to a smaller flask with a 3-in. Vigreux head and subjected to a careful cracking distillation at reduced pressure provided by an aspirator. All material (110 g) boiling from 28–65 °C at a bath temperature of 75–120 °C and a vacuum of 15–40 Torr was collected in an ice-cooled receiver, and the time to stop the distillation was usually indicated by a pressure rise. The orange to black residue (78 g, 122% for 2 mol elemental sulfur) solidified overnight. The crude product, containing ca. 9% (w/w) of S₂Cl₂, was promptly treated with a mixture of pentanes (bp 35–39 °C) (2.4 equiv over the estimated amount of S₂Cl₂, generally ca. 20 mL, 0.18 mol). The mixture was maintained overnight at –15 °C and then fractionated through a 7-in. Vigreux column into a receiver cooled in an ice/salt bath to provide the pale yellow liquid chlorothioformate; yield: 93 g (84%); bp 23–24 °C/12 Torr.

18.10.3.1.3

**Methods 3:
Miscellaneous Methods**

Alternatively, O-alkyl chlorothioformates, such as O-methyl chlorothioformate (**45**), are prepared either by reaction of O,S-dimethyl dithiocarbonate (**44**) with sulfuryl chloride or trichloromethylsulfenyl chloride or by reaction of dichloro(methoxy)methyl methyl disulfide (**46**) with potassium iodide or alkanethiols (Scheme 21).^[53–55] The mechanism for the former reaction is considered to proceed via initial addition of chlorine across the thiocarbonyl group to form the sulfenyl halide and then chlorine-induced chlorination of the methylsulfanyl group to form the O-methyl chlorothioformate (**45**).

Scheme 21 Mechanism for Formation of *O*-Methyl Chlorothioformate from *O,S*-Dimethyl Dithiocarbonate or Dichloro(methoxy)methyl Methyl Disulfide^[53–55]



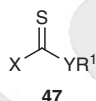
18.10.3.2 Applications of Product Subclass 3 in Organic Synthesis

O-Alkyl chlorothioformates are utilized in the preparation of many thiocarbonic acid derivatives.^[37] Among the aryl derivatives, *O*-phenyl chlorothioformate is a commercially available compound and can be widely used for the synthesis of various thiocarbonate *O,O*-esters. After thiocarbonate *O,O*-esters are formed from the corresponding alcohols and *O*-phenyl chlorothioformate, they undergo facile reduction to the corresponding hydrocarbons upon treatment with tributyltin hydride/2,2'-azobisisobutyronitrile. By this sequence of reactions compounds bearing a hydroxy group can be reduced to hydrocarbons.^[56]

18.10.4 Product Subclass 4: Halodithioformates and Halothioselenoformate *Se*-Esters

This subclass of compounds has the structure **47** (Scheme 22) and contains a dithioformyl or a thioselenoformyl functional group and one halogen atom attached to the thiocarbonyl functional group. These compounds have been reviewed in *Houben-Weyl*, Vol. E 4, p 414.

Scheme 22 Halodithioformates and Halothioselenoformate *Se*-Esters



X = F, Cl; Y = S, Se; R¹ = alkyl, allyl, aryl, hetaryl

Chlorodithioformates are the most frequently utilized in reactions and both the fluoro and bromo derivatives are known, however the iodo derivative has not been reported. Several synthetic methods are available for the preparation of halodithioformates. Substitution of one halogen in a thiocarbonyl dihalide with a thiolate has been successfully employed and is a commonly used procedure. In this synthesis, not only thiolates but also

selenolates can be used leading to thioselenoformate *Se*-esters. In addition, substitution of metal dithioformate salts with an alkyl halide, the reaction of carbon monosulfide and a sulfenyl halide, and the reaction of arenediazonium salts with carbon disulfide have been employed.

18.10.4.1 Synthesis of Product Subclass 4

18.10.4.1.1 Method 1: From Alkali Metal Chlorodithioformates and Alkyl Iodides

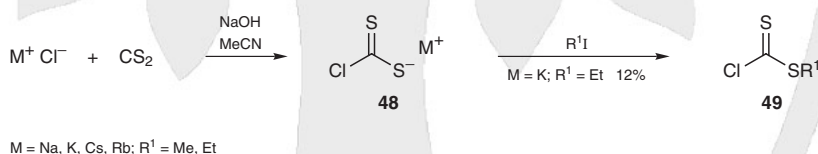
Alkali metal halodithioformates are prepared by similar methodology to the formyl derivatives which are obtained from carbon dioxide and alkali metal fluorides (i.e., cesium fluoride) under pressure in acetonitrile. Interestingly, this treatment results in the formation of the cesium salt of fluoroformates by the insertion of carbon dioxide into the Cs–F bond.^[57–59] However, when carbon disulfide is treated with alkali metal fluorides, no insertion reaction is observed but treatment of carbon disulfide with alkali metal chlorides gives the expected chlorodithioformates **48** (Scheme 23).^[60] The salts **48** are unstable and extreme caution should be exercised when handling them.

A fluorodithioformate metal salt $[F-C(S)S]^-M^+$ was first reported from the insertion reaction of carbon disulfide into the Pt–F bond of the platinum complex $PtF(HF_2)(PPh_3)_3$, which gives $Pt(HF_2)(S_2CF)(PPh_3)_3$ upon treatment with fluorodithioformate. The structure of this unique compound was determined by X-ray crystallographic analysis.^[61]

A modified preparative method for the alkali metal chlorodithioformates **48** uses the reaction of carbon disulfide and alkali metal chlorides (e.g., Na, K, Cs, Rb) in acetonitrile in the presence of catalytic solid sodium hydroxide (Scheme 23).^[62]

The gravimetric analysis of the salts revealed that the content of the alkali metal was identical with those of the calculated values of a simple molecular formula. The attempted synthesis of fluoro-, bromo-, and iododithioformates in a similar manner has been unsuccessful.

Scheme 23 Synthesis of Chlorodithioformates^[62]



The alkali metal chlorodithioformates **48** ($M = Na, K, Cs, Rb$) can be isolated as unstable, yellow-colored compounds that decompose at room temperature with a color change from yellow to white; these compounds must be stored at low temperature. The sodium chlorodithioformate salt **48** ($M = Na$) is strongly hygroscopic, but other metal analogues are not. These compounds are very soluble in methanol and dimethyl sulfoxide as well as water (with decomposition) but insoluble in most organic solvents.

Attempted formation of the free chlorodithioformic acid by acidification of the salt with concentrated hydrochloric acid is unsuccessful.

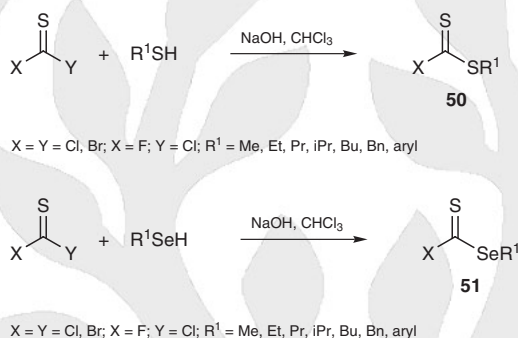
The structure of potassium chlorodithioformate was identified by converting the salt to ethyl chlorodithioformate (**49**; $R^1 = Et$) by reaction with iodoethane and this compared with the authentically prepared compound from thiophosgene and ethanethiol.^[60]

18.10.4.1.2

Method 2:**Halogen Substitution of Thiocarbonyl Dihalides with Thiolates and Selenolates**

In general, halodithioformates **50** and thioselenoformate Se-esters **51** are prepared by the substitution reaction of one halogen atom of a thiocarbonyl dihalide with a thiolate or selenolate (Scheme 24).

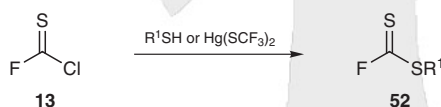
Scheme 24 General Synthesis of Halodithioformates and Halothioselenoformate Se-Esters



Several preparative methods for fluorodithioformates **52** are available. When thiocarbonyl chloride fluoride (**13**) is treated with alkanethiols (e.g., MeSH, EtSH) in the absence of solvent, the chlorine atom is substituted selectively to give alkyl fluorodithioformates **52** ($\text{R}^1 = \text{Me, Et}$) (Scheme 25).^[23]

Similarly, trifluoromethyl fluorodithioformate (**52**, $\text{R}^1 = \text{CF}_3$) is synthesized from trifluoromethanethiol and thiocarbonyl chloride fluoride (**13**) with ammonia or with potassium fluoride in 40 and 58% yield, respectively. When mercury bis(trifluoromethanethiolate) is used the yield of **52** ($\text{R}^1 = \text{CF}_3$) increases to 96%.^[63]

Scheme 25 Synthesis of Fluorodithioformates^[23,63]



R ¹	Reagent, Conditions	Yield (%)	Ref
Me	MeSH	—	[23]
Et	EtSH	—	[23]
CF ₃	F ₃ CSH, NH ₃	40	[63]
CF ₃	F ₃ CSH, KF	58	[63]
CF ₃	Hg(SCF ₃) ₂	96	[63]

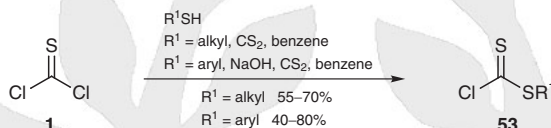
There are several methods for the preparation of alkyl and aryl chlorodithioformates **53** ($\text{R}^1 = \text{alkyl, aryl}$). Generally, the reaction of alkane- or arenethiols with thiophosgene (**1**) in dry carbon disulfide or benzene at room temperature is employed as the standard synthetic procedure for the formation of chlorodithioformates **53** (Scheme 26).^[64] Alkyl chlorodithioformates **53** ($\text{R}^1 = \text{Et, Pr, iPr, Bu, s-Bu}$) are obtained in 55–70% yield in the absence of a base at around room temperature.^[64] Similarly, aryl dithioformates **53** are prepared

from arenethiols and thiophosgene at room temperature in the presence of sodium hydroxide in benzene or carbon disulfide in 40–80% yields.^[37,65] The chlorodithioformates can be stored at -20°C .

Perchloro and perfluoro derivatives are also prepared by treatment of the corresponding thiols and thiophosgene (**1**) in dichloromethane or chloroform in the presence of sodium hydroxide. The alkyl esters are, in general, yellow-gold substances and have an onion-like odor.^[63]

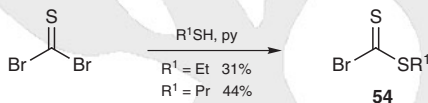
The synthesis of various chlorodithioformates and related derivatives have been reported.^[66–68]

Scheme 26 Synthesis of Chlorodithioformates^[64,65,69]



Bromodithioformates **54** are prepared from thiocarbonyl dibromide with alkane thiols ($\text{R}^1 = \text{Et}$, Pr) in the presence of pyridine as a base (Scheme 27).^[70]

Scheme 27 Synthesis of Bromodithioformates^[70]



Se-Trifluoromethyl fluorothioselenoformate is prepared from bis(trifluoromethylselenanyl)mercury and thiocarbonyl chloride fluoride (**13**) at -78°C .^[71] Se-Ethyl and Se-propyl chlorothioselenoformates are synthesized from thiophosgene (**1**) and ethaneselenol or propane-1-selenol. These seleno esters are viscous oils that are soluble in most organic solvents.^[70]

Alkyl Chlorodithioformates **53** ($\text{R}^1 = \text{Alkyl}$) from Thiophosgene and an Alkanethiol; General Procedure:^[64]

CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

In a flask, thiophosgene (**1**; 0.25 mol) was added to an alkanethiol (0.25 mol) in dry CS_2 (100 mL) at rt, and CS_2 was removed by distillation (50 mL). The apparatus was loosely closed so that HCl was removed but the entrance of moisture was prohibited. The evolved HCl gas together with the remaining thiol and thiophosgene was removed by passing the evolved gas through alkaline KMnO_4 soln. Gas evolution ceased after 30 min to 2 h and the turbid soln became clear. The soln was allowed to stand at rt for 48 h the solvent and the unreacted thiophosgene were also removed by an aspirator and attached with a flask filled with solid KOH between the flask and aspirator. The crude product was purified by vacuum distillation twice. The product was stored at -20°C under argon; yield: 55–70%.

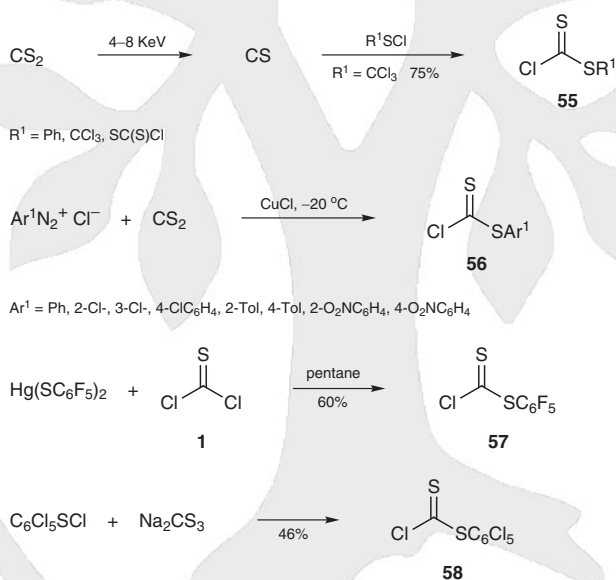
18.10.4.1.3

**Method 3:
From Carbon Disulfide**

There are several procedures for the preparation of chlorodithioformates that use carbon disulfide as a source of the thiocarbonyl group (Scheme 28). Insertion reaction of carbon monosulfide, generated from carbon disulfide by high electric discharge, into the S–Cl bond of a sulfenyl chloride gives chlorodithioformates **55**. This procedure can be used for production of both alkyl and aryl chlorodithioformates; trichloromethyl chlorodithioformate (**55**, $R^1 = CCl_3$) is obtained in 75% yield.^[72] The procedure is carried out by passing carbon disulfide through a high-voltage discharge apparatus and the carbon monosulfide thus generated is introduced into the sulfenyl chloride solution.^[16,21,73–75] Note: carbon monosulfide is a highly reactive species which polymerizes to $(CS)_n$ in an explosive fashion and hence caution is required for the large scale preparation of carbon monosulfide.^[16,21,73–75]

Arenediazonium chlorides react with carbon disulfide in the presence of copper(I) chloride to afford aryl chlorodithioformates **56**, however, yields are generally low, ca. 20%.^[76]

Pentafluorophenyl chlorodithioformate (**57**) is prepared from bis(pentafluorophenyl)sulfanylmercury and thiophosgene (**1**) in 60% yield.^[77] Pentachlorophenyl chlorodithioformate (**58**) is prepared from pentachlorophenylsulfenyl chloride and sodium trithiocarbonate in 46% yield (Scheme 28).^[78]

Scheme 28 Synthesis of Chlorodithioformates^[16,21,72–78]**Trichloromethyl Chlorodithioformate (55, $R^1 = CCl_3$):**^[72]

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

CAUTION: Carbon monosulfide is a highly reactive species which polymerizes to $(CS)_n$ in an explosive fashion and hence caution is required for a large scale preparation of carbon monosulfide.^[16,21,73–75]

CS was generated in a conventional vacuum line by passing CS_2 vapor through a high-voltage AC discharge as described in the literature.^[16,74] After leaving the discharge tube, CS

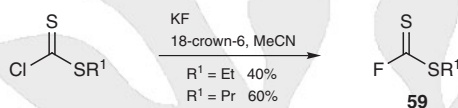
was immediately passed through a stirred soln of Cl_3CSCl (37.2 g, 200 mmol) in toluene (50 mL) kept at -78°C . A color change from yellow to red took place and after the passage of 54 mL (900 mmol) of CS_2 , the reaction was stopped. A small amount of precipitate was removed by filtration and toluene, excess sulfenyl chloride, and excess CS_2 were removed in vacuo. The remaining red oil was purified by column chromatography (silica gel, petroleum ether) to give an orange oil; yield: 25.2 g (75%, corrected for 9.7 g of recovered sulfenyl chloride). The product was distilled (bp $98\text{--}100^\circ\text{C}/14\text{ Torr}$).

18.10.4.1.4 Method 4: By Halogen Exchange

Substitution of the chlorine of ethyl and propyl chlorodithioformates with fluoride under phase-transfer catalyzed conditions using 18-crown-6 in acetonitrile gives the corresponding fluorodithioformate **59** (Scheme 29).^[69,73]

Trifluoromethyl fluorodithioformate is converted into trifluoromethyl chlorodithioformate on treatment with boron trichloride.^[24]

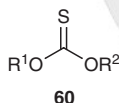
Scheme 29 Fluorodithioformates by Chloro–Fluoro Exchange from Chlorodithioformates^[69,73]



18.10.5 Product Subclass 5: Thiocarbonate O,O-Diesters

These compounds have structure **60** with two alkoxy or aryloxy groups attached to the thiocarbonyl group (Scheme 30), they are discussed in *Houben–Weyl*, Vol. E 4, p 420, and other review articles.^[2]

Scheme 30 Thiocarbonate O,O-Diesters



$\text{R}^1, \text{R}^2 = \text{alkyl, allyl, aryl, hetaryl}$

There are four major starting materials for the synthesis of thiocarbonate O,O-diesters: (1) thiophosgene (**1**), (2) carbon disulfide, (3) O-aryl chlorothioformates, and (4) carbonylbis-azoles. These reagents are mostly commercially available and on treatment with alcohols or phenols in the presence of a suitable base they afford both symmetrical and nonsymmetrical thiocarbonate O,O-diesters in high yields. Several organometallic reagents such as organogermanium or organotin compounds have also been used.

The importance of thiocarbonate O,O-esters lies in their ease of use as synthetic intermediates in many important sequences for the transformation of functional groups, for example, the Schönberg reaction, the Chugaev elimination, the Corey–Winter alkenation synthesis, the Barton–McCombie deoxygenation of alcohols, and radical substitution reactions. As their synthesis and use are inextricably linked, we have included details of their use in the section on the synthesis of thiocarbonate O,O-esters (Section 18.10.5.1), while details of their synthesis can also be found in the applications section (Section 18.10.5.2); cross references are given between these sections.

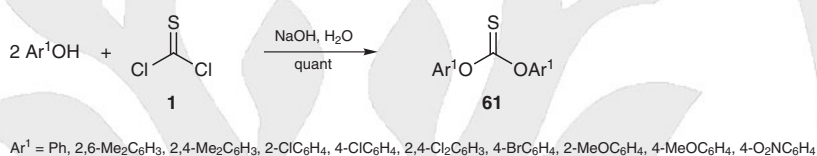
18.10.5.1 Synthesis of Product Subclass 5

18.10.5.1.1 Method 1:
From Thiophosgene and Alcohols and Phenols

The reaction of thiophosgene (**1**) with alcohols or phenols in the presence of base is the simplest and most feasible method for the preparation of symmetrically substituted cyclic and acyclic thiocarbonate *O,O*-diesters. A drawback is that thiophosgene (**1**) is a low boiling liquid and is toxic and hence must be handled with caution and for this reason aryl chlorothioformates and 1,1'-thiocarbonyldiimidazole are preferred.

The reaction of a phenol with thiophosgene (**1**) and sodium hydroxide in water gives *O,O*-diaryl thiocarbonates **61** in quantitative yield (Scheme 31).^[79,80] Similarly, preparation of several other *O,O*-diaryl thiocarbonates including naphthalene and hetaryl derivatives has been reported.^[80–82] There are various examples of the synthesis of *O,O*-dialkyl thiocarbonates from thiophosgene and an alcohol.^[42]

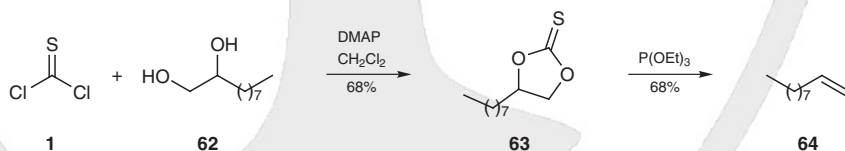
Scheme 31 Synthesis of *O,O*-Diaryl Thiocarbonates^[79–82]



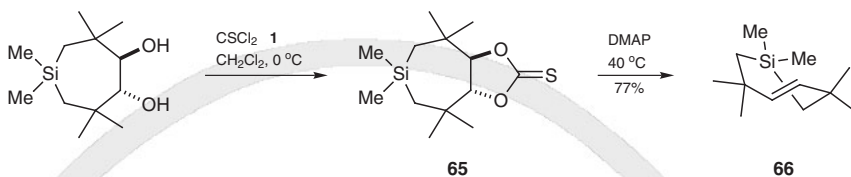
Both cyclic and acyclic 1,2-diols and thiophosgene (**1**) react readily to give the corresponding 1,3-dioxolane-2-thione derivatives in the presence of a base such as 4-(dimethylamino)pyridine. This ring formation proceeds in a stereo- and regioselective fashion and, even in the presence of other functional groups, vicinal hydroxy groups react chemoselectively in high yield.^[83]

An example is the conversion of decane-1,2-diol (**62**), which reacts with thiophosgene (**1**) in dichloromethane in the presence of 4-(dimethylamino)pyridine, into 3-octyl-1,3-dioxolane-2-thione (**63**) in 68% yield (Scheme 32). Thiocarbonate derivative **63** finally gives dec-1-ene (**64**) on treatment with triethyl phosphite in refluxing toluene.^[83]

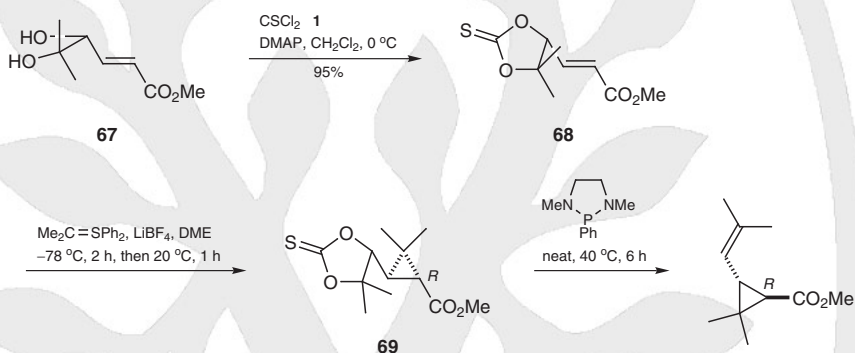
Scheme 32 Synthesis of 1,3-Dioxolane-2-thione^[83]



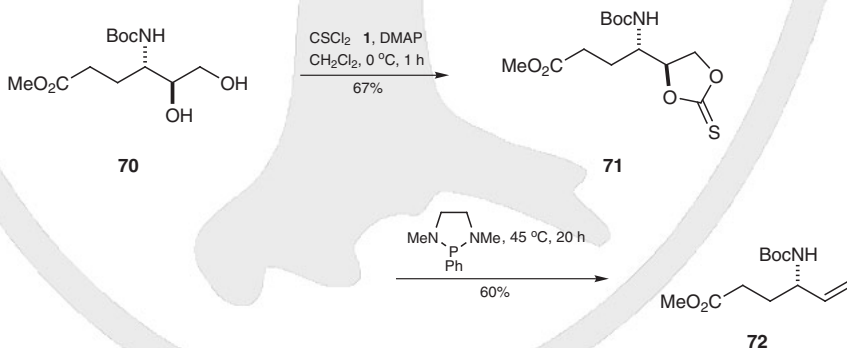
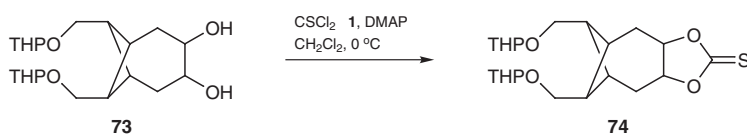
Although compounds containing a C=C bond with *E* geometry inside a six- or seven-membered carbocyclic ring have not been isolated due to ring strain, an enantiomerically pure (*E*)-1,1,3,3,6,6-hexamethyl-1-silacyclohept-4-ene (**66**) has been synthesized from the corresponding *O,O*-cyclic thiocarbonate **65** in 77% yield (Scheme 33). This result indicates that replacement of one carbon by one silicon atom in a cycloheptene reduces the ring strain.^[84]

Scheme 33 Synthesis of an Optically Pure Silacycloheptene^[84]

Optically pure (1*R*)-*trans*-chrysanthemic acid methyl ester is prepared starting from methyl hexa-2,4-dienoate in 4 steps (Scheme 34). Intermediates in this synthesis include the methyl 4,5-dihydroxy-5-methylhex-2-enoate **67** which is converted into the 1,3-dioxolane-2-thione **68**, this reacts with isopropylidenediphenyl-λ⁴-sulfane to give **69**, which undergoes Corey–Winter alkene formation by treatment with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine.^[85]

Scheme 34 Synthesis of (1*R*)-*trans*-Chrysanthemic Acid Methyl Ester^[85]

Various examples of the synthesis of natural products via 1,3-dioxolane-2-thione derivatives are available.^[86–93] These include the formation of (*S*)-vigabatin (**72**) from amino acid ester **70** via 1,3-dioxolane-2-thione **71** (Scheme 35)^[90] The formation of the tricyclic compound **74** from diol **73** has also been reported (Scheme 36).^[93]

Scheme 35 Enantioselective Synthesis of (*S*)-Vigabatin^[90]**Scheme 36** Synthesis of a Tricyclic Thiocarbonate O,O-Ester^[93]

(S)-Vigabatrin (72):^[90]

CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

To a stirred soln of methyl (4*S*,5*S*)-4-(*tert*-butoxycarbonylamino)-5,6-dihydroxyhexanoate (**70**; 95 mg, 0.34 mmol) and DMAP (101 mg, 0.82 mmol) in dry CH_2Cl_2 (1.4 mL) at 0 °C was added 95% thiophosgene (**1**; 33 μL , 0.41 mmol) under N_2 . The mixture was stirred for 1 h at 0 °C. Then, silica gel (0.7 g) was added and the mixture was allowed to warm to 25 °C. After removal of the solvent in vacuo, the remaining solid was loaded onto a column and chromatographed [silica gel (2.0 g), hexanes/ EtOAc 8:2] to afford **71** as a white solid; yield: 73 mg (67%); mp 133–136 °C; $[\alpha]_{\text{D}} -33.5$ (c 1.8, CHCl_3).

A suspension of thiocarbonate *O,O*-ester **71** (41 mg, 0.13 mmol) in 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (75 μL , 0.38 mmol) was stirred under argon at 45 °C for 20 h. After cooling to rt, the crude mixture was purified twice by chromatography on a preparative TLC plate ($\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ 97:3) to afford an oil; yield: 19 mg (60%); $[\alpha]_{\text{D}} +11.4$ (c 1, CHCl_3).

(3*R*,4*S*)-7-*exo*,8-*anti*-Bis[(tetrahydro-2*H*-pyran-2-yloxy)methyl]-3,4-(thiocarbonyldioxy)bicyclo[4.1.1]octane (74):^[93]

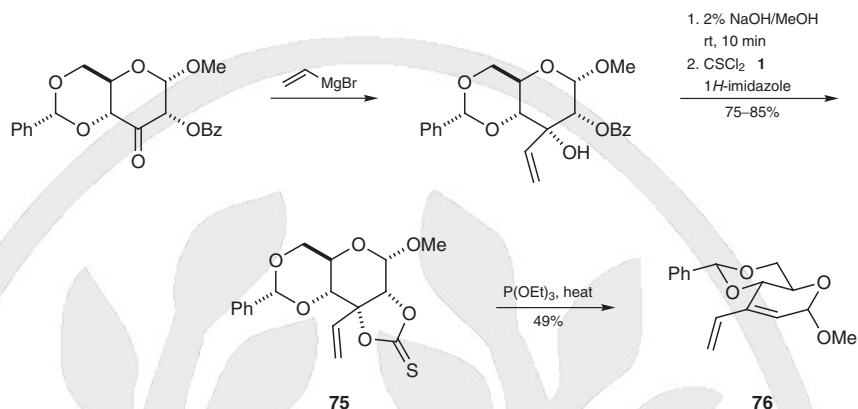
CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

Freshly sublimed DMAP (7.90 g, 64.8 mmol) and (1*R*,4*S*)-7-*exo*,8-*anti*-bis[(tetrahydro-2*H*-pyran-2-yloxy)methyl]bicyclo[4.1.1]octane-3,4-diol (**73**; 10.0 g, 27.0 mmol) were dissolved in anhyd CH_2Cl_2 (100 mL) under N_2 and cooled to 0 °C. An 85% thiophosgene soln in CCl_4 (2.5 mL, 32.4 mmol) was slowly injected with vigorous stirring. The intensively orange-red emulsion quickly faded and a solid precipitated. After one night at 0 °C, Et_2O (100 mL) was added dropwise at 0 °C to precipitate as much DMAP hydrochloride as possible. The suspension was filtered through a sintered-glass funnel, and the solids were washed with Et_2O (3 \times 50 mL). The combined filtrates were concentrated and chromatographed (silica gel, Et_2O) to give **74** as a pale yellow, viscous oil; yield: 13.0 g (theoretical yield: 11.1 g).

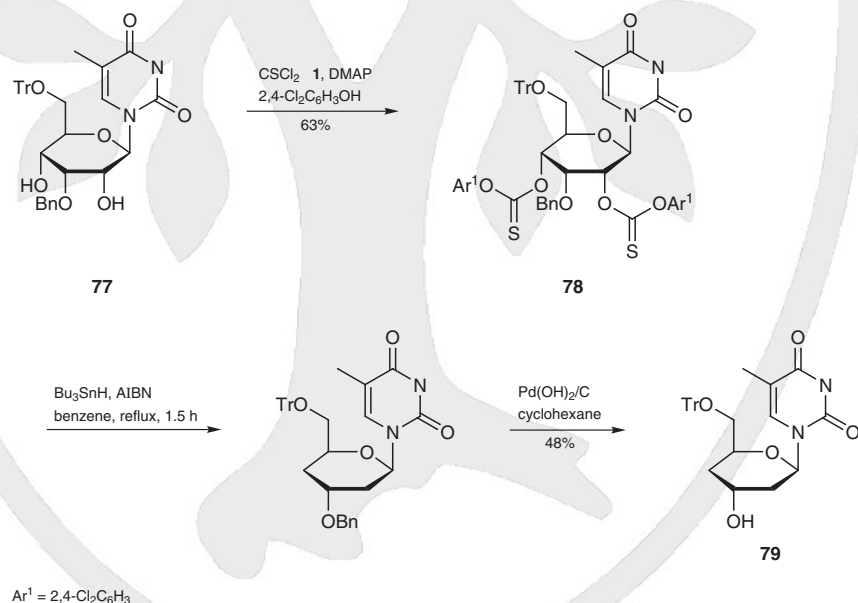
18.10.5.1.1.1

Variation 1:**Synthesis of Thiocarbonate *O,O*-Esters of Sugars**

A carbohydrate derivative bearing vicinal dihydroxy groups is converted into the corresponding 1,3-dioxolane-2-thione fused derivative **75** by reaction with thiophosgene in the presence of an appropriate base (Scheme 37). Further reaction with triethyl phosphite (the Corey–Winter reaction) affords the alkene **76** in high yield. This is a convenient method for conversion of a sugar derivative into a dehydrosugar, which are useful compounds for medicinal chemistry, for example **76** is starting material for the synthesis of antibiotics such as adriamycin.^[94]

Scheme 37 Thiocarbonate of an α -D-Allopyranoside^[94]

The sugar moieties of nucleosides are converted into the dideoxylation product by similar methods. This conversion of the sugar hydroxy groups into the corresponding 1,3-dioxolane-2-thione can be used in a mild and convenient procedure in the synthesis of dideoxynated sugars that are hard to access by other routes. Thus 2,4-dideoxy- β -D-erythrohexopyranosyl nucleoside **79** is synthesized from D-glucose, which was dideoxynated at the 2,4-hydroxy groups after introduction of thymine and conversion of the protected sugar **77** into bis[O-(2,4-dichlorophenyl) thiocarbonate] **78** (Scheme 38).^[95]

Scheme 38 Synthesis of a Dideoxynated Hexopyranosyl Nucleoside^[95]

1-{3-O-Benzyl-2,4-bis-O-[(2,4-dichlorophenoxy)thiocarbonyl]-6-O-trityl- β -D-allopyranosyl}-5-methylpyrimidine-2,4(1H,3H)-dione (78):^[95]

CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

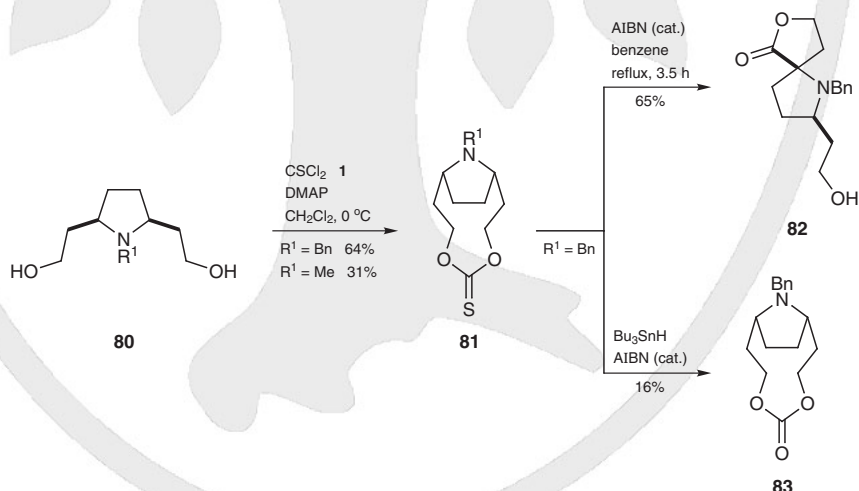
A mixture of **77** (4.97 g, 8.02 mmol) and DMAP (7.84 g, 64.2 mmol) in CH_2Cl_2 (150 mL) was treated with thiophosgene (**1**; 1.29 mL, 16.92 mmol) at -40°C . The mixture was kept for 100 min at a temperature between -40 and -20°C . Then, 2,4-dichlorophenol (5.23 g, 32.08 mmol) was added, and the mixture was stirred for 10 min at rt. After this, the soln was washed with cold 1 M KH_2PO_4 (300 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×200 mL). The combined organic layers were washed with sat. NaCl soln (20 mL), dried (MgSO_4), concentrated, and purified by column chromatography to give a white foam; yield: 5.21 g (63%).

18.10.5.1.1.2

**Variation 2:
By Macrocyclization**

In an interesting extension of thiocarbonate *O,O*-ester chemistry, *cis*-1-benzyl-2,5-bis(2-hydroxyethyl)pyrrolidine (**80**, $\text{R}^1 = \text{Bn}$) and *cis*-2,5-bis(2-hydroxyethyl)-1-methylpyrrolidine (**80**, $\text{R}^1 = \text{Me}$) are converted into the unusual macrocyclic thiocarbonate *O,O*-esters **81** on treatment with thiophosgene (**1**) and 4-(dimethylamino)pyridine in 64 and 31% yields, respectively (Scheme 39). This thiocarbonate *O,O*-ester **81** ($\text{R}^1 = \text{Bn}$) is refluxed in degassed benzene in the presence of only 2,2'-azobisisobutyronitrile for 3.5 hours under argon to afford the unusual spirocycle **82** in 65% yield together with the recovered **81** ($\text{R}^1 = \text{Bn}$) in 30% yield. When the reaction is conducted in the presence of tributyltin hydride according to the normal Barton–McCombie deoxygenation reaction, the spirocycle **82** is not obtained but recovered **81** ($\text{R}^1 = \text{Bn}$) and carbonate **83** are obtained in 65 and 16% yields, respectively.^[96]

Scheme 39 Synthesis of a Macrocyclic Thiocarbonate *O,O*-Ester^[96]



Azabicyclothiocarbonates **81; General Procedure:^[96]**

CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

Thiophosgene (**1**; 0.052 mmol) was added to a soln of a diol **80** (0.048 mmol) and DMAP (0.125 mmol) in CH_2Cl_2 (0.4 mL) at 0°C . The mixture was stirred for 30 min, then silica

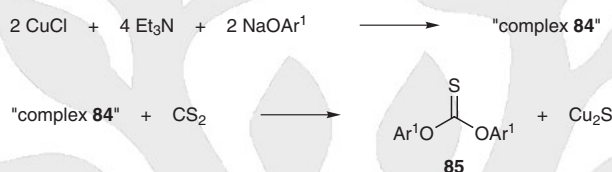
gel (80 mg) was added, and the whole was concentrated under reduced pressure to give an silica gel mass, which was purified by column chromatography (hexane/EtOAc 9:1).

18.10.5.1.2 Method 2: From Carbon Disulfide

Carbon disulfide is a useful starting material for the conversion of alcohols into the corresponding thiocarbonate *O,O*-esters in the presence of sodium hydroxide via the initial formation of *S*-sodium dithiocarbonate *O*-esters.

4-Bromophenol reacts with carbon disulfide in acetonitrile in the presence of triethylamine and copper(I) chloride to give the thiocarbonate *O,O*-ester **85** ($\text{Ar}^1 = 4\text{-BrC}_6\text{H}_4$) in 98% yield (Scheme 40). This reaction initially produces the complex **84** from a sodium phenolate, triethylamine and copper(I) chloride that reacts with carbon disulfide.^[97]

Scheme 40 Preparation of *O,O*-Diaryl Thiocarbonates^[97]



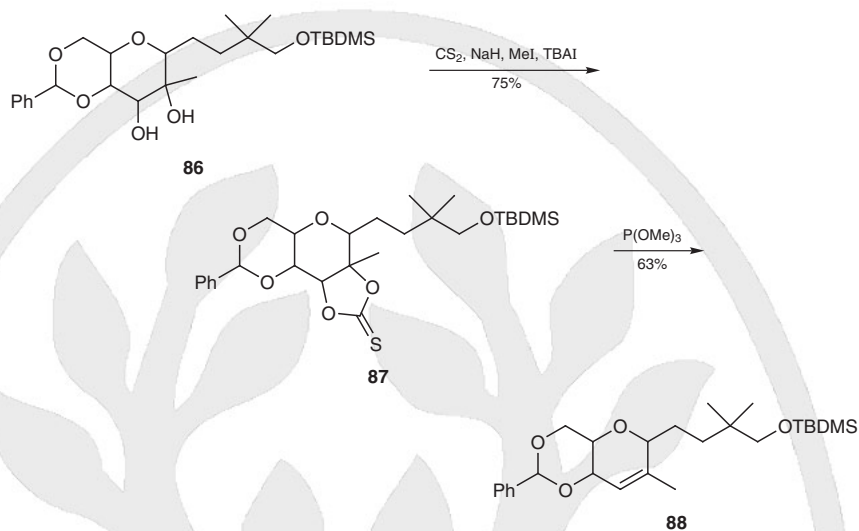
Ar^1	Base	Yield (%)	Ref
Ph	TMEDA	40	[97]
4-MeOC ₆ H ₄	pyridine	88	[97]
4-MeOC ₆ H ₄	Et ₃ N	66	[97]
3,5-Me ₂ C ₆ H ₃	Et ₃ N	71	[97]
4- <i>t</i> -BuC ₆ H ₄	Et ₃ N	76	[97]
4-NCC ₆ H ₄	Et ₃ N	70	[97]
4-MeO ₂ CC ₆ H ₄	Et ₃ N	95	[97]
4-BrC ₆ H ₄	Et ₃ N	98	[97]

The reaction of an alcohol with carbon disulfide in the presence of sodium or potassium hydroxide and then with an alkyl halide affords initially the corresponding dithiocarbonate *O*-esters that react further with alkoxides or phenoxides to give the thiocarbonate *O,O*-esters by eliminating the thiolates. Intramolecular reactions are utilized for the synthesis of cyclic thiocarbonate *O,O*-esters.^[98,99]

Propane-1,2-diol gives 4-methyl-1,3-dioxolane-2-thione in only 5% yield as a byproduct of *O,S*-dimethyl dithiocarbonate (72%) upon treatment of the diol with carbon disulfide in the presence of potassium hydroxide and then iodomethane in dimethyl sulfoxide.^[100] Similar reactions are reported in the literature.^[100,101]

This reaction has been extended to the transformation of the hydroxy groups in carbohydrates and nucleosides. As an example, the diol **86** is converted into the cyclic thiocarbonate *O,O*-ester **87**, which serves as a key intermediate for the synthesis of a sesquiterpenoid (Scheme 41). Treatment of **87** with trimethyl phosphite gives the alkene **88**.^[102,103]

Several other examples of the synthesis of thiocarbonate *O,O*-esters from carbon disulfide and their utilization in organic synthesis have been presented.^[104]

Scheme 41 A Thiocarbonate *O,O*-Ester as an Intermediate in Sesquiterpenoid Synthesis^[102,103]***O,O*-Diaryl Thiocarbonates 85; General Procedure:**^[97]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

Anhyd CuCl (5 mmol) was added to a suspension of a sodium phenolate in dry degassed MeCN (30 mL) under N_2 . After 1 h of stirring at rt, degassed Et_3N (10 mmol) was added as a soln in MeCN and the mixture was stirred a further 1 h, before adding CS_2 (5 mmol). After the mixture had turned brown (4 h), the solvent and Et_3N were removed under reduced pressure and the residue was extracted with Et_2O (3×20 mL) and CH_2Cl_2 (2×20 mL), and the combined organic layers were washed with dil NaOH and H_2O to remove any unreacted phenol, dried, and concentrated to give the crude thiocarbonate **85**. Recrystallization (abs EtOH) yielded analytically pure material.

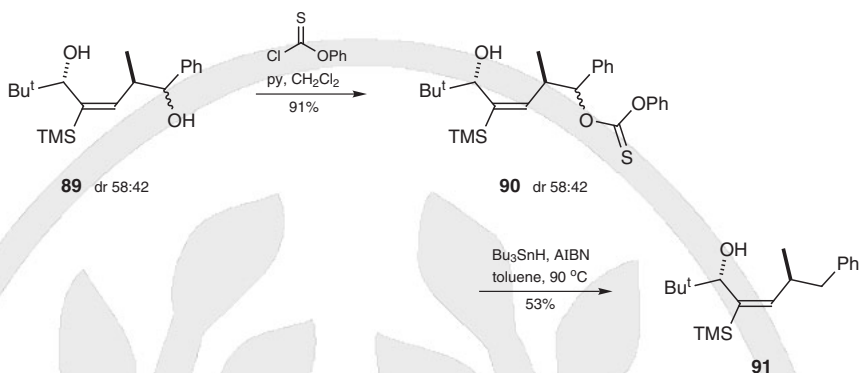
18.10.5.1.3

**Method 3:
From Chlorothioformate *O*-Esters**

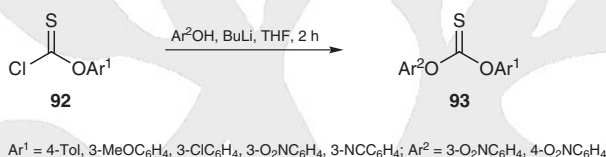
Chlorothioformate *O*-esters (Section 18.10.3) are useful reagents for the synthesis of thiocarbonate *O,O*-esters and several *O*-aryl chlorothioformates are commercially available.

In general, chlorothioformate *O*-esters react with alcohols and phenols in the presence of suitable bases such as 4-(dimethylamino)pyridine in appropriate solvents to afford the corresponding unsymmetrical thiocarbonate *O,O*-esters, which can subsequently undergo deoxygenation to result in the formation of the corresponding hydrocarbons in high yields (Section 18.10.5.2). For example, propan-2-ol reacts with *O*-phenyl chlorothioformate and pyridine in dichloromethane to afford *O*-isopropyl *O*-phenyl thiocarbonate in 92% yield.^[105]

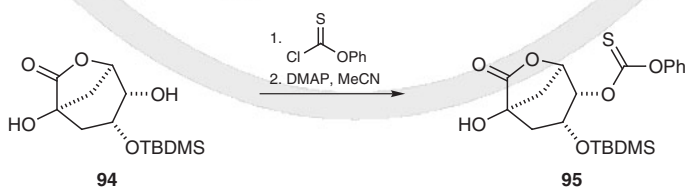
To determine the position of the hydroxy groups, the allenyl diol **89** was thiocarbonated using *O*-phenyl chlorothioformate and pyridine in dichloromethane to give *O*-phenyl thiocarbonate **90** highly chemoselectively in 91% yield. Reduction of **90** afforded the allenyl alcohol **91** as a single isomer (Scheme 42).^[106]

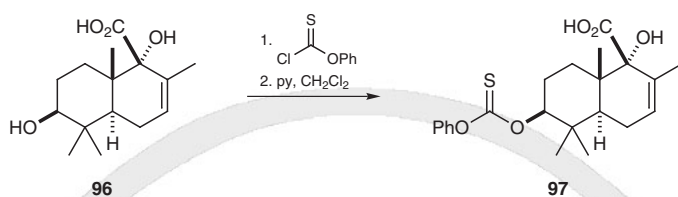
Scheme 42 Structural Determination of a Diol^[106]

There are many reports on the preparation of *O,O*-diaryl thiocarbonates. Both symmetrical and nonsymmetrical *O,O*-diaryl thiocarbonates **93** are prepared from phenols and *O*-aryl chlorothioformates **92** by a modified reaction using butyllithium as the base (Scheme 43).^[107–111]

Scheme 43 Synthesis of Unsymmetrical *O,O*-Diaryl Thiocarbonates^[107–111]

Not only simple alcohols but also many other compounds bearing hydroxy groups including natural products such as steroids and carbohydrates are converted into the corresponding thiocarbonate *O,O*-esters by simple treatment with *O*-aryl chlorothioformates in the presence of base. In the cases of polyol, the order of reactivity of the hydroxy group is primary > secondary > tertiary. Primary hydroxy groups must, therefore, be protected in order to allow selective reaction at a secondary alcohol. *O*-Aryl chlorothioformates bearing bulky substituents or electron-withdrawing substituents at the aryl group can be used to increase the chemoselection. Two examples are given here, in the first the bicyclic compound **94** contains a secondary and a tertiary hydroxy group, the secondary hydroxy group reacts preferentially to give the corresponding *O*-phenyl thiocarbonate **95** (Scheme 44).^[112,113] In the second example, the secondary hydroxy group of bicyclic octahydronaphthalenediol derivative **96** reacts with *O*-phenyl chlorothioformate to give *O*-phenyl thiocarbonate **97** in the presence of pyridine (Scheme 44).^[114]

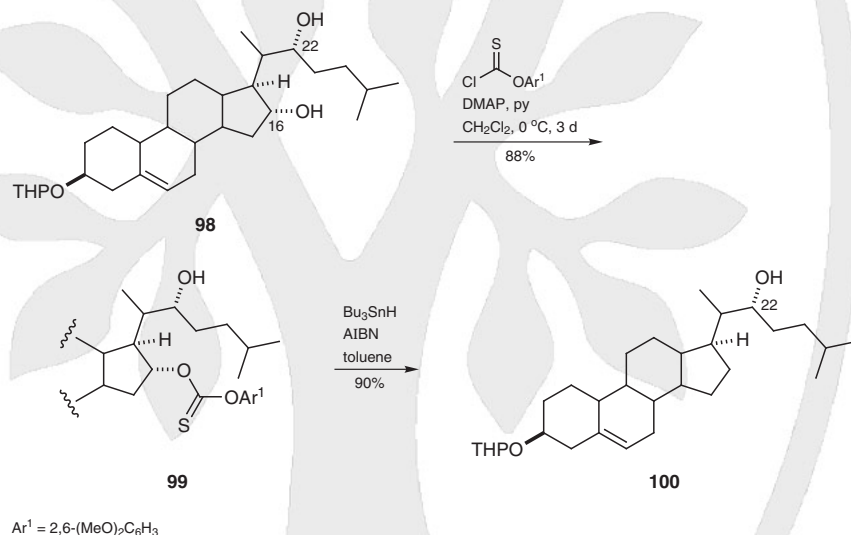
Scheme 44 Examples of the Selective Reaction of a Secondary Hydroxy Group with *O*-Phenyl Chlorothioformate^[112–114]



A hexopyranose in which the four *cis* 1,2- and 3,4-hydroxy groups are protected with acetone is converted into the monothiocarbonate in 90% yield.^[115]

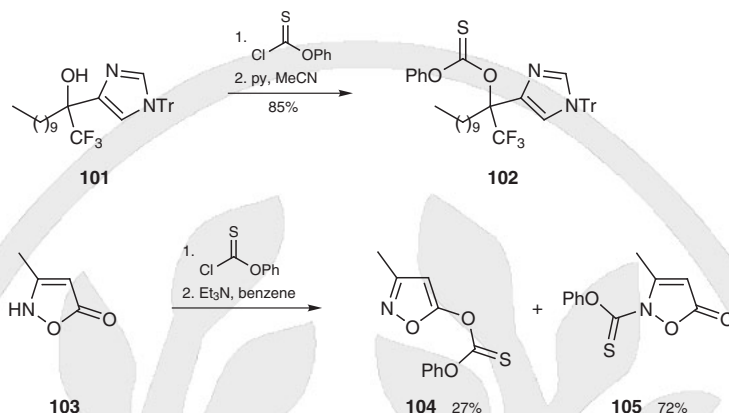
(22*R*)-22-Hydroxycholesterol **99** is prepared from the corresponding 16,22-dihydroxy compound **98** via a regioselective thiocarbonylation by using *O*-2,6-dimethoxyphenyl chlorothioformate with 4-(dimethylamino)pyridine and pyridine in dichloromethane (Scheme 45). The reaction of **98** with *O*-phenyl chlorothioformate gives both the 16- and 22-thiocarbonates each in 48% yield. Therefore, regioselective deoxygenation of the 16-hydroxy group to **100** by the Barton–McCombie method required the use of the bulky *O*-(2,6-disubstituted-aryl) chlorothioformate.^[116]

Scheme 45 Regioselective Thiocarbonylation^[116]



Even the bulky tertiary alcohol **101** bearing three strong electron-withdrawing substituents is converted into the thiocarbonate **102** on treatment with *O*-phenyl chlorothioformate and pyridine in acetonitrile in 85% yield (Scheme 46).^[117]

When oxazolone **103** is treated with *O*-phenyl chlorothioformate in the presence of triethylamine in benzene, thiocarbonylation takes place both at the carbonyl oxygen and the nitrogen of the oxazole ring giving both thiocarbonate **104** and thiocarbamate **105** in 27 and 72% yields indicating that in the presence of a strong base oxazolone **103** undergoes tautomerization to generate both the oxygen and the nitrogen nucleophiles (Scheme 46).^[118]

Scheme 46 Various Thiocarbonylations^[117,118]

Various examples for the regioselective conversion of the hydroxy group in carbohydrates into thiocarbonates *O,O*-esters using *O*-phenyl chlorothioformate are available.^[119–122]

***O*-4-Nitrophenyl *O*-4-Tolyl Thiocarbonate (93, Ar¹ = 4-Tol; Ar² = 4-O₂NC₆H₄);**

Typical Procedure:^[108]

To a soln of 4-nitrophenol (4.17 g, 30 mmol) dissolved in THF (20 mL) in a Schlenk flask in an EtOH/liquid N₂ bath, a soln of 1.6 M BuLi (12.5 mL, 30 mmol) dissolved in THF (20 mL) was added slowly under N₂. This lithium 4-nitrophenoxide soln was added dropwise, with stirring under N₂ during 2 h, to a soln of *O*-4-tolyl chlorothioformate (**92**, Ar¹ = 4-Tol; 5.6 g, 30 mmol) dissolved in THF (40 mL), placed in a Schlenk flask in an EtOH/liquid N₂ bath. After the addition, the mixture was left at rt for 2 h with stirring under N₂. After concentration of the solvent, CHCl₃ was added to this mixture and the soln washed with H₂O and dried (MgSO₄) and filtered under vacuum and the solvent was concentrated. Recrystallization (hexane/CHCl₃) gave the product; yield: not reported; mp 129–130 °C.

***O*-Alkyl *O*-Phenyl Thiocarbonates; General Procedure:**^[105]

Pyridine (0.41 mL, 5 mmol) was added to a soln of alcohol (2.50 mmol) and *O*-phenyl chlorothioformate (0.415 mL, 2.80 mmol) in CH₂Cl₂ (15 mL) at rt. After stirring for 2 h, the resultant mixture was washed with aq 1 M HCl, H₂O, sat. aq NaHCO₃, and brine. The organic layer was dried (Na₂SO₄) and concentrated. Purification of the residue by column chromatography (silica gel, hexane/EtOAc 6:1) gave the thiocarbonate *O,O*-ester. For example: *O*-isopropyl *O*-phenyl thiocarbonate; yield: 92%; bp 115 °C/0.70 Torr; *O*-[(methoxycarbonyl)methyl] *O*-phenyl thiocarbonate; yield: ~100%; bp 135 °C/0.70 Torr.

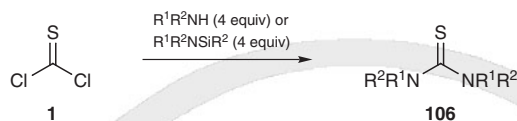
18.10.5.1.4

Method 4:

From 1,1'-Thiocarbonylbisdiazoles

The reaction of 1,1'-thiocarbonylbisdiazoles with alcohols is another useful procedure for the preparation of thiocarbonate *O,O*-esters. The use of both 1,1'-thiocarbonyldiimidazole and the corresponding pyrazole derivative for thionocarbonylation is well known.^[123]

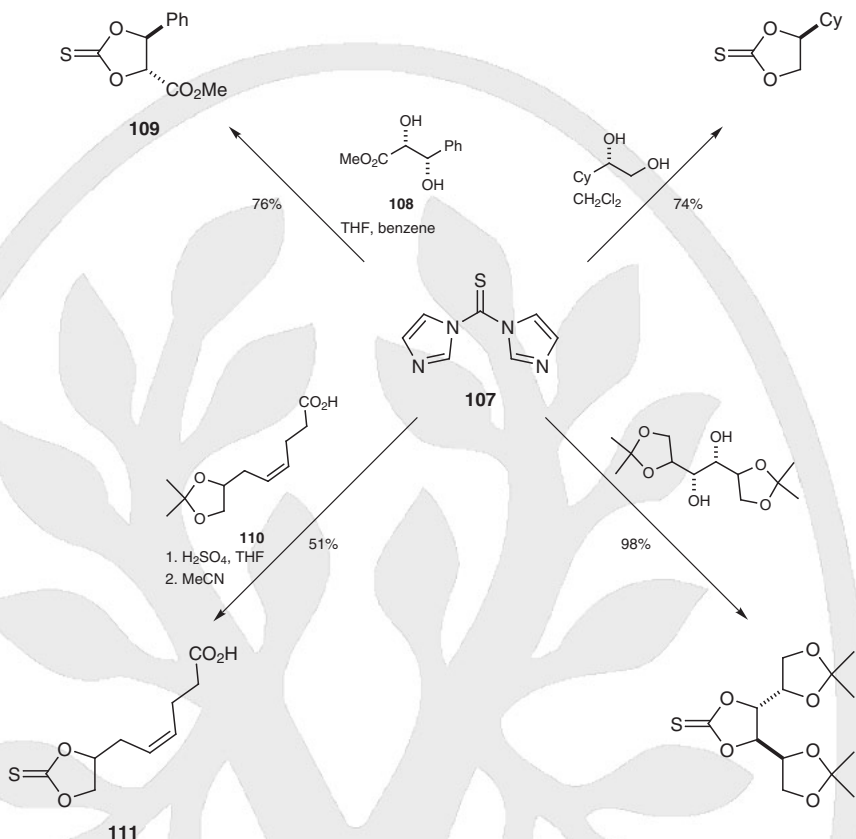
Various 1,1'-thiocarbonylbisdiazoles **106** are synthesized from thiophosgene and the appropriate heterocyclic amines or silylated amines (Scheme 47) and, on comparison of their reactivity, feasibility of handling, and solubility, 1,1'-thiocarbonyldiimidazole (**106**, NR¹R² = imidazol-1-yl) and 1,1'-thiocarbonyldi(1,2,4-triazole) (**106**, NR¹R² = 1,2,3-triazol-1-yl) are the most widely applicable to the synthesis of thiocarbonyl compounds.^[124]

Scheme 47 Preparation of 1,1'-Thiocarbonylbisdiazoles^[124]

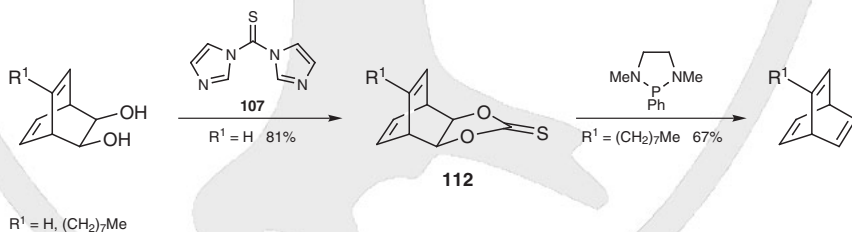
NR ¹ R ²	mp (°C)	Yield (%)	Ref
imidazol-1-yl	105–106	99	[124]
benzimidazol-1-yl	137–138	100	[124]
benzotriazol-1-yl	170–171	90	[124]
pyrazol-1-yl	50–51	92	[124]
1,2,4-triazol-1-yl	99–100	93	[124]

The reactions are generally conducted by refluxing the vicinal diol derivatives with 1,1'-thiocarbonyldiimidazole (**106**, NR¹R² = imidazol-1-yl) in a suitable solvent. When the reaction is complete, the resulting five-membered dioxolanes are separated and purified. Furthermore, the reactions proceed in a stereospecific manner with retention of configuration. The reaction has been utilized for simple diols, synthetically important compounds such as natural products, and also for the conversion of carbohydrates and nucleosides into the corresponding five-membered thiocarbonate *O,O*-esters.

Representative results obtained from the treatment of various vicinal diols and 1,1'-thiocarbonyldiimidazole (**107**) are given in Scheme 48.^[125–128] The 1,3-dioxolane-2-thione **109** obtained from **108** affords methyl (*E*)-cinnamate in 91% yield by refluxing with trimethyl phosphite for 2 hours.^[125] The formation of **111** requires the regeneration of the vicinal diol by saponification of the ketal in **110** with acid before the thiocarbonylation.^[127]

Scheme 48 Reactions with 1,1'-Thiocarbonyldiimidazole with Vicinal Diols^[125–128]

Various examples for the conversion of diols into 1,3-dioxolane-2-thiones with 1,1'-thiocarbonyldiimidazole (**107**) are available.^[129–139] An example is shown in Scheme 49 for the formation of the thiocarbonate O,O-ester **112** of bicyclo[2.2.2]octane-2,3-diols.^[140]

Scheme 49 Synthesis of the Thiocarbonate O,O-Ester of Bicyclo[2.2.2]octane-2,3-diols^[140]

3,5-Dioxatricyclo[5.2.2.0^{2,6}]undeca-8,10-diene-4-thione (**112**, $R^1 = \text{H}$); Typical Procedure:^[140]

Under argon, bicyclo[2.2.2]octa-5,7-diene-2,3-diol (1.64 g, 11.87 mmol) was dissolved in dry toluene (40 mL) in a 250-mL round-bottomed flask, and 1,1'-thiocarbonyldiimidazole (**107**; 2.5 g, 90% pure, 12.62 mmol) was added. The flask was put in an oil bath that had been preheated to 130 °C, and the reaction was stirred for 10 min. 1,1'-Thiocarbonyldiimidazole (**107**; 0.12 g, 90% pure, 0.61 mmol) was then added, and the reaction was stirred for an additional 5 min at 30 °C. After the solvent was removed under vacuum, the solid was redissolved in EtOAc, and silica gel (18 g) was added. Solvent was removed to produce a

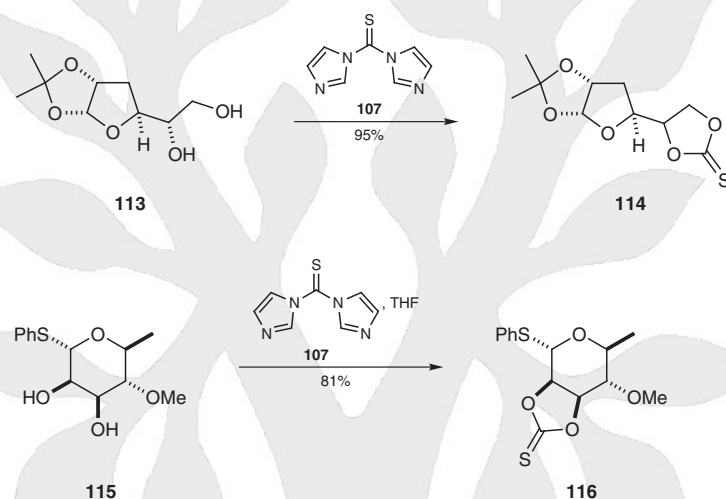
free-flowing powder that was then loaded onto a column (silica gel, 600 g) and chromatographed (40% EtOAc/hexane). Removal of solvent under vacuum gave a white crystalline solid; yield: 1.73 g (81%).

18.10.5.1.4.1

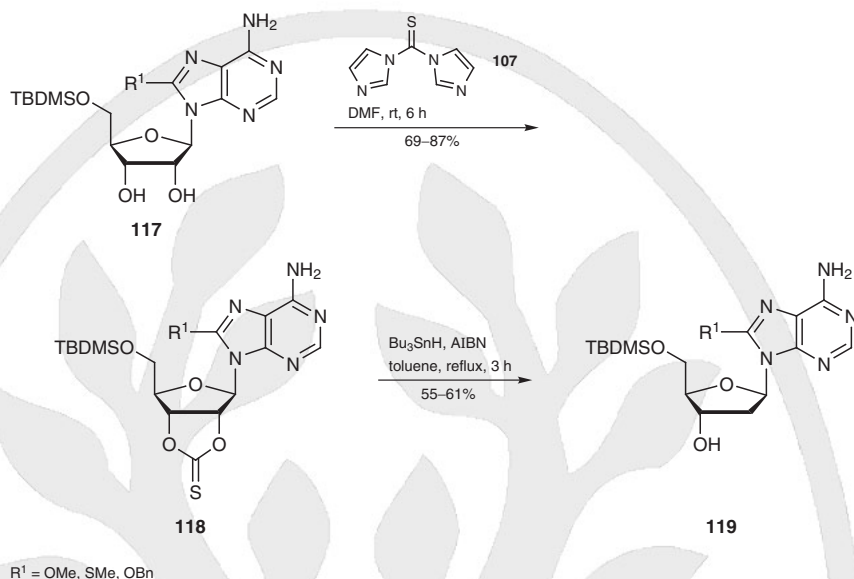
Variation 1:**Synthesis of Thiocarbonate *O,O*-Esters of Sugars and Nucleosides**

Carbohydrates such as pentoses and hexoses are converted into the corresponding thiocarbonate *O,O*-ester derivatives with 1,1'-thiocarbonyldiimidazole (**107**), these derivatives can undergo bisdeoxygenation or elimination reactions according to the Corey–Winter or elimination or Barton–McCombie radical deoxygenation. Typical examples the conversion of pentose **113** and hexose **115** into **114** and **116**, respectively, (Scheme 50).^[141,142]

Scheme 50 Thiocarbonate *O,O*-Esters of a Pentose and a Hexose^[141,142]



Many nucleosides, especially those having vicinal diols in the sugar moiety react with 1,1'-thiocarbonyldiimidazole (**107**) to give 1,3-dioxolane-2-thione ring fused compounds in high yields under mild reaction conditions.^[143,144] For example, treatment of 5'-*O*-*tert*-butyldimethylsilylated adenosine **117** with 1,1'-thiocarbonyldiimidazole (**107**) gives the thiocarbonate *O,O*-ester **118** and this undergoes reaction with tributyltin hydride and 2,2'-azobisisobutyronitrile to give the deoxysugar nucleoside **119** (Scheme 51).^[144]

Scheme 51 Reaction of a 5'-O-*tert*-Butyldimethylsilylated Adenosine with 1,1'-Thiocarbonyldiimidazole^[144]

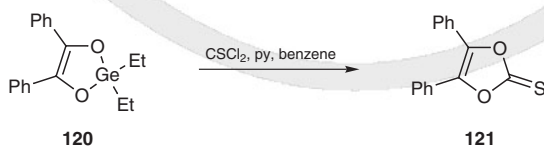
A few examples of the reaction of 1,3-diols with 1,1'-thiocarbonyldiimidazole (**107**) are available, these give the corresponding 1,3-dioxane-2-thiones in high yields.^[145,146]

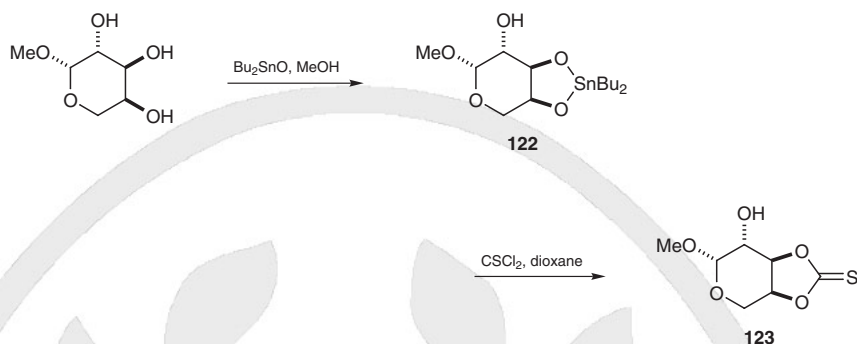
5'-O-(*tert*-Butyldimethylsilyl)-8-(methylsulfanyl)-2',3'-thiocarbonyladenosine (118, $\text{R}^1 = \text{SMe}$); Typical Procedure:^[144]

A soln of **117** ($\text{R}^1 = \text{SMe}$; 0.863 g, 2.02 mmol) and 1,1'-thiocarbonyldiimidazole (**107**; 0.68 g, 90% pure, 3.43 mmol) in dry DMF (15 mL) was stirred at rt for 6 h. The solvent was concentrated and the residue was purified by flash chromatography (MeOH/ CHCl_3 0–5%) to provide the product as a low-melting solid; yield: 0.821 g (87%).

18.10.5.1.5 Methods 5: Miscellaneous Methods

Alternative procedures for the preparation of thiocarbonate O,O-esters using vicinal diols are available, for example, the organogermanium **120** or organotin compounds **122** are converted into the corresponding thiocarbonates O,O-esters **121** and **123** on treatment with thiophosgene (**1**) (Scheme 52). The reactions are useful for preparation of dehydro-sugar derivatives by employing the Corey–Winter elimination or Barton–McCombie deoxygenation.^[147–151]

Scheme 52 Preparation of Thiocarbonate O,O-Esters from Organometallic Reagents^[147–151]



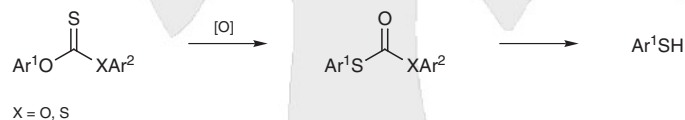
18.10.5.2 Applications of Product Subclass 5 in Organic Synthesis

Application of thiocarbonate *O,O*-diesters in organic synthesis provides many natural products, agrochemicals, and medicines, such as anti-HIV agents, by employing the following chemical procedures (Scheme 53). Applications of thiocarbonate *O,O*-esters are also discussed with the relevant syntheses in Section 18.10.5.1, the relevant sections and schemes are cited here, in addition a few applications not covered previously are given in Section 18.10.5.2.1; examples of their use in total synthesis are given in Section 18.10.5.2.2.

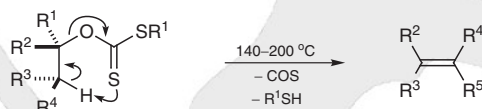
(1) Schönberg arenethiol preparation;^[152,153] (2) Chugaev alkene synthesis via intramolecular *cis*-elimination [for examples see Section 18.10.5.2.1];^[154,155] (3) Corey–Winter elimination reaction involving 1,3-dioxolane-2-thiones with phosphites [for examples see Section 18.10.5.1.1, Schemes 32, 33, 34, and 35; Section 18.10.5.1.1.1, Scheme 37; Section 18.10.5.1.2, Scheme 41; Section 18.10.5.1.4, Scheme 48];^[156–158] (4) Barton–McCombie deoxygenation of vicinal diols via 1,3-dioxolane-2-thiones by radical initiators [for examples see Section 18.10.5.1.1.1, Scheme 38; Section 18.10.5.1.3, Schemes 42 and 45; Section 18.10.5.1.4.1, Scheme 50];^[115,159–161] (5) radical substitution reactions.^[162]

Scheme 53 Synthetically Important Reactions of Thiocarbonates^[115,152–162]

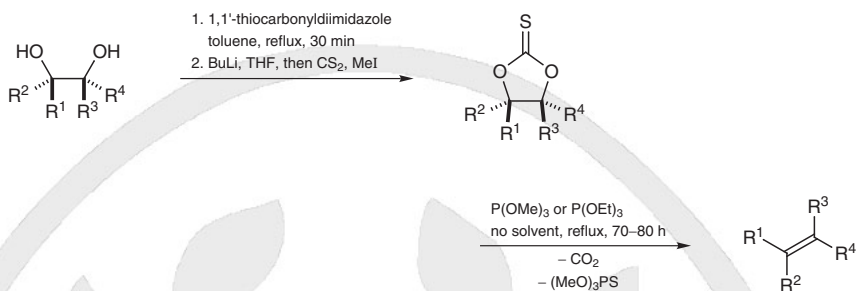
the Schönberg reaction



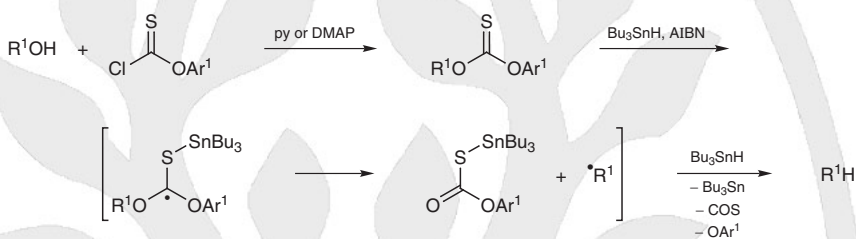
the Chugaev elimination



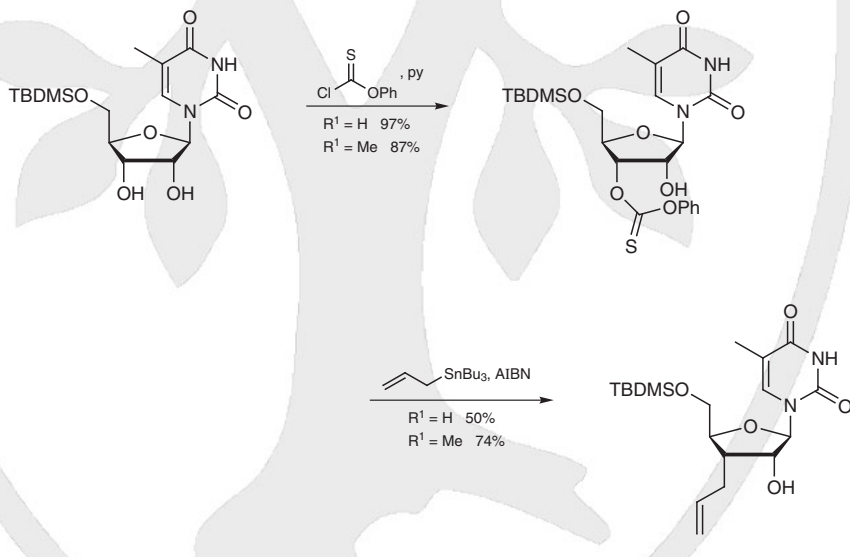
Corey–Winter alkene synthesis



Barton–McCombie deoxygenation of alcohols

Ar¹ = Ph, C₆F₅, 4-Tol, Mes

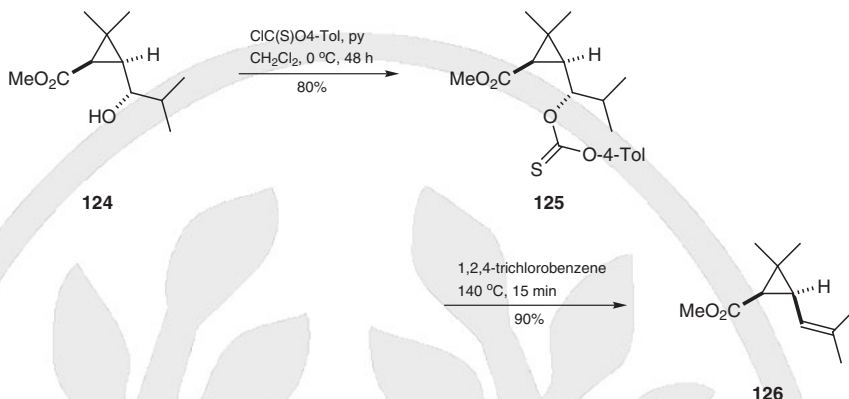
radical substitution reactions



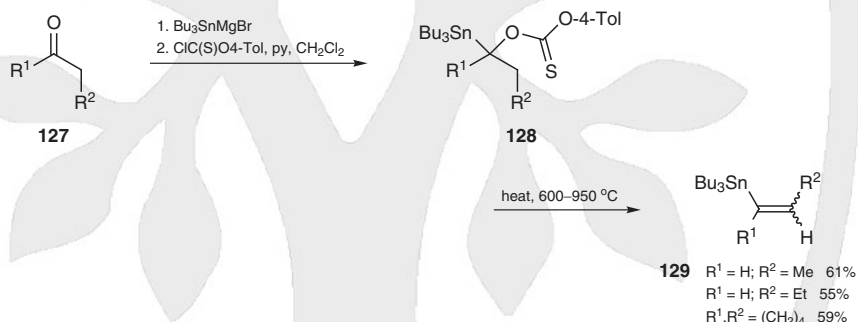
18.10.5.2.1

**Method 1:
Intramolecular Elimination**

There are several examples of the preparation of acyclic and cyclic thiocarbonate O,O-esters, which are used as synthetic intermediates. For example, optically active methyl cyclopropanoate **124** is converted, with retention of stereochemistry, on treatment with O-4-tolyl chlorothioformate and pyridine into the thiocarbonate O,O-ester **125** in 80% yield. The thiocarbonate O,O-ester **125** undergoes Chugaev-type elimination to give optically pure *cis*-chrysanthemic acid methyl ester (**126**) in 90% yield (Scheme 54).^[163]

Scheme 54 Thermolysis of a Thiocarbonate *O,O*-Ester^[163]

Tributylstannyl-substituted *O*-4-tolyl thiocarbonates **128** are prepared from the corresponding carbonyl compounds **127** on treatment, first with tributylstannylmagnesium bromide, and then with *O*-4-tolyl chlorothioformate. The thiocarbonate *O,O*-esters **128** are then subjected to flash-thermolysis at $600\text{--}950\text{ }^\circ\text{C}$ providing the tributyl(vinyl)tin compounds **129** in moderate yields (Scheme 55).^[164]

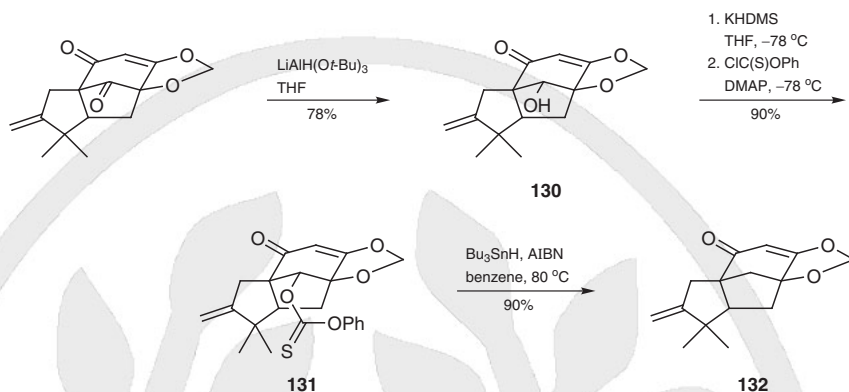
Scheme 55 Synthesis of Vinylstannanes from Thiocarbonate *O,O*-Esters^[164]

In addition, there are a number of examples of the preparation of thiocarbonate *O,O*-esters using *O*-aryl chlorothioformates and hydroxy compounds. These thiocarbonate *O,O*-esters are utilized for the production of various deoxygenated derivatives.^[165–174]

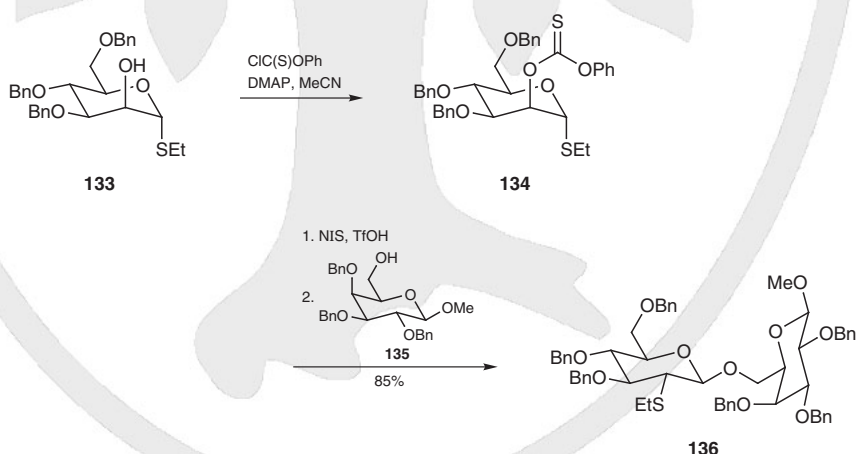
18.10.5.2.2

Method 2:**Application to Selected Organic Syntheses**

The total synthesis of tricycloillicinone (**132**), isolated from a toxic plant, successfully employed the thiocarbonylation of the alcohol **130** and then deoxygenation of the resulting thiocarbonate *O,O*-ester **131** by the Barton–McCombie method (Scheme 56).^[174]

Scheme 56 Synthesis of Tricycloillicinone^[174]

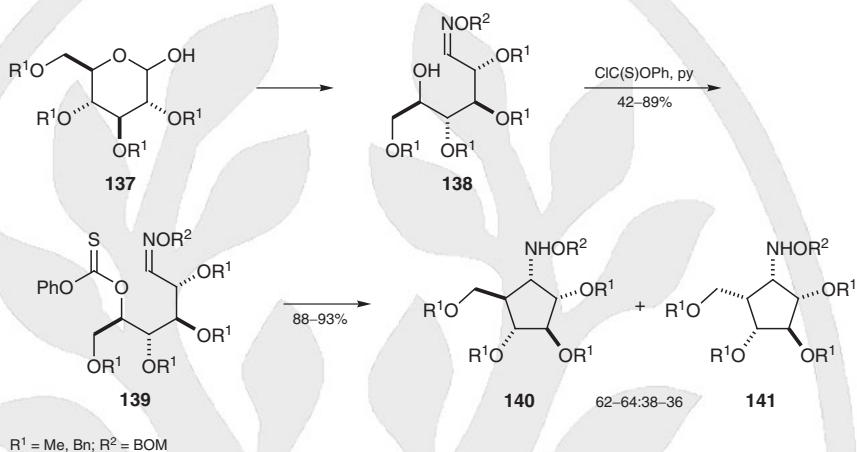
2-Deoxy- α - and - β -glycosides are very important antitumor antibiotics. Such 2-deoxyglycosides have been prepared via the 2-thiocarbonates of glucose or mannose derivatives. For example, saponification of ethyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-thiomannopyranoside with sodium methoxide in methanol gives the 2-hydroxy derivative **133** quantitatively which is treated with *O*-phenyl chlorothioformate to afford the β -2-thiocarbonylated mannopyranoside **134**. Glycosidation of mannose or glucose derivatives is performed with *N*-iodosuccinimide/trifluoromethanesulfonic acid in the presence of a glycosyl acceptor bearing the desired free hydroxy group to give stereospecifically the 1,2-*trans*-pyranoside, e.g. mannose derivative **134** undergoes glycosylation with **135** to give the 1,2-*trans* β -D-glucopyranoside **136** (Scheme 57). The sulfur moiety of the glycoside **136** is removed by treatment with Raney nickel to give finally the 2-deoxy derivative. Several examples for the synthesis of 1-thio- β -D-gluco- and 1-thio- α -D-mannopyranosides are available (Scheme 57).^[175–177]

Scheme 57 Synthesis of a Sugar Derivative^[175–177]

There are a number of reports of deoxygenation of the hydroxy groups in the sugar moiety of nucleosides. The 2-*O*-hydroxy group in a silyl-protected adenosine derivative reacts with *O*-phenyl chlorothioformate to give a thiocarbonate *O,O*-ester which undergoes deoxygenation under radical cleavage conditions with tributyltin hydride/2,2'-azobisisobutyronitrile. After removal of the silyl group the desired 2-*O*-deoxyadenosine is obtained. Similarly, 2-*O*-deoxyuridine is obtained.^[178]

Thionocarbonylation is employed for the transformation of hexoses into carbocyclic pentane derivatives. Initially the hexose **137** is converted into the open-chain oxime ether **138** and then thiocarbonylated by using *O*-phenyl chlorothioformate and pyridine in 42–89% yields. The thiocarbonates **139** are deoxygenated to give cyclopentane derivatives **140** and **141** in 88–93% yield (Scheme 58).^[179]

Scheme 58 Radical Cyclization of Oxime Ethers of Glucose^[179]



Many other examples for the deoxygenation of the carbohydrates in nucleosides have been reported.^[180–193]

18.10.6

Product Subclass 6: Dithiocarbonate *O,S*-Esters

These compounds have the structure **142** with the thiocarbonyl group attached to one thiolate and one alkoxy group (Scheme 59), they are discussed in *Houben–Weyl*, Vol. E 4, p 425. Alkali metal dithiocarbonate *O*-esters have been referred to in the older literature as xanthates, but this nomenclature is no longer recommended.

Scheme 59 Dithiocarbonate *O,S*-Esters



There are several methods for the preparation of dithiocarbonate *O,S*-esters:

(1) They can be prepared from an appropriate alcohol and carbon disulfide either by using a strong base such as sodium hydride or butyllithium in tetrahydrofuran or acetonitrile or by using an alkali metal hydroxide in alcohol. In both cases this is followed by treatment with an alkyl halide or sulfonate to give the corresponding dithiocarbonate *O,S*-esters (Section 18.10.6.1.1). This preparation has been used for the reaction between alcohols with complex structures (such as natural products), carbon disulfide, and simple alkyl halides such as iodomethane.

(2) Treatment of commercially available potassium or sodium *O*-ethyl (or *O*-methyl) dithiocarbonates with alkyl halides or sulfonates affords the corresponding *O*-alkyl di-

thiocarbonates (Section 18.10.6.1.2). On the other hand, potassium (or sodium) *O*-ethyl (or *O*-methyl) dithiocarbonate and arenediazonium salts are used for the preparation of aryl dithiocarbonates, which are converted to arenethiols in moderate yields by alkaline hydrolysis.

(3) The reactions of thiophosgene (**1**) with 2-sulfanyl alcohols, and of chlorothioformate *O*-esters or chlorodithioformates with thiols or alcohols are the alternative procedures for the preparation of dithiocarbonate *O,S*-esters but there are few examples (Section 18.10.6.1.3).

(4) Dithiocarbonates *O,S*-esters readily undergo radical fission between the C–S bond on UV irradiation to generate thiol radicals and carbon radicals. The carbon radicals undergo addition reactions to the C=C bond to give a new dithiocarbonate *O,S*-esters containing an additional C2 unit (Section 18.10.6.1.5).

(5) There are a few examples of the dithiocarbonates of organometallic compounds (e.g., Hg, Ge, Sn, Sb, P, Te) (Section 18.10.6.1.4).

Dithiocarbonate *O,S*-esters together with thiocarbonate *O,S*-esters and trithiocarbonates can be used as versatile intermediates in modern organic synthesis.

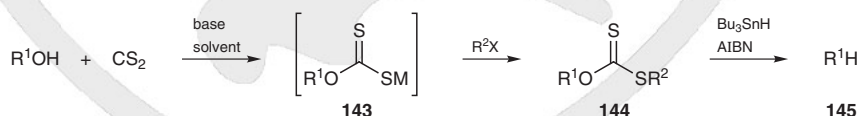
18.10.6.1 Synthesis of Product Subclass 6

18.10.6.1.1 Method 1: From Carbon Disulfide, Alcohols, and Alkyl Halides

This procedure is generally conducted by the initial conversion of hydroxy groups of the alcohol into their metal alkoxides by either using metallic sodium (or potassium) in an appropriate solvent or strong bases such as sodium hydride, butyllithium, or potassium *tert*-butoxide in an anhydrous solvent. The alkoxide anions thus generated are treated with carbon disulfide to afford the corresponding alkali metal *O*-alkyl dithiocarbonates **143** which are not isolated but treated in situ with simple alkyl halides, normally iodomethane, thus producing the desired dithiocarbonate *O,S*-esters **144** in high yields (Scheme 60). These syntheses can be conducted as one-pot reactions and almost any kind of compound bearing hydroxy groups including natural products and complex synthetic intermediates can be converted into the corresponding dithiocarbonate *O,S*-ester. The major purpose for the preparation of dithiocarbonates of complex molecules is the deoxygenation to form the corresponding reduction products **145**. This reduction is accomplished using Barton–McCombie deoxygenation with radical sources such as a combination of 2,2'-azobisisobutyronitrile and tributyltin hydride.

The general reaction is illustrated in Scheme 60. Several examples of dithiocarbonate *O,S*-esters synthesized from simple alcohols and carbon disulfide are summarized in Table 2.^[194–210]

Scheme 60 General Scheme for Preparation of Dithiocarbonate *O,S*-Esters^[194,196]



R¹ = alkyl, aryl, benzyl

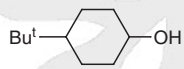
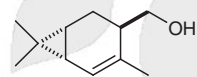
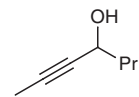
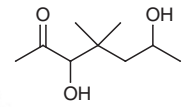
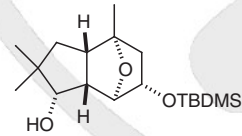
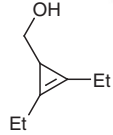
base/solvent = NaOH or KOH, H₂O; BuLi, THF; NaH, DMSO; *t*-BuOK, *t*-BuOH; Na, toluene

R²X = MeI, EtI

R ¹	R ²	Base	Yield (%) of 144	Ref
Et	Me	NaOH	87	[194]
iPr	Me	NaOH	82	[194]
CH ₂ CH ₂ iPr	Me	NaOH	92	[194]
(CH ₂) ₇ Me	Me	NaOH	95	[194]
(CH ₂) ₁₁ Me	Me	NaOH	89	[194]
(CH ₂) ₁₅ Me	Me	NaOH	92	[194]
Cy	Me	NaOH	80	[194]
Bn	Me	NaOH	90	[194]
s-Bu	Me	NaH/DMSO	73	[196]
CH(Ph)Me	Me	NaH/DMSO	78	[196]

^a One-pot procedure.

Table 2 Synthesis of Dithiocarbonates from Alcohols and Carbon Disulfide^[194–210]

$\text{R}^1\text{OH} + \text{CS}_2 \xrightarrow[\text{base, solvent}]{\text{R}^2\text{X}} \text{R}^1\text{O}-\text{C}(=\text{S})-\text{SR}^2$				
R ¹ OH	Base, Solvent	R ² X	Yield (%)	Ref
EtOH	NaOH	MeI	87	[194]
MeOH	KOH	4-AcOC ₆ H ₄ CH ₂ Br	100	[195]
s-BuOH	NaH, THF	MeI	73	[196–198]
	NaH	Br(CH ₂) ₃ Cl	80	[199,200]
	Na, toluene	MeI	63	[201]
	Na, benzene	MeI	48	[202–204]
	NaH, THF	MeI	72	[205,206]
	NaH, THF	MeI	100	[207]
	NaOH, H ₂ O	MeI	80	[208]
[HO(CH ₂) ₃] ₂ O	NaOH, H ₂ O	MeI	87	[209]
HO(CH ₂) ₃ Ph	CS ₂ CO ₃ , DMF, TBAI	MeI	94	[210]

O,S-Dialkyl Dithiocarbonates 144; General Procedure:^[194]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

Alcohol (10 mmol) and MeI (11 mmol) were added to a two-phase system of CS₂ (10 mL) in H₂O (5 mL) and 50% NaOH (5 g) in H₂O (10 mL) containing Bu₄NHSO₄ (1 mmol) in a 50-mL round-bottomed flask. The mixture was stirred vigorously at rt by a magnetic stirrer. The reaction was monitored by checking the ¹H NMR spectrum of the CS₂ layer. To workup the reaction, the CS₂ layer was separated and the aqueous layer was separated and extracted with CS₂ (3 × 10 mL). The combined CS₂ layers were dried (Na₂SO₄) and filtered. Concentration of the solvent under reduced pressure afforded pure dithiocarbonate.

These dithiocarbonates are utilized for the synthesis of alkenes by Chugaev reaction.^[155]

O-sec-Butyl S-Methyl Dithiocarbonates (144, R¹ = s-Bu; R² = Me); Typical Procedure:^[196]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

Anhyd DMSO (150 mL) was added under argon to NaH (3.6 g, 0.15 mol) and the mixture was heated at 70–75 °C with stirring for 45 min. After cooling, s-BuOH (7.4 g, 0.10 mol) was added dropwise and the mixture was stirred at rt for 1 h. A soln of CS₂ (9.2 g, 0.12 mol) in anhyd DMSO (25 mL) was then added slowly, keeping the temperature of the reaction vessel under 45 °C with an external ice–water bath. After stirring at rt for 1 h, a soln of MeI (17 g, 0.12 mol) in anhyd DMSO (25 mL) was added. The mixture was stirred at rt for 1 h and then quenched with ice water. The aqueous phase was extracted with hexane (3 × 50 mL). The combined organic fractions were washed several times with H₂O, dried (Na₂SO₄), and concentrated. The residue was distilled under reduced pressure; yield: 12 g (73%); bp 70–72 °C/10 Torr.

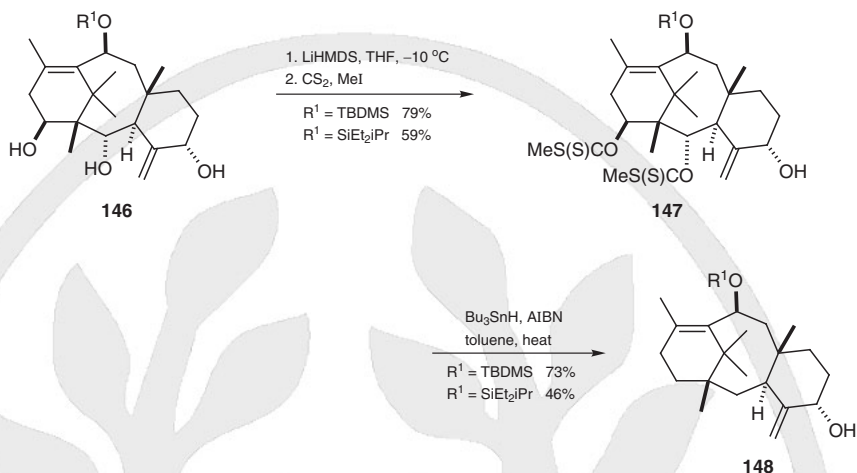
These dithiocarbonate O,S-esters undergo thermal thioxo to thiol rearrangement to give the corresponding dithiocarbonate S,S-esters in high yields.

18.10.6.1.1.1

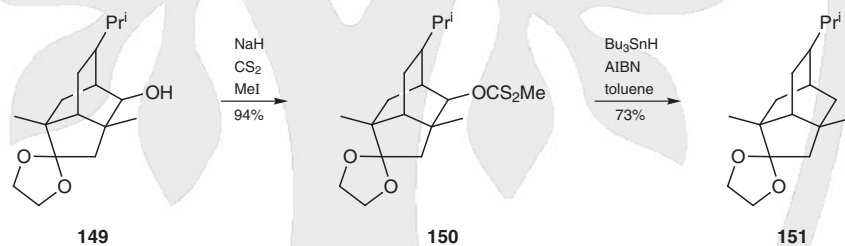
Variation 1:**From Carbon Disulfide and Complex Hydroxy Compounds**

There are many reports of the synthesis of dithiocarbonate O,S-esters prepared from carbon disulfide and alcohol derivatives as intermediates during the total synthesis of complex molecules and natural products such as sugars and nucleosides. A few typical synthetic procedures of such dithiocarbonate O,S-esters are discussed here.

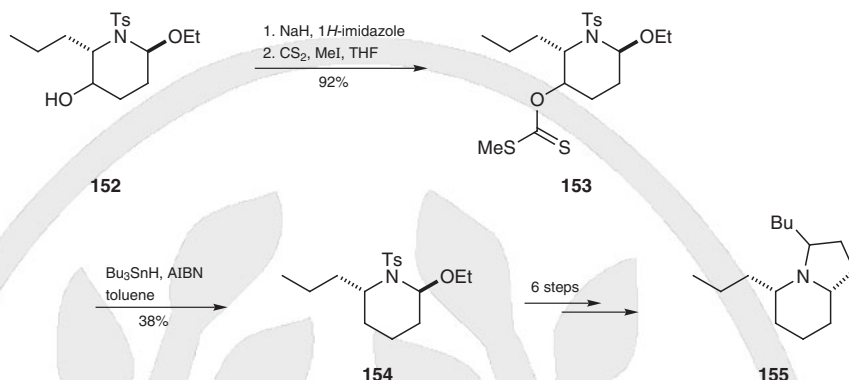
Taxol, an important anticancer reagent extracted from yew stems, is an attractive synthetic target for biochemists and synthetic chemists. In a study toward taxol, hydroxy compound **146** undergoes conversion into the bis(dithiocarbonate O,S-ester) **147** which is subjected to Barton–McCombie deoxygenation using tributyltin hydride/2,2'-azobisisobutyronitrile to give the reduced product **148** (Scheme 61).^[211–216]

Scheme 61 Taxol Synthesis via Dithiocarbonate O,S-Esters^[211–216]

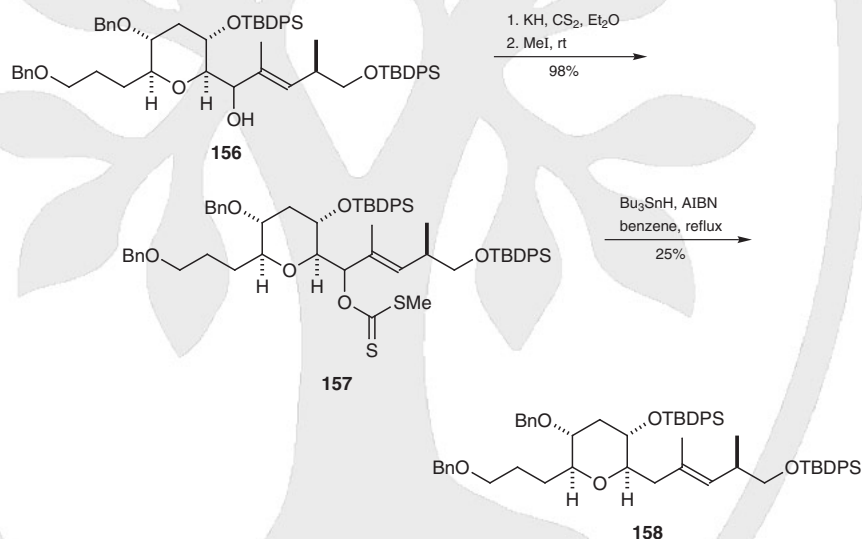
In the total synthesis of the marine natural product (–)-4-thiocyanatoneopupukeanane, an isotwistane based sesquiterpene, monohydroxy derivative **149** is treated successively with carbon disulfide in the presence of sodium hydride and then iodomethane to give the *S*-methyl dithiocarbonate **150** in 94% yield. The Barton–McCombie deoxygenation of **150** with tributyltin hydride/2,2'-azobisisobutyronitrile in toluene affords the reduced product **151** in 73% yield (Scheme 62).^[217,218]

Scheme 62 *S*-Methyl Dithiocarbonate O-Ester of Isotwistane and Barton–McCombie Deoxygenation^[217,218]

A synthetic route for an alkaloid containing the indrizidine skeleton **155** starts from a chiral 2-(tosylaminomethyl)furan which gives, after oxidation and cyclization, the alcohol derivative having the indrizidine skeleton **152**. This alcohol is converted into the dithiocarbonate O,*S*-ester **153** in 92% yield by treatment with sodium hydride and 1*H*-imidazole, and then carbon disulfide and iodomethane in tetrahydrofuran. The O,*S*-ester **153** is subjected to deoxygenation by the Barton–McCombie reaction using tributyltin hydride and 2,2'-azobisisobutyronitrile in refluxing toluene to afford the desired product **154** in 38% yield. Indrizidine 223AB (**155**) is obtained after six further steps from **154** (Scheme 63).^[219]

Scheme 63 Synthesis of Indrizidine 223AB via a Dithiocarbonate O,S-Ester^[219]

In a total synthesis of gambieric acid, during the stereoselective synthesis of the important j-ring of this acid **158**, the dithiocarbonate O,S-ester **157** is prepared from the alcohol **156** using carbon disulfide, potassium hydride in diethyl ether and then methylation by iodomethane at room temperature in 98% yield. Barton–McCombie deoxygenation of **157** gives **158** (Scheme 64).^[220]

Scheme 64 Synthesis of the J-Ring of Gambieric Acid^[220]

Many other examples of the preparation of dithiocarbonate O,S-esters from structurally complex hydroxy derivatives are available.^[221–231]

0-6-Ethoxy-2-propyl-1-tosylpiperidin-3-yl S-Methyl Dithiocarbonate (**153**):^[219]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

To a stirred soln of NaH (337 mg, 9.84 mmol, 60% oil dispersion) in THF was added a soln of 6-ethoxy-2-propyl-1-tosylpiperidin-3-ol (560 mg, 1.64 mmol) in THF (40 mL), and the mixture was refluxed for 1.5 h. After cooling to 0°C, CS₂ (0.49 mL, 8.2 mmol) was added to

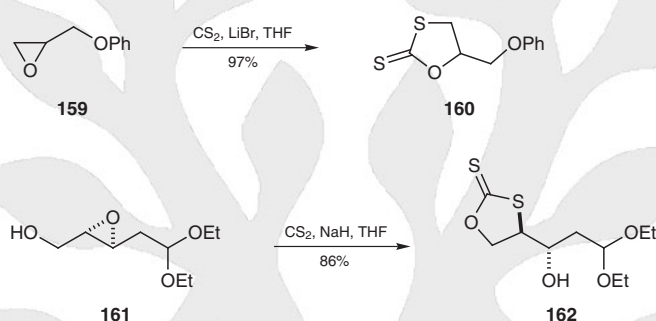
for references see p 956

the mixture, which was refluxed for 0.5 h. MeI (0.53 mL, 8.5 mmol) was added dropwise to the resulting mixture at 0 °C, and it was refluxed for 0.5 h. The reaction was quenched by the addition of sat. aq NaCl at 0 °C, extracted with EtOAc, dried (Na₂SO₄), and concentrated. The crude product was passed through a short column (silica gel, hexane/Et₂O 4:1) to give the title dithiocarbonate as a pale yellow oil; yield: 691 mg (92%).

18.10.6.1.1.2 Variation 2: Insertion Reactions of Carbon Disulfide

Reaction of oxirane **159** with carbon disulfide in the presence of sodium hydroxide or lithium bromide gives the five-membered dithiocarbonate O,S-ester, 1,3-oxathiolane-2-thione derivative **160** in 97% yield (Scheme 65). In this reaction carbon disulfide inserts regioselectively into the less-substituted C–O bond.^[232]

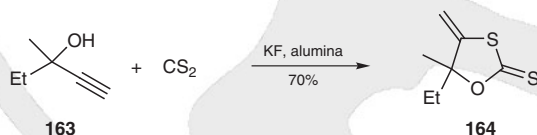
Scheme 65 Insertion of Carbon Disulfide into an Oxirane^[232–235]



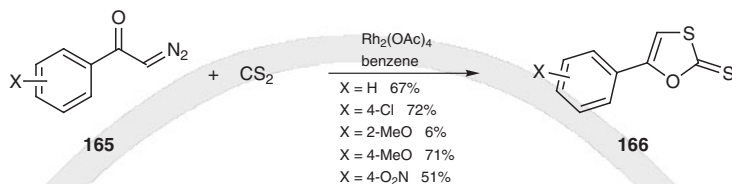
Reaction of oxirane **161** with sodium hydride and then carbon disulfide in tetrahydrofuran gives the 1,3-oxathiolane-2-thione **162** in 86% yield. The reaction is considered to proceed via an S_N2 type ring opening of the oxirane by the initially formed dithiocarbonate sulfur anion (Scheme 65).^[233–235]

When 3-methylpent-1-yn-3-ol (**163**) is treated with potassium fluoride and carbon disulfide on alumina, intramolecular cyclization takes place to afford the 1,3-oxathiolane-2-thione **164** in 70% yield (Scheme 66). This reaction proceeded via the initial formation of the dithiocarbonate O,S-ester.^[236–238]

Scheme 66 Formation of a 1,3-Oxathiolane-2-thione from 3-Methylpent-1-yn-3-ol and Carbon Disulfide^[236–238]



Diazo compound **165** reacts with carbon disulfide in the presence of dirhodium tetraacetate in benzene. This reaction may proceed via a carbene intermediate which acts as a 1,3-dipole, adding across the C=S bond of carbon disulfide to give the product **166** in 72% yield (Scheme 67).^[239]

Scheme 67 Reaction of Carbon Disulfide with a Diazo Compound^[239]**(4R)-4-[(1S)-3,3-Diethoxy-1-hydroxypropyl]-1,3-oxathiolane-2-thione (162):^[233]**

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

To a dispersion of NaH (383 mg, 60% in mineral oil) in a mixture of THF (15 mL) and CS₂ (15 mL) was added the epoxy alcohol **161** (900 mg, 4.78 mmol) in THF (5 mL) during 5 min. With careful monitoring of the desired compound (*R_f* 0.31) and the starting material (*R_f* 0.15) by TLC (40% EtOAc/hexane), the mixture was slowly warmed from -40 to -30 °C during 1 h. The reaction was stopped when the less polar material (*R_f* 0.9 in the same eluent) appeared. Powdered NH₄Cl (100 mg) and sat. NH₄Cl (8 mL) were added. The mixture was extracted with Et₂O (100 mL) and the extract was washed with H₂O (4 mL) and brine (4 mL). The organic layer was dried (MgSO₄) and the solvent was concentrated. The crude compound was purified by column chromatography (silica gel, 60% EtOAc/hexane) to give **162** as an oil; yield: 1.09 g (86%); [α]_D²⁴ -40.9 (*c* 1.0, CHCl₃).

18.10.6.1.2

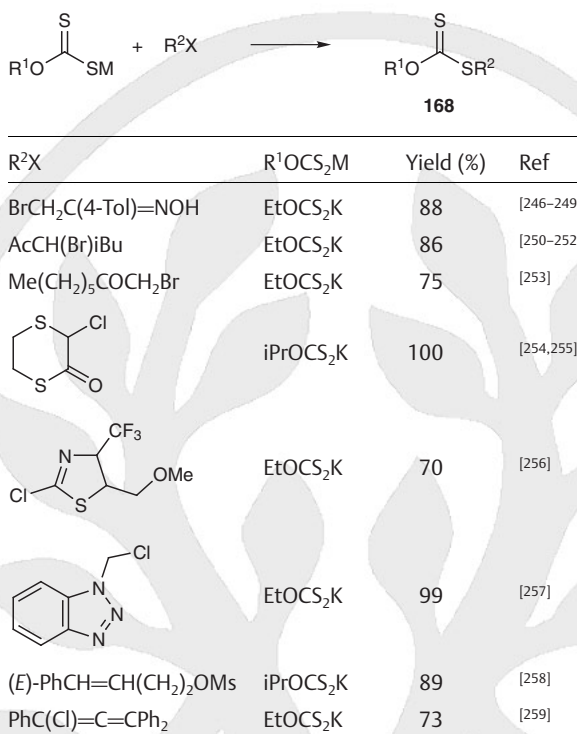
Method 2:**From Sodium or Potassium O-Alkyl Dithiocarbonates, Alkyl Halides (or Sulfonates), and Arenediazonium Salts**

Since sodium and potassium O-alkyl dithiocarbonates are commercially available and their handling is feasible, they are commonly used for the preparation of many dithiocarbonate O,S-esters **167**. Examples are shown in Scheme 68.^[53,54,240–245]

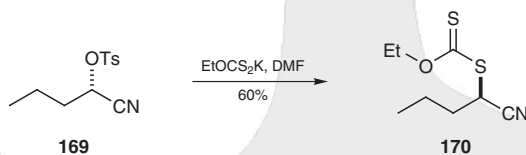
Scheme 68 Dithiocarbonates from Sodium or Potassium O-Alkyl Dithiocarbonates^[53,54,240–245]

R ¹ X	R ²	M	Yield (%)	Ref
Mel	Et	K	78	[240]
EtI	Et	K	55	[53]
PhCH ₂ CH ₂ Br	Et	K	83	[241,242]
H ₂ C=CHCH ₂ Br	Et	K	100	[243]
BrCH ₂ CO ₂ t-Bu	Et	K	85	[244]
Mel	iPr	K	70	[54]
PhCH(Br)Me	1-menthyl	Na	85	[245]

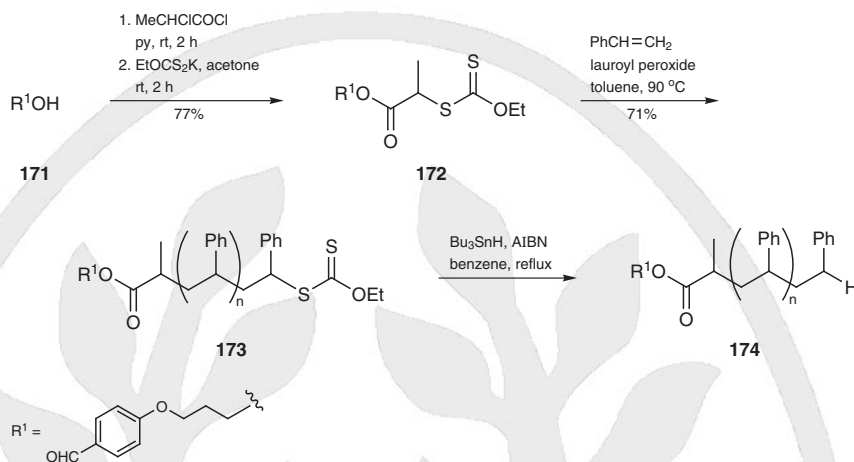
Halogen atoms or sulfonates attached to the carbon α to strong electron-withdrawing groups such as carbonyl, carboxyl, and oxime are readily substituted by sodium or potassium O-alkyl dithiocarbonates to give the corresponding dithiocarbonate O,S-esters **168** in good yields (Scheme 69).^[246–259]

Scheme 69 Preparation of Dithiocarbonate O,S-Esters from Sodium or Potassium O-Alkyl Dithiocarbonates^[246–259]

Stereochemical studies of these substitution reactions have been carried out using optically active (*S*)-2-tosyloxypentanenitrile (**169**) and potassium *O*-ethyl dithiocarbonate in dimethylformamide resulting in the formation of the corresponding dithiocarbonate *O,S*-ester **170** in 60% yield with complete inversion of configuration (Scheme 70).^[260,261]

Scheme 70 Stereochemical Outcome of the Reaction of (*S*)-2-Tosyloxypentanenitrile and Potassium *O*-Ethyl Dithiocarbonate^[260,261]

If the reactant has no suitable site for attack by potassium *O*-ethyl dithiocarbonate, manipulation is required to introduce the dithiocarbonate moiety.^[262–265] For example, the dithiocarbonate **172** is synthesized from alcohol **171** and 2-chloropropanoyl chloride followed by reaction with potassium *O*-ethyl dithiocarbonate. Dithiocarbonate **172** is converted into the polymeric addition product **173** by lauroyl peroxide promoted radical C–S bond fission and addition of the resulting species to styrene. The dithiocarbonate group is removed from **173** by Barton–McCombie deoxygenation to give the desired polymer **174** (Scheme 71).^[262]

Scheme 71 Synthesis of Styrene Polymer Initiated by Potassium O-Ethyl Dithiocarbonate^[262]**O-Ethyl S-[1-({[3-(4-Formylphenoxy)propyl]oxy}carbonyl)ethyl] Dithiocarbonate (172).**^[262]

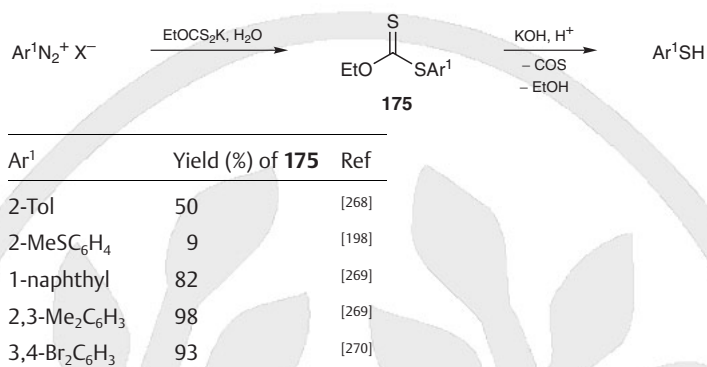
To a soln of alcohol **171** (3.8 g, 21.11 mmol) and pyridine (2.1 mL, 25.96 mmol, 1.2 equiv) in CH₂Cl₂ (20 mL) cooled to 0 °C was added dropwise, with stirring, 2-chloropropanoyl chloride (2.5 mL, 25.75 mmol, 1.2 equiv). The mixture was stirred at rt for 2 h and then diluted with Et₂O (200 mL). The organic layer was washed with H₂O (100 mL), 5% HCl (100 mL), H₂O (100 mL), and brine (100 mL). The organic phase was then dried (MgSO₄), filtered and concentrated to dryness under vacuum. The residue was dissolved in acetone (50 mL) and potassium O-ethyl dithiocarbonate (4.1 g, 25.60 mmol, 1.2 equiv) was added portionwise, with stirring, at rt. After 2 h, the mixture was poured into H₂O (100 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were dried (MgSO₄), filtered, and the solvents were concentrated in vacuo to give crude **172** (6.02 g) as a yellow oil. Chromatography (silica gel, Et₂O/petroleum ether 1:1 to 3:2) furnished pure **172** as a pale yellow oil; yield: 5.82 g (77%).

Synthesis of Polymer 173.^[262,263]

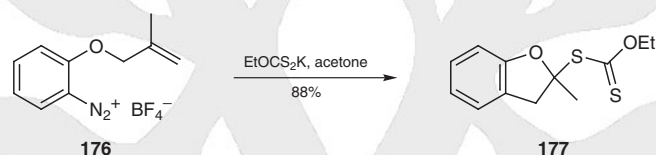
To a degassed soln of dithiocarbonate **172** (5.35 g, 15.34 mmol) in toluene (15 mL) and styrene (35 mL, 20 equiv) heated at 90 °C under argon was added lauroyl peroxide (60 mg, 1 mol%) every 1.5 h. After 13 mol% of lauroyl peroxide had been added, the polymer was precipitated; yield: 32.13 g (71%).

18.10.6.1.2.2**Variation 2:****Synthesis of Arenethiols By Diazotization of Aromatic Amines**

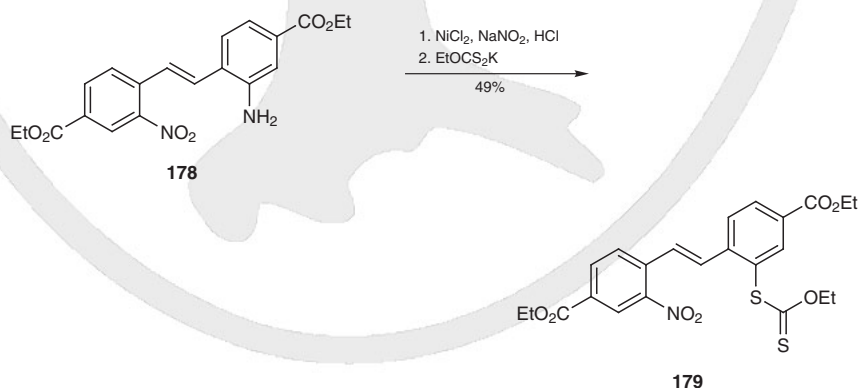
Aromatic diazonium salts either in situ or after conversion into the tetrafluoroborate salt react with dithiocarbonates, i.e. potassium O-ethyl dithiocarbonate, to give the dithiocarbonate O,S-esters **175** in good to moderate yields. Either alkaline hydrolysis or treatment with lithium aluminum hydride of these dithiocarbonates affords thiols. The characteristic features of this synthetic process are the easy handling process, high yields of the arenethiols and the wide range of suitable aromatic amines. Examples of this method are shown in Scheme 72.^[198,266–271] This synthetic method has been extended to produce many other useful sulfur compounds.

Scheme 72 Preparation of Arenethiols from Potassium *O*-Ethyl Dithiocarbonate^[198,268–270]

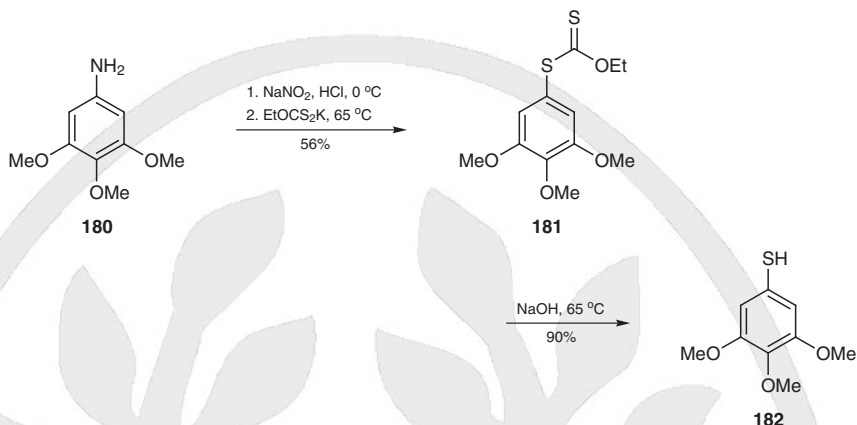
2-(2-Methylallyloxy)-substituted benzenediazonium tetrafluoroborate salt **176** is treated with potassium *O*-ethyl dithiocarbonate in acetone to give the ring-contracted benzofuran derivative **177** in 88% yield (Scheme 73).^[271]

Scheme 73 Reaction of 2-(2-Methylallyloxy)benzenediazonium Tetrafluoroborate and Potassium *O*-Ethyl Dithiocarbonate^[271]

Diazotization and subsequent treatment of (*E*)-1-[2-amino-4-(ethoxycarbonyl)phenyl]-2-[4-(ethoxycarbonyl)-2-nitrophenyl]ethene (**178**) with potassium *O*-ethyl dithiocarbonate in the presence of nickel(II) chloride affords (*E*)-1-{4-(ethoxycarbonyl)-2-[ethoxy(thiocarbonyl)sulfanyl]phenyl}-2-[4-(ethoxycarbonyl)-2-nitrophenyl]ethene (**179**) in 49% yield (Scheme 74).^[272] The amino groups of 4-(4-hydrobutyl)aniline and 2,2'-bipyridin-4-amine are also converted into the *O*-ethyl dithiocarbonate *S*-ester then to the corresponding thiols.^[272,273]

Scheme 74 Formation of the Dithiocarbonate *O,S*-Ester of a Stilbene^[272]

The dithiocarbonate **181** is synthesized from the corresponding aniline **180** via the diazonium salt (Scheme 75). Dithiocarbonate **181** is subsequently converted into the arenethiol **182** which has been used as an efficient aryl-transfer auxiliary for peptide synthesis.^[274]

Scheme 75 Synthesis of an S-Aryl O-Ethyl Dithiocarbonate^[274]**O-Ethyl S-3,4,5-Trimethoxyphenyl Dithiocarbonate (181):**^[274]

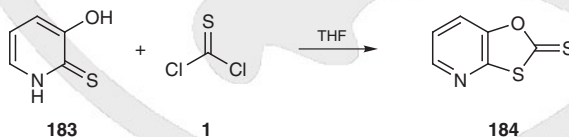
3,4,5-Trimethoxyaniline (**180**; 9.97 g, 0.054 mol) was dissolved in MeOH (10 mL) and 10% aq HCl and then was cooled to $0\text{ }^\circ\text{C}$. A soln of NaNO_2 (5.0 g, 0.073 mol) in H_2O (20 mL) was added dropwise over 1 h. The mixture was stirred at $0\text{ }^\circ\text{C}$ for an additional 15 min at which time the soln was added to a soln of potassium O-ethyl dithiocarbonate (17.3 g, 0.108 mol) in H_2O (50 mL) at $65\text{ }^\circ\text{C}$. The mixture was then extracted with EtOAc ($3 \times 200\text{ mL}$), dried (Na_2SO_4), and the combined organic extracts were washed with brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 20% EtOAc/hexane) afforded the product; yield: 8.80 g (56%).

18.10.6.1.3

Method 3:**From Thiophosgene, Chlorothioformate O-Esters, Chlorodithioformates, or 1,1'-Thiocarbonyldiimidazole**

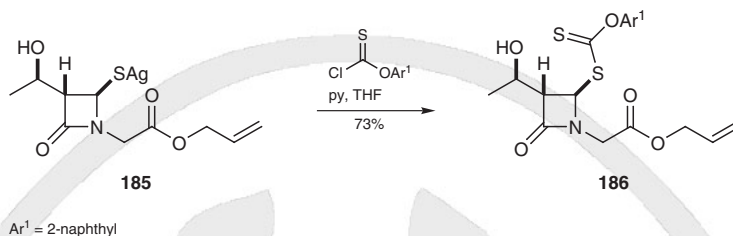
There are few reports on the preparation of dithiocarbonate O,S-esters from reagents other than carbon disulfide (Section 18.10.6.1.1) or sodium or potassium O-alkyl dithiocarbonates (Section 18.6.1.2).

Thiophosgene (**1**) is used for the synthesis of 1,3-benzoxathiole-2-thione from 2-sulfanyphenol in the presence of base.^[275] 1,1'-Thiocarbonyldiimidazole also affords the same compound quantitatively. Similarly, 3-hydroxypyridine-2(1H)-thione (**183**) affords 1,3-oxathio[4,5-*b*]pyridine-2-thione (**184**) upon treatment with thiophosgene (**1**) in tetrahydrofuran (Scheme 76).^[276]

Scheme 76 Formation of 1,3-Oxathio[4,5-*b*]pyridine-2-thione^[276]

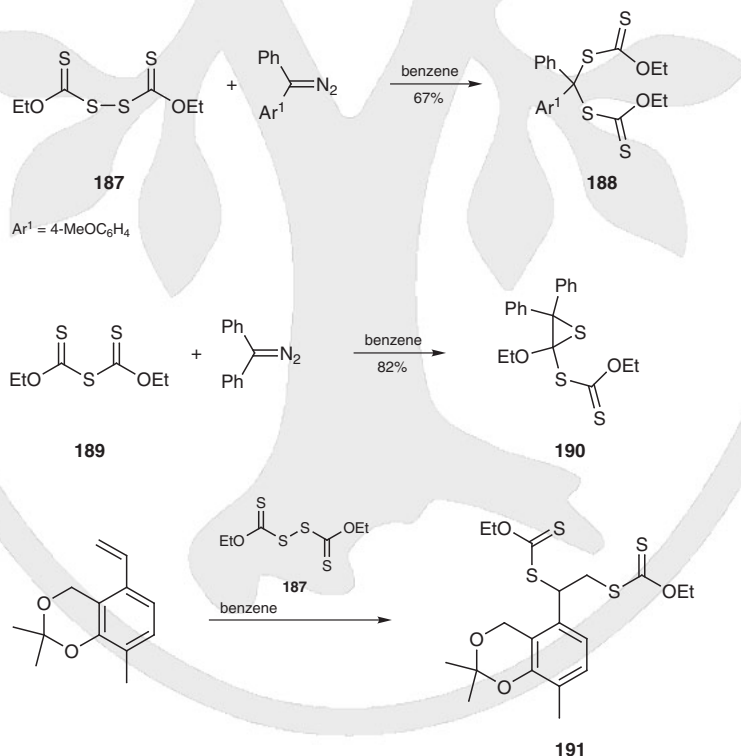
1,2-Bis[(triisopropylsilyl)sulfanyl]dec-1-ene reacts with either thiophosgene or O-phenyl chlorothioformate to provide a mixture of 1,3-dithiole-2-thione and 1,2-bis{[(phenoxy)-thiocarbonyl]sulfanyl}dec-1-ene in 88 and 12% yields respectively.^[277]

The silver salt of penicillin- β -lactam **185** reacts with O-2-naphthyl chlorothioformate to give the substitution product **186** in pyridine/tetrahydrofuran solution in 73% yield (Scheme 77).^[278]

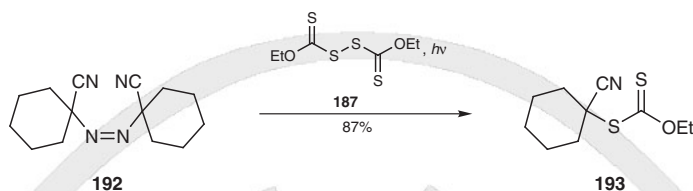
Scheme 77 Formation of the Dithiocarbonate O,S-Ester of a β -Lactam^[278]

Potassium *O*-isopropyl dithiocarbonate gives the corresponding disulfide, bis[(isopropoxy)thiocarbonyl] disulfide, on oxidation with iodine in propan-2-ol and water.^[42] This disulfide and the analogous ethyl ester, bis[(ethoxy)thiocarbonyl] disulfide (**187**), and monosulfide, *O,O*-diethyl trithiodicarbonate (**189**) act as a sodium or potassium *O*-alkyl dithiocarbonate equivalent and several interesting reactions have been reported.

When **187** was treated with diazo(4-methoxyphenyl)phenylmethane, the disulfide **187** undergoes S–S bond insertion to afford the product **188** (Scheme 78).^[279] However, monosulfide **189** on treatment with diazodiphenylmethane gives episulfide **190** as a result of insertion into the C=S bond (Scheme 78).^[280] The disulfide **187** undergoes addition reactions to double and triple bonds as shown for the formation of **191** in Scheme 78.^[281,282]

Scheme 78 Reactions of Bis[(ethoxy)thiocarbonyl] Disulfide and *O,O*-Diethyl Trithiodicarbonate with Diaryldiazomethanes^[279–282]

In a radical reaction 1,1'-azobiscyclohexanenitrile (**192**) reacts with bis[(ethoxy)thiocarbonyl] disulfide (**187**) under photochemical conditions to give the substitution product *S*-1-cyanocyclohexyl *O*-ethyl dithiocarbonate (**193**) (Scheme 79).^[283]

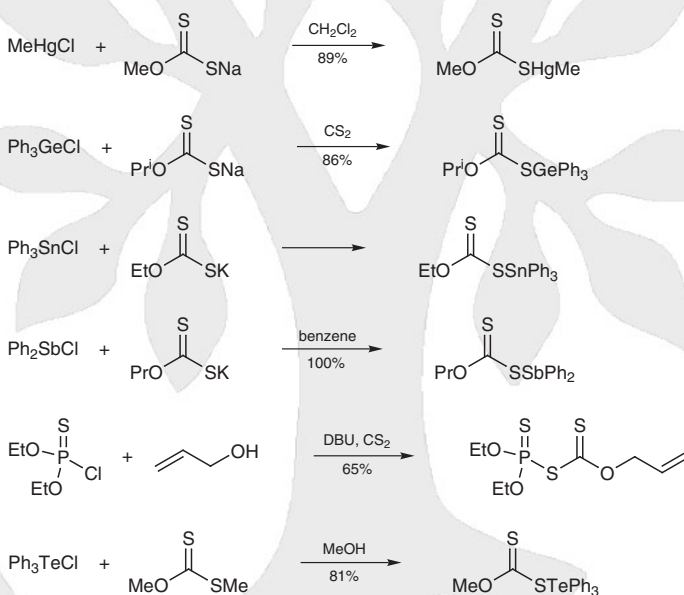
Scheme 79 Radical Reaction of Bis[(ethoxy)thiocarbonyl] Disulfide^[283]

18.10.6.1.4

Method 4:
From Organometallic Reagents and Sodium or
Potassium O-Alkyl Dithiocarbonates

The organometallic reagents used in these reactions are mercury, germanium, antimony, tin, phosphorus, and tellurium compounds. Essentially, the halides of these organometallic reagents are employed in the reactions while sodium or potassium O-alkyl dithiocarbonates act as nucleophiles.

Various representative results are shown in Scheme 80.^[284–299]

Scheme 80 Reaction of Sodium or Potassium O-Alkyl Dithiocarbonates with Organometallics^[284–299]

18.10.6.1.5

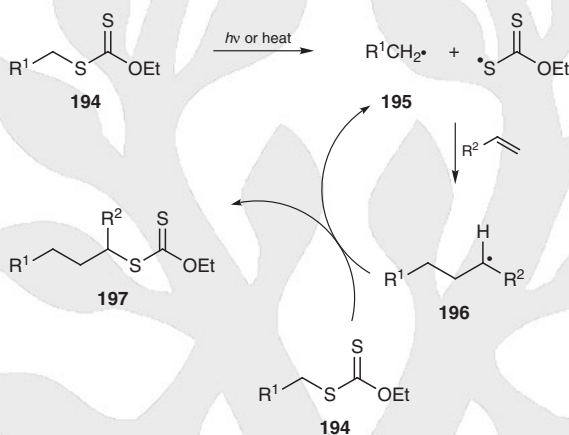
Method 5:
Photochemical and Radical-Initiated Addition of
Dithiocarbonates O,S-Esters to Terminal Alkenes

Dithiocarbonate O,S-esters **194** bearing an electron-withdrawing benzyl, propynyl, cyanomethyl or carbonylmethyl group connected to the sulfur undergo facile C–S bond fission on UV irradiation or on heating in the presence of hydroperoxides such as *tert*-butyl hydroperoxide to generate reactive carbon radicals **195**. If these reactions are carried out in the presence of an alkene, the carbon radical initially undergoes addition to the terminal carbon of the alkene thus producing a new radical species **196** which may react at the thiocarbonyl group of the dithioester O,S-ester **194** and gives **197** and a new carbon radi-

cal **195**. This newly formed radical repeats the same reaction providing a chain reaction. In these reactions carbon radicals add exclusively to the terminal carbon of the alkene and the sulfur atom is always connected to the internal carbon atoms. Thus, this radical-chain reaction can be utilized for carbon chain elongation reactions; the dithiocarbonate *O,S*-ester group is readily removed. If the substrates have a double bond at an appropriate position, then intramolecular radical addition is observed to afford cyclic compounds. The reaction mechanism is illustrated in Scheme 81.

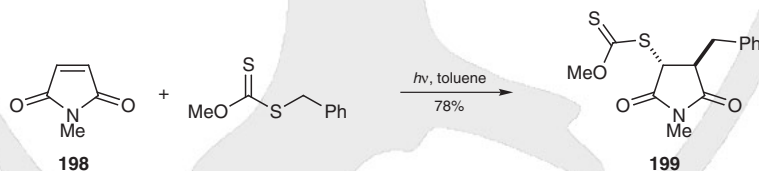
In the case where hydroperoxide is used as the initiator, the peroxide radicals generated may attack at the thiocarbonyl group thus generating the carbon radical, which adds to the alkene double bond. The chain reactions are repeated in the same manner as the photochemical reactions.

Scheme 81 Photochemical Addition of Dithiocarbonate *O,S*-Esters to Alkenes



As a simple photochemical reaction, the stereoselective *trans* addition of *S*-benzyl *O*-methyl dithiocarbonate to *N*-methylsuccinimide (**198**) in toluene gives dithiocarbonate *O,S*-ester **199** in 78% yield (Scheme 82).^[300,301] Stereochemical investigations also show that the reactions using cyclopropene and cyclobutene derivatives also proceed in a *trans*-selective manner.^[302,303]

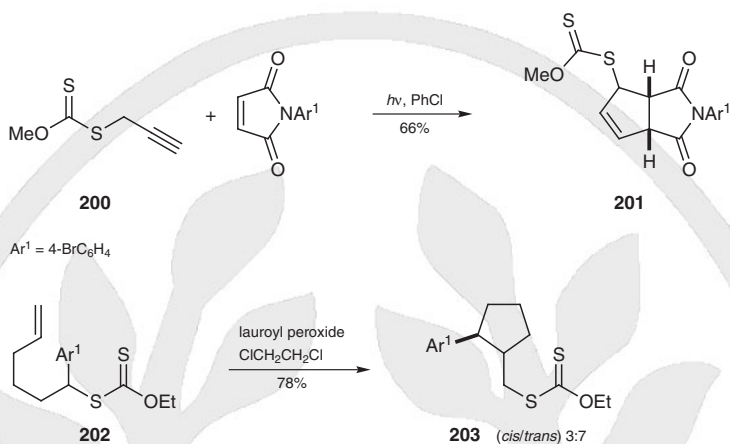
Scheme 82 *trans*-Selective Addition of *S*-Benzyl *O*-Methyl Dithiocarbonate to *N*-Methylsuccinimide^[300,301]



Many other simple intermolecular addition reactions of dithiocarbonate *O,S*-esters have been reported.^[304–314]

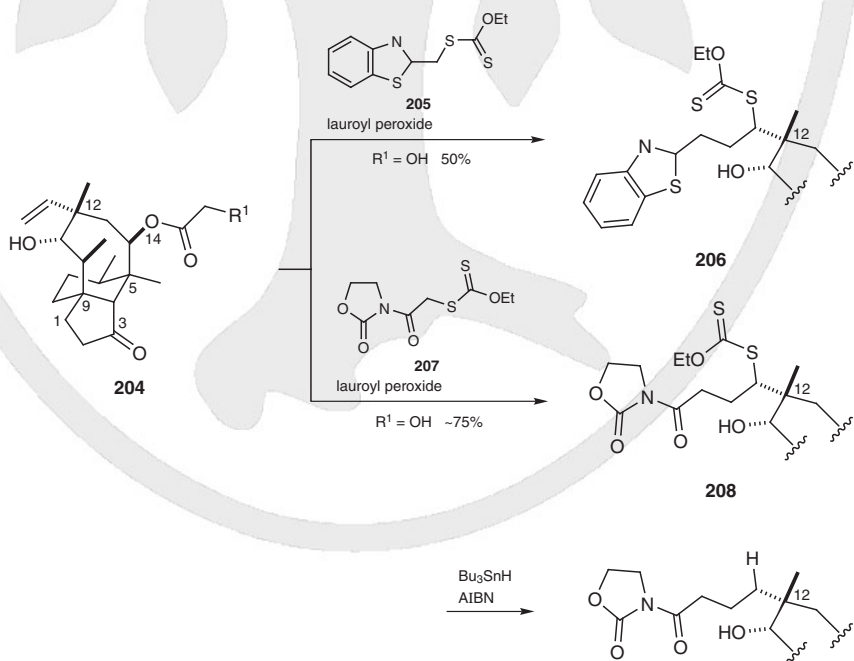
With a suitable substrate, such as **200**, the product of cyclization of the carbon radical generated under photolysis or thermal reaction in the presence of hydroperoxide **201** is formed (Scheme 83). Both inter- and intramolecular cyclizations have been reported.^[315–320]

Treatment of the dithiocarbonate *O,S*-ester **202** with lauroyl peroxide in 1,2-dichloroethane gives cyclization product **203** as a *cis/trans* 3:7 mixture. After separation of these stereoisomers and treatment with tributyltin hydride the product of the removal of the dithiocarbonate *O,S*-ester group is formed, i.e. *trans*-1-(3-methoxyphenyl)-2-methylcyclopentane is obtained in 70% yield.^[320]

Scheme 83 Intramolecular Radical Cyclization Reactions of Dithiocarbonate O,S-Esters^[315–320]

A number of examples of the peroxide initiated addition reactions of dithiocarbonate O,S-esters bearing electron-withdrawing groups to alkenes are available, these include various new types of reaction, including cyclization, addition to aromatic rings, and creation of new reagents for organic synthesis by radical didethiocarbonation.

For example, dithiocarbonate O,S-esters **205** and **207** are used in the peroxide-promoted addition to the alkene group in the naturally obtained antibacterial pleuromultilin **204** without affecting the other functional groups giving **206** and **208**, respectively (Scheme 84).^[321] Several other reactions of the peroxide promoted addition of dithiocarbonate O,S-esters to alkenes have been reported.^[304,307,322,323]

Scheme 84 Radical Addition of Dithiocarbonate O,S-Esters to the Alkene Group in Pleuromultilin^[321]

A large numbers of radical reactions have been utilized and have provided attractive procedures for modern organic synthesis.^[324,325] The present photochemical or peroxide catalyzed reactions of dithiocarbonate *O,S*-esters with alkenes are highly useful procedures for radical-mediated organic synthesis.

***O*-Ethyl *S*-[2-Oxo-2-(2-oxooxazolidin-3-yl)ethyl] Dithiocarbonate (207):**^[321]

At -10°C and under N_2 , 1.5 M BuLi in hexane (11.5 mL, 1 equiv) was added dropwise to a stirred soln of oxazolidin-2-one (1.5 g, 17 mmol) in dry THF (35 mL). Chloroacetyl chloride (1.5 mL, 1.1 equiv) was then added dropwise. After 15 min of stirring, the mixture was poured into a mixture of sat. NH_4Cl and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried (MgSO_4), and filtered. The solvent was removed under reduced pressure and the residue was purified by chromatography (silica gel) to give 3-(2-chloroacetyl)oxazolidin-2-one as a white solid; yield: 1.8 g (65%). This material was used directly in the next step.

At rt and under N_2 , KSC(S)OEt (1.9 g, 1.1 equiv) was slowly added to a stirred soln containing 3-(2-chloroacetyl)oxazolidin-2-one (1.75 g, 10.7 mmol) in acetone (5 mL). After a few minutes of stirring, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and brine. The organic layer was dried (MgSO_4) and the solvent was removed under reduced pressure to give 2.9 g of a yellow solid. Recrystallization (heptane/EtOAc) afforded **207** as colorless needles; yield: 2.4 g (90%); mp 96°C .

Addition Product 208 ($\text{R}^1 = \text{H}$) from 204 and *O*-Ethyl *S*-[2-Oxo-2-(2-oxooxazolidin-3-yl)ethyl] Dithiocarbonate (207):^[321]

Lauroyl peroxide (60 mg, 0.1 equiv) was added to a refluxing soln of *O*-ethyl dithiocarbonate **207** (1.8 g, 7.2 mmol) and (+)-pleuromutilin (**204**, $\text{R}^1 = \text{OH}$; 0.54 g, 1.4 mmol) in 1,2-dichloroethane (2 mL) under N_2 . Further portions of lauroyl peroxide (30 mg, 0.05 equiv) were added every 90 min until completion of the reaction, which took about 10 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (silica gel) to give **208** as a colorless oil; yield: 0.67 g (ca. 75%); mixture of epimers.

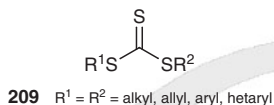
18.10.6.2 Applications of Product Subclass 6 in Organic Synthesis

The major purpose for preparation of dithiocarbonate *O,S*-esters of complex molecules is the deoxygenation to form the corresponding reduction products. This reduction is accomplished using Barton–McCombie deoxygenation with radical sources such as a combination of 2,2'-azobisisobutyronitrile and tributyltin hydride. This reduction procedure is discussed in Section 18.10.5 and various examples are given in Section 18.10.6.1 as they are generally performed as part of an overall sequence that includes formation of the dithiocarbonate *O,S*-ester.

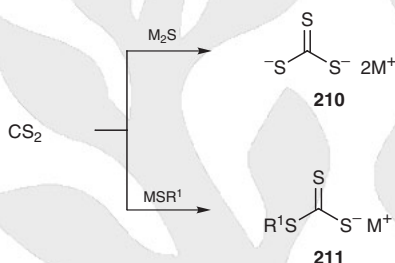
Dithiocarbonate *O,S*-esters formed from aromatic diazonium salts either in situ or after conversion into the tetrafluoroborate salt and dithiocarbonates, i.e. potassium *O*-ethyl dithiocarbonate, can subsequently undergo either alkaline hydrolysis or treatment with lithium aluminum hydride to afford thiols. The characteristic features of this synthetic process are the ease of handling, high yields of the arenethiols, and the wide range of suitable aromatic amines; see examples in Section 18.10.6.1.2.2.

18.10.7 Product Subclass 7: Trithiocarbonates

Trithiocarbonates have structure **209** and are sulfur analogues of carbonates (Scheme 85). Both cyclic and acyclic trithiocarbonates have been synthesized.

Scheme 85 Trithiocarbonates

Trithiocarbonic acid itself is unstable and decomposes readily at temperatures $> -80^\circ\text{C}$ to give carbon disulfide and hydrogen sulfide. On the other hand, its alkali or alkali earth metal salts **210** and monoesters thereof **211** are prepared from carbon disulfide and alkali or alkali earth metal salts or thiolates in an alcohol (Scheme 86). They are sufficiently stable to be isolated and are used in situ for the preparation of trithiocarbonates.

Scheme 86 Synthesis of Trithiocarbonate Derivatives

There are several other procedures for preparation of trithiocarbonates and the methods are well-established. The general preparative methods for trithiocarbonates before the early 1980s are described in *Houben-Weyl*, Vol. E 4, p 447.

Since the 1980s these compounds have attracted considerable attention since, in particular, 1,3-dithiole-2-thione and its derivatives have been found to possess high electroconductive properties. These compounds are referred to as organometals and variety of examples have been synthesized.

The dialkyl trithiocarbonates are utilized as agrochemicals, especially as pesticides, and lubricating additives, a number of patents on their preparation and utilities are available.

18.10.7.1 Synthesis of Product Subclass 7**18.10.7.1.1 Method 1:
From Carbon Disulfide and Hydrogen Sulfide or Thiols with Alkyl Halides**

Generally, the reaction of alkyl bromides with carbon disulfide and a suitable sulfur source such as hydrogen sulfide, sodium sulfide, or amino disulfides in the presence of a base or alkanethiolates and carbon disulfide has been employed for the preparation of symmetric and unsymmetrical dialkyl trithiocarbonates. These procedures have provided many dialkyl trithiocarbonates and 1,3-dithiole-2-thione derivatives in high yields.^[326–329]

The synthesis of many symmetric **212** and unsymmetrical trithiocarbonates **213** has been accomplished under phase-transfer catalysis conditions in almost quantitative yields. The advantages of phase-transfer catalysis reactions in trithiocarbonate syntheses compared to the normal conditions are their high yields, short reaction times, and the fact that the reaction is not solvent dependent.^[330–333]

Representative examples are shown in Tables 3 and 4.^[330–333]

Table 3 Synthesis of Trithiocarbonates from Sodium Trithiocarbonate^[330]

$$\text{Na}_2\text{S} + \text{CS}_2 \xrightarrow[\text{rt, 90 min}]{\text{PTC, H}_2\text{O}} \text{NaS}=\text{C}=\text{SNa} \xrightarrow[\text{80–100\%}]{\text{R}^1\text{X, 70 }^\circ\text{C}} \text{R}^1\text{S}=\text{C}=\text{SR}^1$$

212

R ¹ or R ¹ –R ¹	X	Phase-Transfer Catalyst ^a (mmol)	Time ^b (h)	Yield (%)	Ref
iPr	Br	A (2.5)	2	90	[330]
Bu	Br	A (0.5)	1	90	[330]
CH(Me)Pr	Br	A (2.5)	6	90	[330]
cyclopentyl	Br	A (0.5)	3	95	[330]
(CH ₂) ₇ Me	Br	A (0.5)	1.5	100	[330]
(CH ₂) ₇ Me	Cl	A (2.5)	7	92	[330]
(CH ₂) ₇ Me	Cl	T (3)	7	90	[330]
(CH ₂) ₇ Me	Cl	H (10)	5	96	[330]
(CH ₂) ₁₇ Me	Br	A (0.5)	3	100	[330]
Bn	Cl	A (0.5)	1	91	[330]
CH ₂ CH=CH ₂	Cl	A (0.5)	2 ^c	90	[330]
CH ₂ CH ₂	2 Cl	A (0.5)	1.5	93	[330]

^a Catalyst; A = Aliquat 336, H = hexadecyltributylphosphonium bromide, T = TBAB.^b Step 2.^c At rt.**Table 4** Synthesis of Unsymmetrical Trithiocarbonates from Potassium Alkyl Trithiocarbonates^[330]

$$\text{R}^2\text{SH} + \text{CS}_2 + \text{KOH} \xrightarrow{\text{H}_2\text{O}} \text{R}^1\text{S}=\text{C}=\text{SK} \xrightarrow[\text{50–100\%}]{\text{R}^2\text{X}} \text{R}^1\text{S}=\text{C}=\text{SR}^2$$

213

R ¹	R ² X	Phase-Transfer Catalyst ^a (mmol)	Yield (%)	Ref
iPr	Me(CH ₂) ₇ Br	A (0.5)	100	[330]
Bu	BuBr	A (0.5)	95	[330]
Bu	Me(CH ₂) ₇ Br	A (0.5)	98	[330]
t-Bu	BuBr	A (0.5)	92	[330]
Bn	BuBr	A (0.5)	98	[330]
Ph	BuBr	H (2)	50	[330]
Bu	CH ₂ Br ₂	A (0.5)	95	[330]

^a Catalyst; A = Aliquat 336, H = Hexadecyltributylphosphonium bromide, T = TBAB.**Diocetyl Trithiocarbonate [212, R¹ = (CH₂)₇Me]; Typical Procedure:**^[330]

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

A mixture of Na₂S•9H₂O (24 g, 0.1 mol), CS₂ (7.6 g, 0.1 mol), and Aliquat 336 (0.2 g, 0.5 mmol) in H₂O (30 mL) was vigorously stirred at rt for 90 min. To the red Na₂CS₃ thus obtained, 1-bromooctane (38.6 g, 0.2 mol) was added in one portion with stirring. The

temperature of the mixture was then slowly raised to 70 °C over 15–20 min and maintained for an additional 90 min until the aqueous soln became completely colorless. After cooling, petroleum ether (150–200 mL) was added and the organic layer was separated, dried (MgSO₄), and filtered over a small layer of silica gel (petroleum ether). The solvent was removed on a rotary evaporator to afford virtually pure dioctyl trithiocarbonate according to ¹H NMR, TLC and GC analysis; yield: quant; bp 190–193 °C/0.3 Torr. Without catalyst, heating at 70 °C for 40 h, dioctyl trithiocarbonate was obtained in 41% yield by GC analysis, together with some of the starting octyl bromide (28%).

Butyl Octyl Trithiocarbonate [213, R¹ = Bu; R² = (CH₂)₇Me]; **Typical Procedure**:^[330]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

CS₂ (7.6 g, 0.1 mol) and Aliquat 336 (0.2 g, 0.5 mmol) were added to a soln of butane-1-thiol (9 g, 0.1 mol) in 20% KOH (31 mL). The mixture was vigorously stirred at rt for 15 min. To the orange soln of potassium butyl trithiocarbonate so obtained, 1-bromooctane (19.3 g, 0.1 mol) was added in one portion and under stirring and the mixture was then slowly heated up to 70 °C over a period of 15–20 min. The temperature was maintained until the aqueous soln became colorless (15 min). GC analysis showed the complete disappearance of the starting BuSH and 1-bromooctane. After cooling, the mixture was extracted with petroleum ether (150–200 mL), which was separated, dried (MgSO₄), and filtered over a small layer of silica gel (petroleum ether). After concentration in vacuo, virtually pure butyl octyl trithiocarbonate was obtained; yield: 98%; bp 173–174 °C/0.4 Torr.

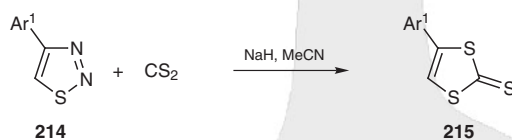
18.10.7.1.1.1

Variation 1:
Cyclization of Oxiranes, Thiiranes, and Acetylenic Compounds with Carbon Disulfide

Oxiranes and thiiranes are also utilized as starting materials for the synthesis of 1,3-dithiole-2-thione derivatives in moderate yields.^[334,335]

1,2,3-Thiadiazoles **214** upon treatment with sodium hydride and then carbon disulfide in acetonitrile afford 1,3-dithiole-2-thione derivatives **215** (Scheme 87).^[336,337]

Scheme 87 Synthesis of 1,3-Dithiole-2-thiones from 1,2,3-Thiadiazoles^[336,337]

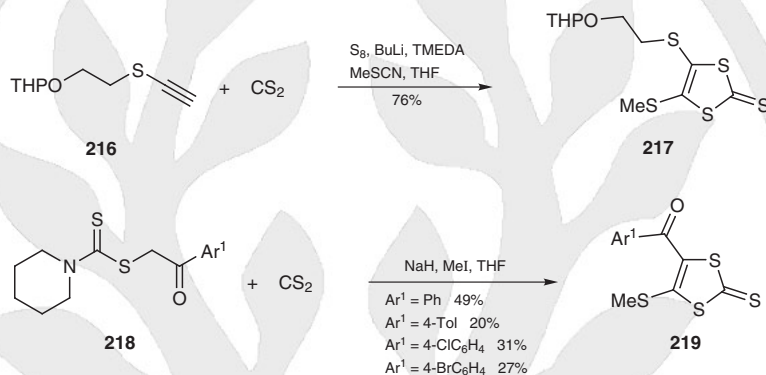


Ar ¹	Yield (%)	Ref
4-NCC ₆ H ₄	57	[336]
4-O ₂ NC ₆ H ₄	98	[336]
5-cyano-2-thienyl	74	[336]
2-thienyl	75	[336]
3-thienyl	83	[336]
1,3-dioxolan-2-yl	98	[336]

Many acetylene derivatives are converted into the corresponding 1,3-dithiole-2-thione derivatives in the presence of base and carbon disulfide. For example, tetrahydropyran-protected 2-(ethynylsulfanyl)ethanol **216** affords the 1,3-dithiole-2-thione **217** (Scheme 88). Carbon diselenide gave, in a similar manner, the selenium analogue in good yields.^[238,338–341]

S-Phenacyl dithiocarbamates **218** bearing an active methylene afford substituted 1,3-dithiole-2-thiones **219** upon treatment with sodium hydride and then carbon disulfide in tetrahydrofuran as solvent (Scheme 88).^[342]

Scheme 88 Cyclization of Carbon Disulfide^[338,342]



4-(Methylsulfanyl)-5-[2-(2H-tetrahydropyran-2-yloxy)ethylsulfanyl]-1,3-dithiole-2-thione (217):^[338]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

To a mixture of 2-(ethynylsulfanyl)ethyl 2H-tetrahydropyran-2-yl ether (**216**; 4.6 g, 25 mmol) and TMEDA (7.4 mL, 49 mmol) in THF (100 mL) cooled to -70°C was added 1.61 M BuLi in hexane (15 mL, 25 mmol) and the soln was stirred for 30 min to form the lithium acetylide species. Sulfur (780 mg, 25 mmol) was added in one portion, and the mixture was warmed to 0°C over a period of 1 h and stirred at 0°C for an additional 2 h. The mixture was cooled again to -90°C , and then CS_2 (1.5 mL, 25 mmol) and methyl thiocyanate (5.1 mL, 74 mmol) were added. The resulting mixture was allowed to warm to 9°C over a period of 2 h and stirred at 0°C for an additional 0.5 h. Then, the mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with brine (2×100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography [silica gel, benzene (**CAUTION: carcinogen**)] to afford a yellow oil; yield: 6.3 g (76%).

5-Benzoyl-4-(methylsulfanyl)-1,3-dithiole-2-thiones 219; General Procedure:^[342]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

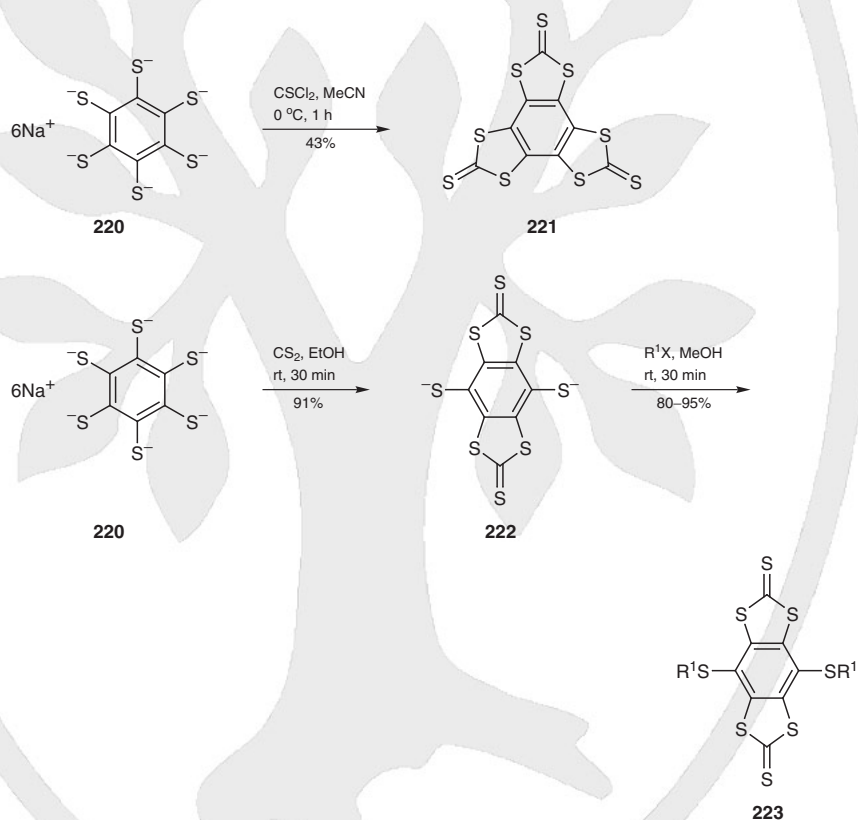
CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

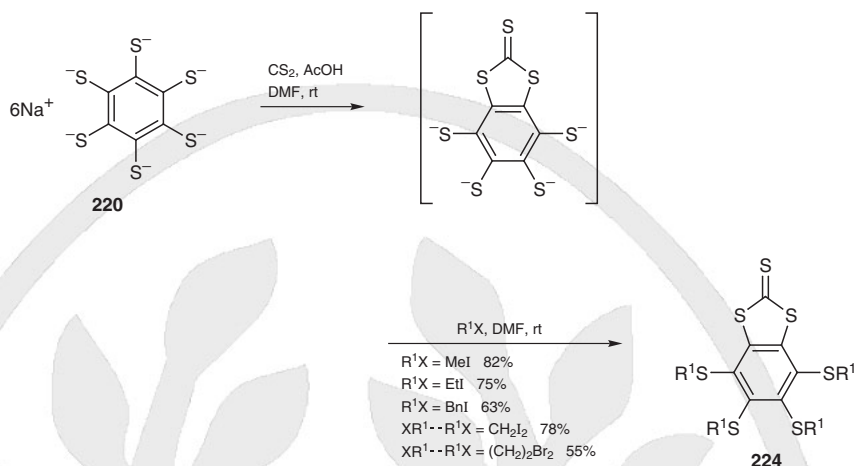
Compound **218** (5 mmol) and CS_2 (5 mmol) were dissolved in dry THF (50 mL). Under cooling (-10°C) and N_2 , NaH (10 mmol) was added in portions. The mixture was stirred at rt for 2 h. Then MeI (12 mmol) was added in one portion. After 2 h the soln was poured into ice. The precipitate **219** was collected and recrystallized (BuOH).

18.10.7.1.1.2

**Variation 2:
Poly-1,3-dithiole-2-thione**

Many benzene–poly-1,3-dithiole-2-thione derivatives are available using benzenehexathiols and carbon disulfide or thiocarbonyl dichloride under alkaline conditions. Hexasodium benzenehexathiolate (**220**) reacts with carbon disulfide in ethanol at room temperature to afford 2,6-dithioxobenzo[1,2-*d*:4,5-*d'*]bis[1,3]dithiole-4,8-dithiolate (**222**) in 91% yield, which after alkylation gives 4,8-bis(alkylsulfanyl) derivatives **223** in 80–95% yields (Scheme 89). Reaction of **220** and carbon disulfide under weakly acidic conditions and a 1:1 molar ratio of thiols and carbon disulfide, followed by alkylation, gives 4,5,6,7-tetrakis(alkylsulfanyl)-1,3-benzodithiole-2-thiones **224** in 55–82% yield. Reaction of **220** with thiophosgene (**1**) in acetonitrile at 0 °C for 2 hours gives benzo[1,2-*d*:3,4-*d'*:5,6-*d''*]tris[1,3]-dithiole-2,5,8-trithione (**221**) in 43% yield. The related reaction of polybenzenethiols and carbon disulfide has been described.^[343]

Scheme 89 Poly-1,3-dithiole-2-thiones^[343]



4,5,6,7-Tetrakis(alkylsulfanyl)-1,3-benzothiole-2-thiones **224**; General Procedure:^[343]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

To a suspension of hexasodium benzenehexathiolate (**220**; 0.66 g, 1.7 mmol) in DMF (100 mL) was added CS_2 (0.1 mL, 1.66 mmol). Then a mixture of AcOH and DMF (2:5, ca. 30 mL) was added dropwise until the solid dissolved. After 10 min stirring at rt, the alkylating agent [8 mmol for MeI, EtI, BnI, 4 mmol for CH_2I_2 , $(\text{CH}_2)_2\text{Br}_2$] was added. The mixture was stirred for 10 min and then cooled with dry ice. The precipitated 1,3-dithiole-2-thiones **224** were collected by filtration and recrystallized.

18.10.7.1.2

Method 2:

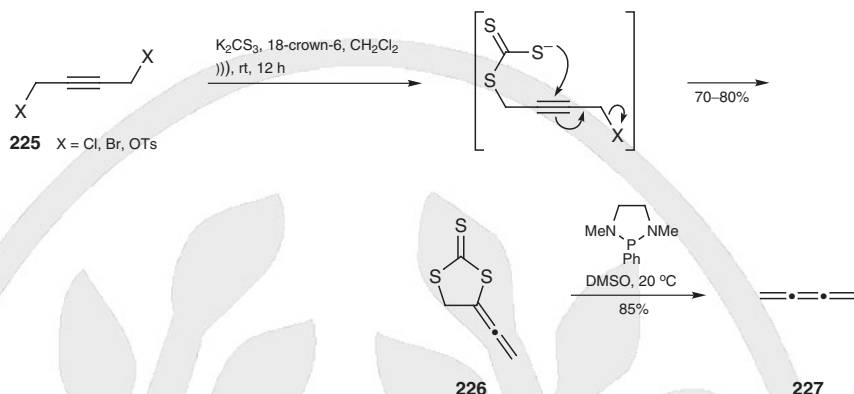
From Salts of Trithiocarbonic Acid and Monoesters of Trithiocarbonic Acid

Alkali and alkali earth metal salts of trithiocarbonic acid and its monoesters are sufficiently stable to be isolated.^[344]

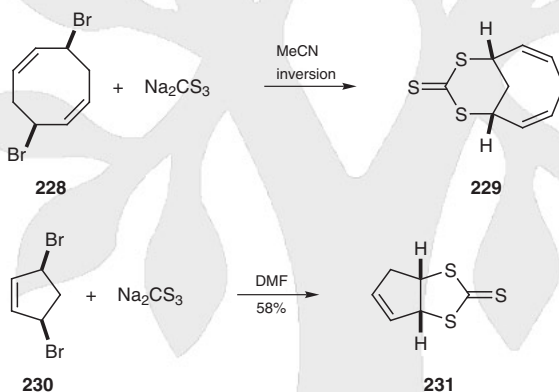
These salts are widely utilized for the synthesis of trithiocarbonates as well as those salts generated in situ from carbon disulfide and sodium or potassium sulfide (Section 18.10.7.1.1). The reactions are clean and aprotic polar solvent or phase-transfer catalysts are frequently used to promote the reactions and to avoid the low solubility of the salts.^[78,345]

One equivalent of a trithiocarbonate salt and an alkyl halide gives monoalkylated trithiocarbonates that produce, on further treatment with alkyl halides, both symmetric and unsymmetrical dialkyl trithiocarbonates in high yields.^[346] In the case of dihalides and ditosylates, 1,3-dithiole-2-thiones and 1,3-dithiane-2-thione are obtained in high yields in the presence of 18-crown-6 in benzene.^[347–349]

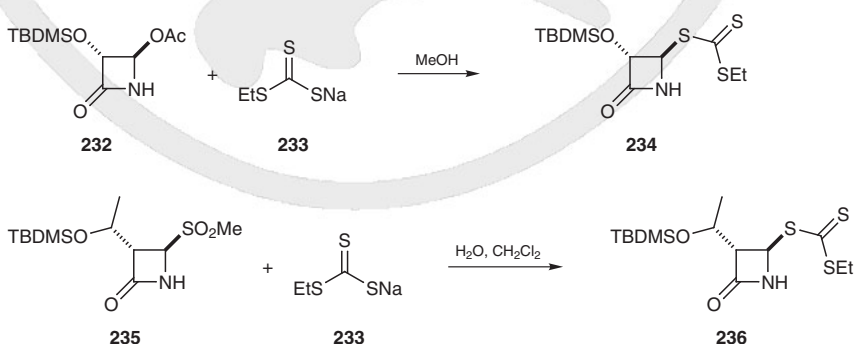
1,4-Dichloro-, 1,4-dibromo-, and 1,4-bis(tosyloxy)but-2-yne **225** are treated with potassium trithiocarbonate in dichloromethane in the presence of 18-crown-6 as a phase-transfer catalyst to afford 4-vinylidene-1,3-dithiolane-2-thione (**226**) in yields of 70–80% which on further treatment with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine in dimethyl sulfoxide at 220°C under nitrogen undergoes Corey–Winter alkenation to afford buta-1,2,3-triene (**227**), obtained at –40°C, in 85% yield as an unstable colorless liquid (Scheme 90).^[350,351]

Scheme 90 Synthesis of 4-Vinylidene-1,3-dithiolane-2-thione^[350,351]

cis-3,7-Dibromocycloocta-1,5-diene (**228**) reacts with sodium trithiocarbonate in acetonitrile to afford bicyclic 1,3-dithiane-2-thione **229**, while similar treatment of *cis*-3,5-dibromocyclopent-1-ene (**230**) with sodium trithiocarbonate in dimethylformamide affords 4,6a-dihydro-3a*H*-cyclopenta[*d*]-1,3-dithiole-2-thione (**231**) in moderate yield (Scheme 91).^[255]

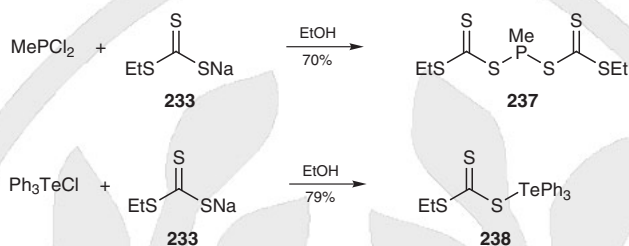
Scheme 91 Addition of Sodium Trithiocarbonate to Halocycloalkenes^[255]

β -Lactam derivatives **232** and **235** react with sodium ethyl trithiocarbonate (**233**) in methanol to give the penam trithiocarbonate derivatives **234** and **236**, respectively, with retention of configuration (Scheme 92).^[352–354]

Scheme 92 Formation of Trithiocarbonates of β -Lactam^[352–354]

Dichloro(methyl)phosphine and chlorotriphenyl- λ^4 -tellane also undergo substitution of a halogen with sodium ethyl trithiocarbonate (**233**) in ethanol to give the products **237** and **238** in 70 and 79% yield, respectively (Scheme 93).^[295]

Scheme 93 Heteroatom-Substituted Trithiocarbonates^[295]



4-Vinylidene-1,3-dithiolane-2-thione (226**); Typical Procedure:**^[350,351]

1,4-Dichlorobut-2-yne (**225**, X = Cl; 1.23 g, 10 mmol), 18-crown-6 (10 mg, 0.04 mmol), and K_2CS_3 (2.23 g, 12 mmol) were suspended in anhyd N_2 flushed CH_2Cl_2 (100 mL). The suspension was reacted under N_2 at rt using ultrasound for 12 h (ultrasound speeds up the reaction by a factor of about 10). KCl and excess of K_2CS_3 were removed by filtration, the solvent was reduced to 20 mL in vacuo and the yellow soln chromatographed (silica gel, CH_2Cl_2) (only one product was observed on TLC). The product **226** was obtained as a malodorous, yellow liquid, which polymerized rapidly at rt. The product **226** was stable in solution, under N_2 at $-30^\circ C$ for several days; yield: 1.2 g (75%).

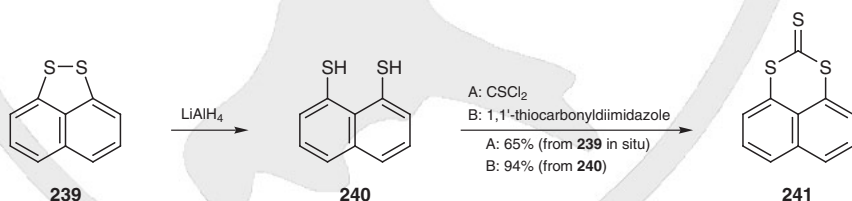
18.10.7.1.3

Method 3:

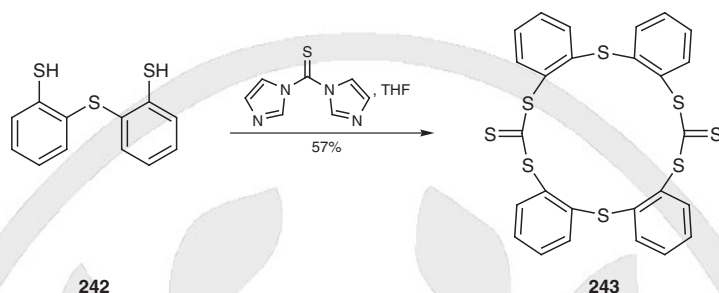
From Thiophosgene or 1,1'-Thiocarbonyldiimidazole

Dithiols are known to react with thiophosgene and 1,1'-thiocarbonyldiimidazole to give the corresponding 1,3-dithiole-2-thione derivatives. Naphthalene-1,8-diyl disulfide (**239**) undergoes initial reduction with lithium aluminum hydride in diethyl ether and the resulting naphthalene-1,8-dithiol (**240**) is then treated with thiophosgene in situ to afford the 1,3-dithiin **241** in moderate yield (Scheme 94).^[355] Similarly, naphthalene-1,8-dithiol (**240**) is treated with 1,1'-thiocarbonyldiimidazole to provide the same dithiine **241** in 94% yield.^[356]

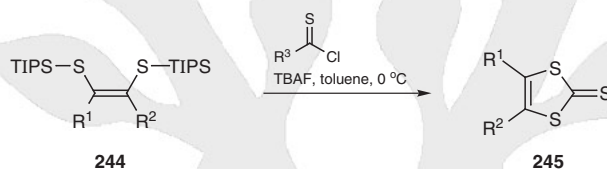
Scheme 94 Formation of Naphtho[1,8-*de*]-1,3-dithiin-2-thione^[355,356]



Bis(1-sulfanyphenyl) sulfide (**242**) reacts with 1,1'-thiocarbonyldiimidazole to give the macrocyclic trithiocarbonate **243** in 57% yield (Scheme 95).^[357]

Scheme 95 Formation of a Macrocyclic Trithiocarbonate^[357]

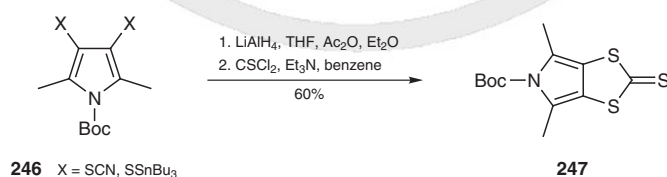
The triisopropylsilyl-protected dithiol derivatives **244** are deprotected by treatment with tetrabutylammonium fluoride followed by reaction with thiophosgene or *O*-phenyl chlorodithioformate to give the corresponding 1,3-dithiole-2-thiones **245** in high yields (Scheme 96).^[277]

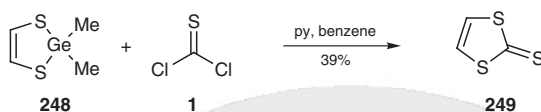
Scheme 96 Synthesis of 1,3-Dithiole-2-thiones from Silyl-Protected Alkenes and Thiocarbonyl Dichloride^[277]

R ¹	R ²	Yield (%) of 245		Ref
		R ³ = Cl	R ³ = OPh	
Cy	H	56	83	[277]
cyclohex-1-enyl	H	59	89	[277]
H	(CH ₂) ₇ Me	58	88	[277]
H	<i>t</i> -Bu	51	85	[277]
Me	Me	38	78 ^a	[277]
Me	Pr	–	63	[277]
Et	Et	–	35 ^a	[277]

^a Reaction at –23 °C.

The tin groups in **246** or the germanium group in **248** undergo substitution with thiophosgene (**1**) to give the corresponding 1,3-dithiole-2-thiones **247** and **249** in good yields (Scheme 97).^[147,358,359] These 1,3-dithioles and the corresponding selenium analogues can be utilized for the synthesis of tetrathiafulvalenes.^[356]

Scheme 97 Reaction of Metal-Protected Thiols with Thiocarbonyl Dichloride^[147,358,359]



2-Thioxo-1,3-dithiole-4,5-dithiolates react with thiophosgene to give a bis(trithiocarbonate), 1,3-dithiolo[4,5-*d*][1,3]dithiole-2,5-dithione.^[360]

4-Cyclohexyl-1,3-dithiole-2-thione (245, R¹ = Cy; R² = H); Typical Procedures:^[277]

CAUTION: Thiophosgene (CSCl₂) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

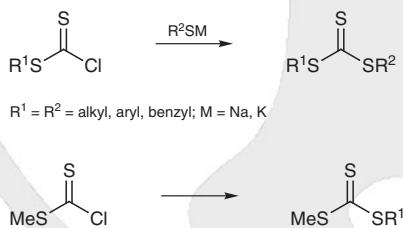
With Thiophosgene: To a soln of {1,2-bis[(triisopropylsilyl)sulfanyl]vinyl}cyclohexane (**244**, R¹ = Cy; R² = H; 400 mg, 0.82 mmol) in toluene (2 mL) at 0 °C was added thiophosgene (69 μL, 0.91 mmol) followed by 1 M TBAF in THF (1.9 mL, 1.9 mmol). The mixture was stirred 1 h at 0 °C then diluted with MeOAc. The organic layer was washed with 25% NH₄OAc soln, H₂O, and dried (MgSO₄). After concentration to dryness, the compound was purified by flash chromatography (2% EtOAc/hexane) to afford the desired compound; yield: 100 mg (56%).

With O-Phenyl Chlorothioformate: To a soln of {1,2-bis[(triisopropylsilyl)sulfanyl]vinyl}cyclohexane (**244**, R¹ = Cy; R² = H; 343 mg, 0.62 mmol) in toluene (1.4 mL) at 0 °C was added O-phenyl chlorothioformate (95 μL, 0.70 mmol) followed by 1 M TBAF in THF (1.6 mL, 1.6 mmol). The mixture was stirred for 1 h at 0 °C then diluted with EtOAc and washed with 25% NH₄OAc soln, H₂O, and brine. The organic layer was dried (MgSO₄), filtered, and concentrated to dryness. After flash chromatography (30% toluene/1% EtOAc/hexane) the product was obtained as an orange solid; yield: 126 mg (83%); mp 64–65 °C.

18.10.7.1.4 Method 4: From Chlorodithioformates

In general, chlorodithioformates react with thiolates and other sulfur nucleophiles to give the corresponding trithiocarbonates as shown in Scheme 98.^[62,361–363]

Scheme 98 Synthesis of Trithiocarbonates from Chlorodithioformates^[62,361–363]



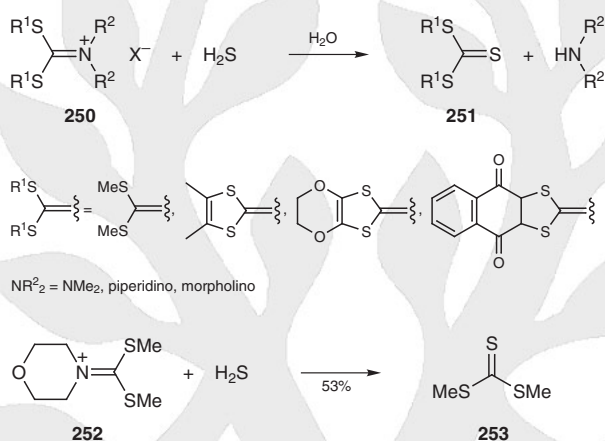
SR ¹	Conditions	Yield (%)	Ref
SCN	NaSCN, HCO ₂ Et	83 (Me), 91 (Ph)	[62]
SO ₂ Ph	NaSO ₂ Ph, benzene, H ₂ O	45	[361]
CCl ₃	H ₂ NC(=NH)NHC(=NH)CCl ₃	26	[362]
SC(S)SMe	KSCS ₂ Me, Et ₂ O	79	[363]

18.10.7.1.5

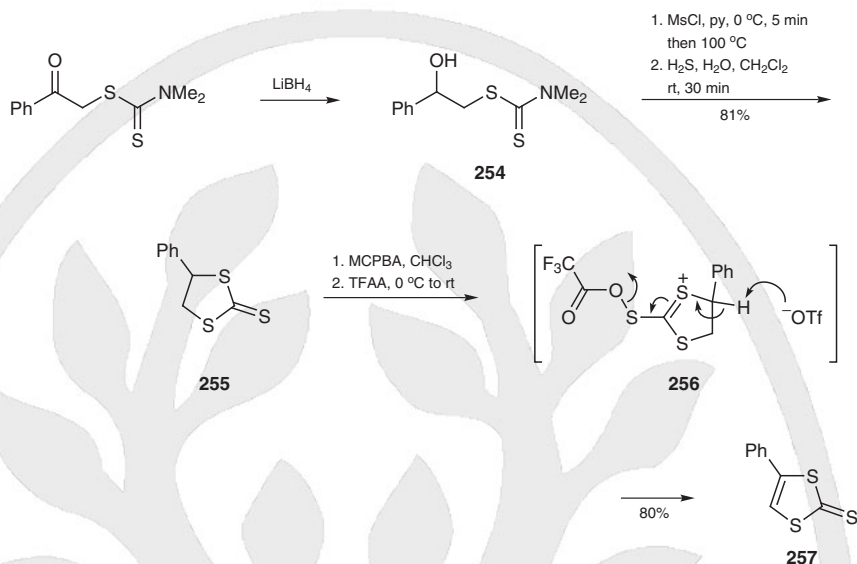
**Methods 5:
Miscellaneous Methods**

N,N-Dimethyliminium, *N*-alkyldenepiperidinium, and *N*-alkyldenemorpholinium salts **250** are utilized for the synthesis of trithiocarbonates upon treatment with hydrogen sulfide or sodium hydrosulfide in water. This process provides mainly 1,3-dithiole-2-thione derivatives **251** (Scheme 99).^[364–369] Dimethyl trithiocarbonate (**253**) is also obtained in 53% yield from 4-[bis(methylsulfanyl)methylene]morpholinium salt **252** and hydrogen sulfide.^[370]

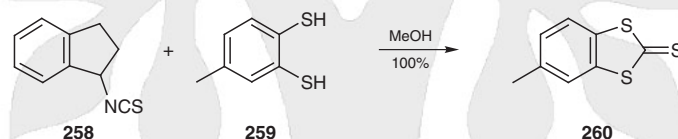
Scheme 99 Synthesis of Trithiocarbonates with Iminium Salts and Hydrogen Sulfide or Sodium Hydrosulfide^[364–370]



S-Phenacyl dimethyldithiocarbamate is reduced to the corresponding alcohol **254** and this is then converted into 4-phenyl-1,3-dithiolane-2-thione (**255**) in 81% yield. The trithiocarbonate **255** is then transformed to 4-phenyl-1,3-dithiole-2-thione (**257**) via an intermediate **256** in 80% yield upon treatment of **255** with 3-chloroperoxybenzoic acid and trifluoroacetic anhydride (Scheme 100). This transformation from thiolane to thiole has been applied to the oxidation of many trithiocarbonate derivatives and is a useful process for producing ethene-1,2-dithiol.^[371]

Scheme 100 Formation of 4-Phenyl-1,3-dithiolane-2-thione and Its Oxidation to 4-Phenyl-1,3-dithiole-2-thione^[371]

Isothiocyanate **258** reacts with 4-methylbenzene-1,2-dithiol (**259**) in methanol to give the corresponding 5-methyl-1,3-benzodithiole-2-thione (**260**) in quantitative yield (Scheme 101).^[372]

Scheme 101 Formation of 5-Methyl-1,3-benzodithiole-2-thione^[372]**4-Phenyl-1,3-dithiolane-2-thione (255):**^[371]

To a soln of the alcohol **254** (1 g, 4.1 mmol) in pyridine (5 mL) at 0°C was added MsCl (0.42 g, 3.7 mmol). The mixture was brought to rt, heated on a steam bath for 5 min and then cooled and H_2S bubbled through it for 10 min. After a further 30 min at rt, $\text{N}_2(\text{g})$ was bubbled through the mixture to remove any residual H_2S and then H_2O and CH_2Cl_2 were added. The organic layer was dried (MgSO_4) and concentrated under reduced pressure to give the crude material which was purified by recrystallization ($\text{CH}_2\text{Cl}_2/\text{hexane}$); yield: 0.71 g (81%); mp $85\text{--}87^\circ\text{C}$.

4-Phenyl-1,3-dithiole-2-thione (257):^[371]

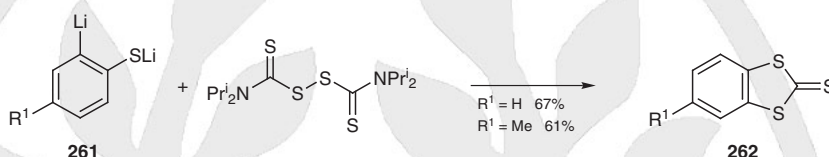
To a stirred soln of the trithiocarbonate **255** (100 mg, 0.47 mmol) in dry CHCl_3 (5 mL) at 0°C was added MCPBA (60 mg, 0.35 mmol). The CHCl_3 soln was then washed with NaHCO_3 , dried (MgSO_4), and concentrated under reduced pressure to give a residue which was redissolved in dry CHCl_3 (5 mL). TFAA (90 mg, 0.43 mmol) was then added with stirring at 0°C to this soln. The mixture was brought to rt and stirred for a further 2 h, after which the mixture was washed with aq NaHCO_3 , dried (MgSO_4), and concentrated to give an orange gum. Crystallization of this (CH_2Cl_2) gave **257** as yellow crystals; yield: 79 mg (80%); mp $116\text{--}118^\circ\text{C}$.

18.10.7.1.5.1

**Variation 1:
Thiocarbonyl as Functional Group**

Tetraalkylthiuram disulfide provides a source of trithiocarbonate. Lithium 2-lithiobenzenethiolate **261** is treated with tetraisopropylthiuram disulfide to afford 1,3-benzodithiole-2-thione **262** in good yield (Scheme 102).^[373] Enamines can also be used as the starting materials.^[374]

Scheme 102 1,3-Benzodithiole-2-thione from Lithium 2-Lithiobenzenethiolates and Tetraisopropylthiuram Disulfide^[373]

**1,3-Benzodithiole-2-thiones 262; General Procedure:**^[373]

A soln of the appropriate dianion **261** was cooled to -10°C and a soln of tetraisopropylthiuram disulfide (1 mol per mol of dianion; i.e., 3.41 g, 9.7 mmol for dianion) in THF (10 mL) was added. The mixture was stirred for 1 h at -10°C , then acidified by addition of 3 M HCl, and extracted with EtOAc. The organic layer was washed with H_2O , dried (MgSO_4), and concentrated to leave a dark oil. The crude product was purified by flash chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{hexane}$ 1:1) to give a yellow crystalline product that was recrystallized.

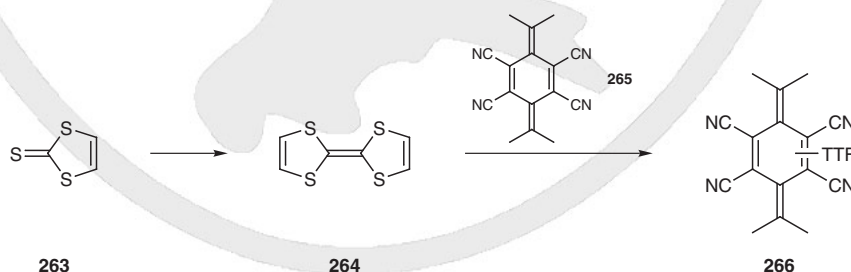
18.10.7.2

Applications of Product Subclass 7 in Organic Synthesis

1,3-Dithiole-2-thiones, such as 1,3-dithiole-2-thione (**263**), are important starting materials for the synthesis of organic superconductors, i.e. a simple material is tetrathiafulvalene **264**, which together with tetracyanoquinodimethane **265** forms the complex **266**, a very good electroconducting substance (Scheme 103).^[375,376]

Since the discovery of this phenomenon, many compounds having a tetrathiafulvalene structure have been synthesized in the search for more efficient organic superconductors. This has promoted the chemistry of trithiocarbonates and related derivatives.

Scheme 103 Formation of a Tetrathiafulvalene–Tetracyanoquinodimethane Charge-Transfer Complex^[375,376]



18.10.7.2.1

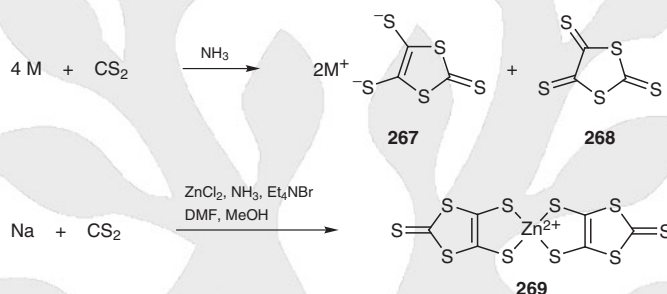
Method 1:**From 2-Thioxo-1,3-dithiole-4,5-dithiolate and Its Zinc Complex**

There are many demands for the preparation of 1,3-dithiole-2-thione derivatives. Their conversion into the tetrathiafulvalene derivatives is useful for the rapid development of new materials as electroconductors.

Essentially there are four possible chemical routes for the synthesis of the 1,3-dithiole-2-thione skeleton. The first method is the formation of 2-thioxo-1,3-dithiole-4,5-dithiolate **267** as its sodium, potassium, or ammonium salt, together with 1,3-dithiolane-2,4,5-trithione (**268**) is prepared from carbon disulfide and potassium metal (Scheme 104).^[377]

The second process involves the conversion of the zinc complex of **267**, the zinc “ate” complex salt **269**, which is prepared from carbon disulfide and sodium metal with zinc(II) chloride in methanol (Scheme 104).^[378,379]

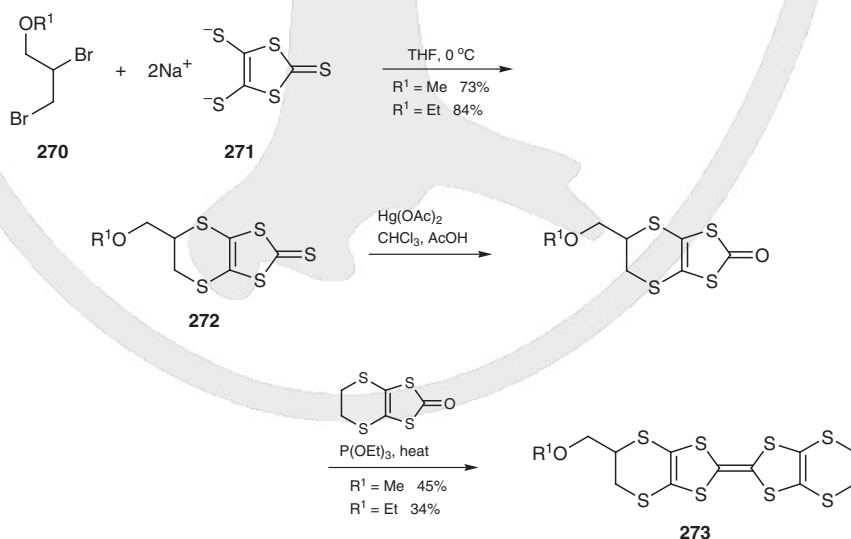
Scheme 104 Formation of Potassium 2-Thioxo-1,3-dithiole-4,5-dithiolate and a 2-Thioxo-1,3-dithiole-4,5-dithiolate–Zinc Complex^[377–379]



2-Thioxo-1,3-dithiole-4,5-dithiolate **267** can be used for the preparation of many 4,5-disubstituted thiole derivatives by reaction with alkyl halides.^[380]

2,3-Dibromo ether derivatives **270** react with sodium 2-thioxo-1,3-dithiole-4,5-dithiolate (**271**) to afford the alkylated compound **272** in moderate yields. The tetrathiafulvalene derivative **273** is prepared from this via a two-step process (Scheme 105).^[380]

Scheme 105 Alkylation of 2-Thioxo-1,3-dithiole-4,5-dithiolate^[380]

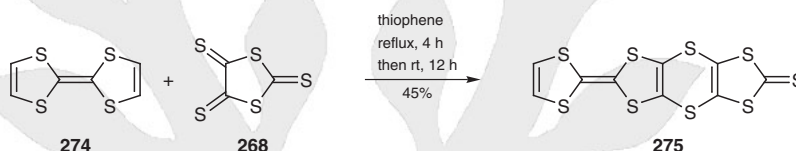


Many other reactions of 2-thioxo-1,3-dithiole-4,5-dithiolates with alkylating reagents are available. Examples of alkylating agents used are thiophosgene,^[360] bis(2-bromoethyl) ether,^[381] 1,4-dibromobutane,^[382] 4,5-*trans*-dimethyl-1,3,2-dioxathiolane 2,2-dioxide,^[383] pentaerythritol sulfate,^[384] phenacyl bromide,^[385] and 2-chloro-1,2-diphenylethan-1-one.^[386]

1,3-Dithiolane-2,4,5-trithione (**268**) acts as a diene analogue and hence undergoes [4+2] cycloaddition upon treatment with alkenes, particularly, electrophilic alkenes. This reaction is utilized for the preparation of many 1,3-dithiolane- or 1,3-dithiole-fused ring compounds which have been used as new materials for electronics. As an example, tetrathiafulvalene **274** undergoes a [4+2]-cycloaddition reaction with 1,3-dithiolane-2,4,5-trithione (**268**) on refluxing in thiophene for 4 hours and then on standing at room temperature for 12 hours, producing the cycloadduct **275** in 45% yield (Scheme 106).^[387]

Several other [4+2]-cycloaddition reactions are available with 1,3-dithiolane-2,4,5-trithione (**268**) and various dienophiles^[388–391] or a 1,3-dithiolane-2,4,5-trithione analogue and dimethylacetylene dicarboxylate.^[392]

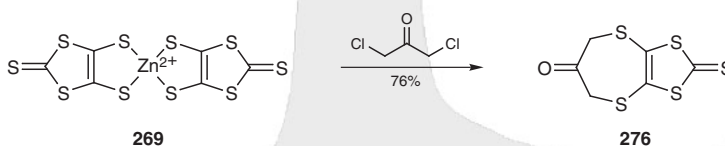
Scheme 106 An example of a [4+2]-Cycloaddition Reaction with 1,3-Dithiolane-2,4,5-trithione^[387]



A number of reactions starting from zinc “ate” complex **269**, made from carbon disulfide and zinc(II) chloride which acts as an analogue of 2-thioxo-1,3-dithiole-4,5-dithiolate **267**, typically **269** reacts with iodomethane to give 4,5-bis(methylsulfanyl)-1,3-dithiole-2-thione in 80% yield^[393] and with dichloroacetone to give **276** in 76% yield (Scheme 107).^[394] Other examples are available.^[393–405]

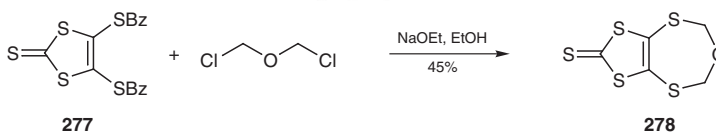
There are several other metal “ate” complexes (e.g., involving Pd, Re, Sb, Cd, Ti, W, Sn),^[406] these “ate” complexes can be used as 2-thioxo-1,3-dithiole-4,5-dithiolate analogues. The selenium derivatives are also available.^[396,407]

Scheme 107 Synthesis of a 1,3-Dithiole-2-thione Derivative from a Zinc “Ate” Complex^[394]



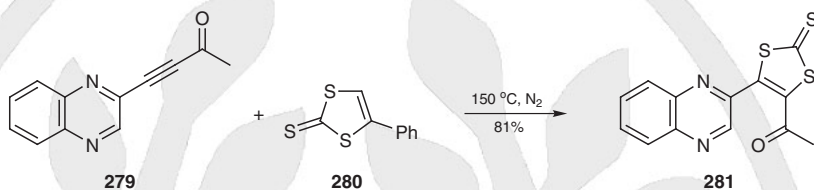
4,5-Bis(benzoylsulfanyl)-1,3-dithiole-2-thione (**277**) is also utilized as a benzoyl-protected species which liberates dithiolate anion **267** in 100% yield under alkaline conditions^[408] and reacts with alkyl halides to afford the S-substituted 1,3-dithiole derivatives. For example, when compound **277** is treated with sodium ethoxide in ethanol and then bis(chloromethyl) ether it gives 1,3,6-oxadithiepane derivative **278** in 45% yield (Scheme 108).^[409] Several other examples are available.^[410–414]

Scheme 108 Synthesis of 1,3-Dithiolo[4,5-*d*][1,3,6]oxadithiepine-2-thione^[409]



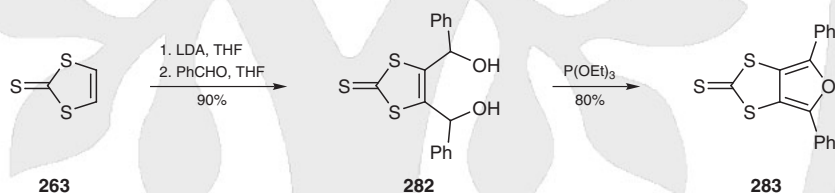
The third method is the reaction between 1,3-dithiolane or -dithiole-2-thione with acetylenes bearing strong electron-withdrawing substituents.^[415–418] This reaction seems to involve a nucleophilic attack by the thiocarbonyl sulfur on the reactant acetylene and extrusion of ethene or acetylene. A typical example is shown in Scheme 109 for the reaction of 4-phenyl-1,3-dithiolane-2-thione (**280**) with acetylene **279** giving **281**.^[419]

Scheme 109 Formation of a 1,3-Dithiole-2-thione from a 1,3-Dithiolane-2-thione and an Acetylene^[419]

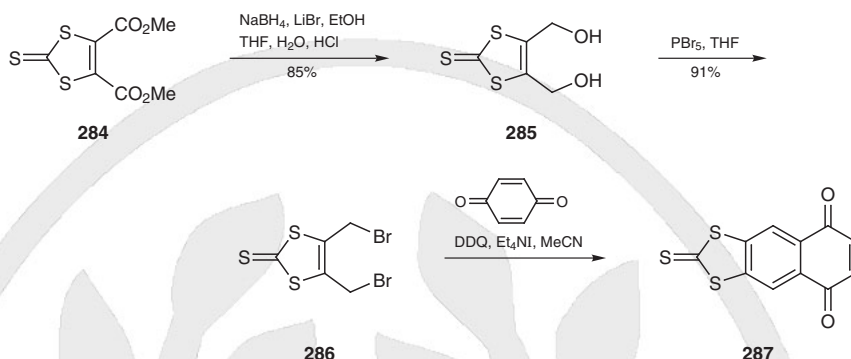


The fourth method is the initial treatment of 1,3-dithiole-2-thione (**263**) with a strong base such as butyllithium in tetrahydrofuran or lithium diisopropylamide in tetrahydrofuran and then trapping of the resulting carbanion formed at the 4- and 5-positions of 1,3-dithiole-2-thione (**263**) with appropriate electrophiles such as an aldehyde. An example is shown in Scheme 110 for the reaction of the dianion of 1,3-dithiole-2-thione (**263**) with benzaldehyde to give the bis[hydroxy(phenyl)methyl]-substituted product **282**, which is cyclized to the furan derivative **283** with triethyl phosphite.^[420,421]

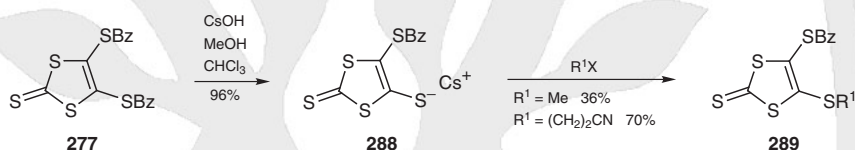
Scheme 110 An Example of the Addition of a 1,3-Dithiole-2-thione Dianion to an Aldehyde^[420,421]



Dimethyl 2-thioxo-1,3-dithiole-4,5-dicarboxylate (**284**) is reduced to the corresponding hydroxymethyl compound **285** by sodium borohydride in tetrahydrofuran/ethanol in 85% yield.^[422] The compound **285** is converted into the bromomethyl derivative **286**, which on treatment with benzo-1,4-quinone in the presence of tetraethylammonium iodide and 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone in acetonitrile gives the [4+2] adduct **287** (Scheme 111).^[423,424]

Scheme 111 Synthesis of 1,3-Dithiole-2-thione Derivatives^[422–424]

4,5-Bis(benzoylsulfanyl)-1,3-dithiole-2-thione (**277**) undergoes cleavage of one benzoyl group with cesium hydroxide in methanol/chloroform to give the monobenzoyl thiolate cesium salt **288**, which can be alkylated to give **289** (Scheme 112).^[413]

Scheme 112 Synthesis of (Alkylsulfanyl)-5-(benzoylsulfanyl)-Substituted Derivatives of 1,3-Dithiole-2-thione^[413]

4-Acetyl-5-(quinoxalin-2-yl)-1,3-dithiole-2-thione (**281**).^[419]

A soln of 4-(quinoxalin-2-yl)but-3-yn-2-one (**279**; 400 mg, 2.04 mmol) and 4-phenyl-1,3-dithiolane-2-thione (**280**; 2.0 g, 9.4 mmol) in CH_2Cl_2 was concentrated on a rotary evaporator to produce a homogeneous solid. The flask was fitted with a condenser and then heated to 150°C under N_2 for 35 min. Flash chromatography of the cooled mixture (silica gel, CH_2Cl_2) provided **281** (0.58 g, 94%) as a yellow solid. Recrystallization (acetone) gave pure ketone as yellow needles; yield: 0.5 g (81%); mp 205°C .

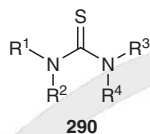
4-(Alkylsulfanyl)-5-(benzoylsulfanyl)-1,3-dithiole-2-thiones **289**; General Procedure.^[413]

To a stirred soln of 4,5-bis(benzoylsulfanyl)-1,3-dithiole-2-thione (**277**; 1 mmol) in CHCl_3 (10 mL) was added CsOH (0.17 g, 1 mmol) in MeOH (2 mL). After about 1 min, the cesium 5-(benzoylsulfanyl)-2-thioxo-1,3-dithiole-4-thiolate **288** started to separate. Et_2O (30 mL) was added to precipitate the product completely. The solid monocation salt was recovered by filtration, washed with Et_2O and air dried. Crystallization ($\text{MeOH}/\text{Et}_2\text{O}$) gave pure samples. The reaction of this salt with alkyl halides afforded 4-(alkylsulfanyl)-5-(benzoylsulfanyl)-1,3-dithiole-2-thiones **289** in moderate yields; the analogous selenium compounds could also be used.

18.10.8 Product Subclass 8: Thioureas

This product subclass of compounds, thioureas, has the structure **290** (Scheme 113) and is described in *Houben–Weyl*, Vol. E 4, p 506 and a review is also available.^[2] This section is organized according to the principal reagents used as primary sources for the synthesis of these compounds.

Scheme 113 Thioureas



$R^1, R^2, R^3, R^4 = \text{H, alkyl, aryl, benzyl, hetaryl}$

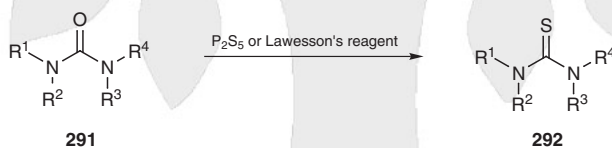
In general, thioureas **290** are stable and highly crystalline compounds except for a few tetrasubstituted compounds that are liquids. Since thiourea and its derivatives were first synthesized around 1870, a large number of studies on these species have been reported.

These species are important starting materials in the syntheses of a variety of heterocyclic compounds. In harmony with their highly polarized molecular structures and consistent lack of color, neither thioureas nor thiosemicarbazides exhibit IR or UV-vis spectroscopic properties that unambiguously class these compounds as thiocarbonyl compounds.

18.10.8.1 Synthesis of Product Subclass 8

18.10.8.1.1 Method 1:
From Urea

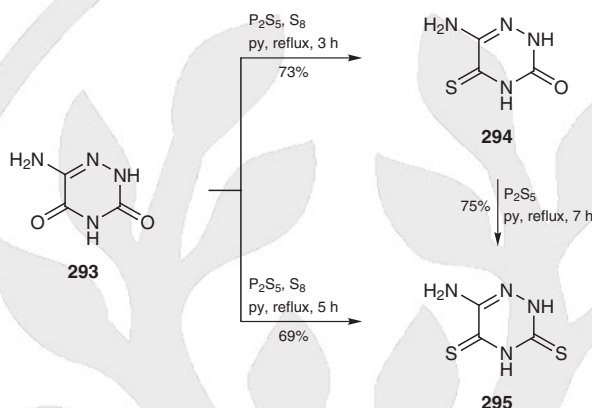
The carbonyl group of a urea **291** is converted into the corresponding thiocarbonyl function of the thiourea **292** by treatment with various phosphorus derivatives, such as phosphorus pentasulfide or Lawesson's reagent. The reaction is widely applicable for all ureas; examples shown in Scheme 114 are for the conversion of tetrasubstituted ureas **291** into the corresponding thioureas **292** using phosphorus pentasulfide.^[425]

Scheme 114 Conversion of Ureas into Thioureas^[425]

R ¹	R ²	R ³	R ⁴	Reagent	Solvent	Yield (%)	Ref
Me	Me	Me	Me	P ₂ S ₅	pyridine	78	[425]
Me	Me	Me	iPr	P ₂ S ₅	pyridine	66	[425]
Me	Me	Me	Cy	P ₂ S ₅	pyridine	56	[425]
Me	Me	Me	Bn	P ₂ S ₅	pyridine	41	[425]
Me	Me	Me	Ph	P ₂ S ₅	benzene	46	[425]
Me	Me	iPr	iPr	P ₂ S ₅	pyridine	27	[425]
Me	Me	iPr	Bn	P ₂ S ₅	pyridine	59	[425]
Me	Me	Bn	Bn	P ₂ S ₅	pyridine	52	[425]
Me	Me	Ph	Ph	P ₂ S ₅	benzene	43	[425]
Me	Ph	Me	Ph	P ₂ S ₅	benzene	39	[425]
Me	Ph	Ph	Ph	P ₂ S ₅	benzene	6	[425]

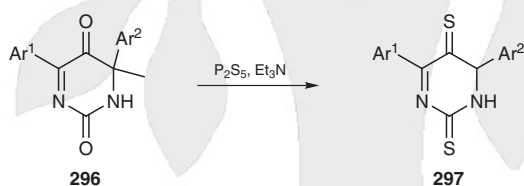
Selective thionation of 6-amino-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**293**) provides two key intermediates, 6-amino-5-thioxo-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (**294**) and 6-amino-1,2,4-triazine-3,5(2*H*,4*H*)-dithione (**295**), using phosphorus pentasulfide with pyridine containing a small amount of water (Scheme 115).^[426]

Scheme 115 Synthesis of 6-Amino-5-thioxo-4,5-dihydro-1,2,4-triazin-3(2*H*)-one and 6-Amino-1,2,4-triazine-3,5(2*H*,4*H*)-dithione Using Phosphorus Pentasulfide^[426]



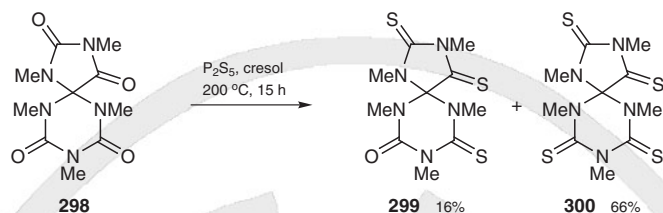
Heterocyclic thioureas, 4,6-diaryl-1,6-dihydropyrimidine-2,5-dithiones **297**, are also formed from the corresponding ureas **296** using phosphorus pentasulfide (Scheme 116).^[427]

Scheme 116 Synthesis of 4,6-Diaryl-1,6-dihydropyrimidine-2,5-dithiones Using Phosphorus Pentasulfide^[427]



Ar ¹	Ar ²	Yield (%)	Ref
Ph	Ph	46	[427]
Ph	4-ClC ₆ H ₄	50	[427]
4-ClC ₆ H ₄	Ph	60	[427]
4-ClC ₆ H ₄	4-ClC ₆ H ₄	33	[427]
Ph	4-BrC ₆ H ₄	46	[427]
4-Tol	Ph	43	[427]

The thermal reaction of the [4.5]-spirocyclic compound 1,3,6,8,10-pentamethyl-1,3,6,8,10-pentaazaspiro[4.5]decane-2,4,7,9-tetrone (**298**) with phosphorus pentasulfide leads to the complete series of mono- to tetrathiones, such as **299** and **300**. The thionation occurs at first in the five-membered ring of the spiro-system. The formation of isomers is not observed (Scheme 117).^[428]

Scheme 117 Synthesis of Spirocyclic Thioureas Using Phosphorus Pentasulfide^[428]**6-Amino-5-thioxo-4,5-dihydro-1,2,4-triazin-3(2H)-one (294):**^[426]

A mixture of 6-amino-1,2,4-triazine-3,5(2H,4H)-dione (**293**; 2.56 g, 20 mmol), flowers of sulfur (S_8) (1.28 g, 5 mmol), P_2S_5 (8.89 g, 40 mmol), H_2O (0.5 mL), and pyridine (180 mL) was refluxed for 3 h with vigorous stirring. After this period, the solvent was removed under diminished pressure (water bath, $65\text{ }^\circ\text{C}$) and the residual solid was covered with H_2O (150 mL) and boiled for 10 min on a steam bath. The suspension was allowed to cool to rt, and the solid was collected by filtration and washed with H_2O ($2 \times 50\text{ mL}$). This solid was then resuspended in distilled H_2O (150 mL) and concd NH_4OH was added dropwise with stirring until pH 10 was reached. The mixture was treated with Norit and filtered through a Celite pad. The filtrate was carefully acidified to pH 4 with 6 M HCl. A yellow precipitate formed during the acidification procedure. The mixture was allowed to stand at rt for 1 h, and then the solid was collected by filtration. The yellow solid was washed with cold, distilled H_2O ($2 \times 20\text{ mL}$) and air-dried to provide the product; yield: 2.1 g (73%); mp $242\text{--}244\text{ }^\circ\text{C}$ (slow dec).

6-Amino-1,2,4-triazine-3,5(2H,4H)-dithione (295):^[426]

P_2S_5 (8.89 g, 40 mmol) was added to a stirred, warm soln of 6-amino-5-thioxo-4,5-dihydro-1,2,4-triazin-3(2H)-one (**294**; 2.88 g, 20 mmol) in pyridine (200 mL). The mixture was refluxed for 7 h. After this period, the mixture was allowed to cool and stand at rt for 16 h. The clear, reddish-brown soln was decanted from the reaction flask and the pyridine removed under diminished pressure (water bath, $60\text{ }^\circ\text{C}$). The resulting residue was covered with distilled H_2O (200 mL), boiled for 10 min, and allowed to stand at $4\text{ }^\circ\text{C}$ for 18 h. The precipitate was collected by filtration, resuspended in distilled H_2O (140 mL), and basified to pH 10 by the dropwise addition of concd NH_4OH . The mixture was treated with Norit and filtered through a Celite pad, and the pad was washed with basic H_2O (pH 10) ($2 \times 20\text{ mL}$). The combined filtrates were carefully acidified with 6 M HCl to pH 4. Upon acidification, the product began to precipitate as an orange solid. The solid was collected by filtration, washed with cold, distilled H_2O ($3 \times 50\text{ mL}$), and air-dried to furnish the product; yield: 2.4 g (75%); mp $>300\text{ }^\circ\text{C}$.

4,6-Diphenyltetrahydropyrimidine-2,5-dithione (297, $Ar^1 = Ar^2 = Ph$):**Typical Procedure:**^[427]

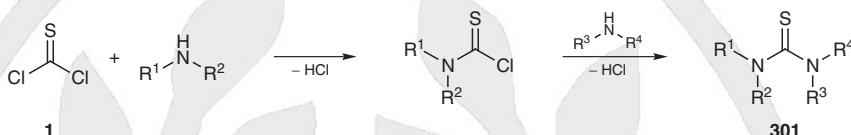
4,6-Diphenyltetrahydropyrimidine-2,5-dione (**296**, $Ar^1 = Ar^2 = Ph$; 0.25 g, 1 mmol) in MeCN (8 mL) was treated with P_4S_{10} (0.45 g, 1 mmol) and to this stirred suspension was added Et_3N (0.41 g, 4 mmol) in three portions, while cooling the mixture in ice water to moderate the exothermic reaction. The resulting soln was left at rt for 24 h and poured into cold H_2O . The product was collected by filtration, washed with H_2O , and recrystallized (EtOH); yield: 0.14 g (46%); mp $95\text{ }^\circ\text{C}$.

18.10.8.1.2

**Method 2:
From Thiophosgene or Carbon Disulfide**

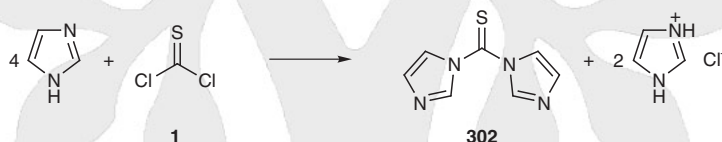
Thiourea derivatives can be produced from the reaction of thiophosgene (**1**) with ammonia, primary amines, or secondary amines. Unsymmetrical thioureas **301** are prepared by stepwise reaction with each amine (Scheme 118).

Scheme 118 General Procedure for the Synthesis of Thioureas from Thiophosgene

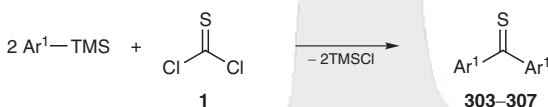


Heterocyclic thiocarbonyl transfer reagents, first prepared by Staab and co-workers,^[123,429] have found important application in the synthesis of new compounds. Among these reagents predominantly 1,1'-thiocarbonyldiimidazole (**302**) has been used synthetically, though reactions involving the use of 1,1'-thiocarbonylbis(3,5-dimethylpyrazole) have also been reported (Scheme 119).^[430] The synthesis of thiourea derivatives by using other members of this series, 1,1'-thiocarbonyldibenzimidazole (**304**), 1,1'-thiocarbonyldibenzotriazole (**305**), 1,1'-thiocarbonyldipyrazole (**306**), and 1,1'-thiocarbonyldi(1,2,4-triazole) (**307**) have also been reported (Scheme 120). In all cases, the yields in the synthesis of **303–307** are excellent (90–100%) and the purity of the crude product very high. The data of these compounds are summarized in Scheme 120.^[124]

Scheme 119 Synthesis of 1,1'-Thiocarbonyldiimidazole^[430]



Scheme 120 Synthesis of Thiocarbonyl Transfer Reagents^[124]



Compound	Ar ¹	mp (°C)	Yield (%)	Ref
303	1 <i>H</i> -imidazol-1-yl	105–106	99	[124]
304	1 <i>H</i> -benzimidazol-1-yl	137–138	100	[124]
305	1 <i>H</i> -benzotriazol-1-yl	170–171	90	[124]
306	1 <i>H</i> -pyrazol-1-yl	50–51	92	[124]
307	1 <i>H</i> -1,2,4-triazol-1-yl	99–100	93	[124]

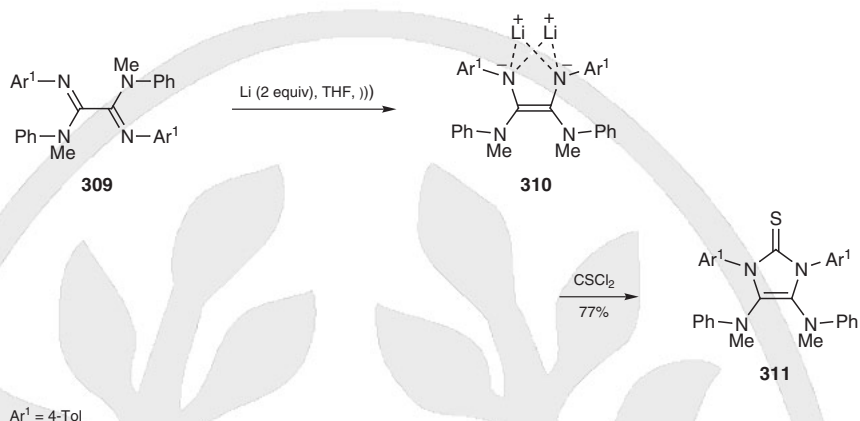
Tetraalkylthiourea derivatives **308** are prepared from the reaction of the corresponding primary or secondary amines with thiophosgene (**1**), and in one case by the reaction of 1,1,3,3-tetramethylguanidine with carbon disulfide^[431] (Table 5).^[432–436]

Table 5 Preparation of Tetraalkylthioureas Using Thiophosgene^[431–442]

$ \begin{array}{c} \text{S} \\ \parallel \\ \text{Cl}-\text{C}-\text{Cl} \\ \text{1} \end{array} + \text{R}^1\text{H}-\text{R}^2 \xrightarrow{-\text{HCl}} \text{R}^1\text{N}(\text{R}^2)\text{C}(=\text{S})\text{Cl} \xrightarrow{\text{R}^3\text{H}-\text{R}^4, -\text{HCl}} \text{R}^1\text{N}(\text{R}^2)\text{C}(=\text{S})\text{N}(\text{R}^3)\text{R}^4 \\ \text{308} $					
Entry	R ¹ R ² NH	R ³ R ⁴ NH	Product	Yield (%)	Ref
1	^a	^a		83	[431]
2	iPr ₂ NH	iPr ₂ NH		44, 57	[431, 437]
3				46	[438]
4				62	[439]
5				61	[440]
6				69	[441]
7				84	[442]

^a Reaction of 2-(*tert*-butyl)-1,1,3,3-tetramethylguanidine with carbon disulfide.

Reaction of the 1,4-diazabuta-1,3-diene substructure of hexasubstituted amidines **309** with lithium metal yields the dilithio-diamides **310**. Subsequent reaction of these with thiophosgene gives 4,5-bis[methyl(phenyl)amino]-1,3-di(4-tolyl)-1,3-dihydro-2*H*-imidazole-2-thione (**311**) (Scheme 121).^[443]

Scheme 121 Formation of 4,5-Bis[methyl(phenyl)amino]-1,3-di(4-tolyl)-1,3-dihydro-2*H*-imidazole-2-thione^[443]**1,1'-Thiocarbonyldiimidazole (302); Typical Procedure:**^[124]

CAUTION: Thiophosgene (CS₂) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

To a stirred soln of 1-(trimethylsilyl)-1*H*-imidazole (23.6 g, 0.169 mol) in CCl₄ (150 mL) (**CAUTION:** toxic), a soln of thiophosgene (9.73 g, 0.085 mol) in CCl₄ (25 mL) was added dropwise over a 90 min period. When ca. two-thirds of the thiophosgene soln had been added, yellow crystals of **302** began to precipitate. To ensure complete reaction, stirring was continued for 8 h. After cooling the mixture in an ice-water bath, the crystals were collected, giving 13.10 g of analytically pure **302**. Upon flash evaporation of the filtrate, an additional 1.95 g of slightly impure **302** was obtained; total yield 15.05 g (99%).

Compounds **304**, **305**, and **307** were all prepared according to the typical procedure. In all cases, the crude products were analytically pure. The reaction product **306** from thiophosgene and silylated pyrazole remained in solution. Flash evaporation of the solvent and TMSCl left a brown oil which crystallized after seeding with crystals obtained by chilling a few drops of the oil in liq N₂ and subsequent addition of hexane. The crystals were recrystallized (Et₂O/hexane) to give analytically pure 1,1'-thiocarbonyldipyrzazole (**306**).

1,1,3,3-Tetramethylthiourea (308, R¹ = R² = R³ = R⁴ = Me; Table 5, Entry 1):^[431]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

To 2-(*tert*-butyl)-1,1,3,3-tetramethylguanidine (0.787 g, 4.6 mmol) was added an excess of CS₂ (2 mL) and the soln was left for 0.5 h. The mixture was concentrated under reduced pressure to remove excess of CS₂ and was then concentrated to dryness on a high vacuum pump. The crystalline residue was recrystallized (hexane) to give crystals; yield: 0.50 g (83%); mp 71–79 °C.

1,1,3,3-Tetraisopropylthiourea (308, R¹ = R² = R³ = R⁴ = *i*Pr; Table 5, Entry 2):^[431]

CAUTION: Thiophosgene (CS₂) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

To dried distilled *i*Pr₂NH (100 mL, 0.71 mol), cooled to –50 °C, was slowly added thiophosgene (10 mL, 0.1 mol). The mixture was warmed to 0 °C and after 15 min a further quantity of *i*Pr₂NH (50 mL, 0.35 mol) was added and the mixture was refluxed for 8 h. After

cooling the excess $i\text{PrNH}$ was evaporated off and the residue was partitioned between Et_2O and 1 M aq HCl. The organic phase was washed with H_2O , sat. aq NaHCO_3 , H_2O , and brine. The soln was dried, filtered, and concentrated to give a dark red liquid that was purified by low-pressure column chromatography to give a pale yellow liquid; yield: 14.13 g (44%); bp 100°C .

Imidazo[2,1-b][1,3,5]benzothiadiazepine-5(6H)-thione (Table 5, Entry 5):^[440]

CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

To a stirred soln of 2-(2-aminophenylsulfanyl)-1H-imidazole (1.9 g, 0.01 mol) and Et_3N (2.02 g, 0.02 mol) in CH_2Cl_2 (150 mL) was added dropwise a soln of thiophosgene (1.15 g, 0.01 mol) in CH_2Cl_2 (50 mL) over a period of 30 min at -5°C . Stirring continued at rt overnight. The white precipitate which was formed was collected by filtration, washed with CH_2Cl_2 and H_2O , and dried under vacuum to give the product; yield: 1.42 g (61%). Recrystallization (THF) gave analytically pure material; mp $152\text{--}154^\circ\text{C}$.

4,5-Bis[methyl(phenyl)amino]-1,3-di(4-tolyl)-1,3-dihydro-2H-imidazole-2-thione (311):^[443]

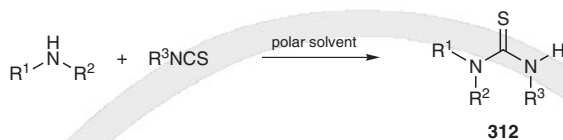
CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

In a 250-mL Schlenk vessel, $\text{N}^1, \text{N}^{1'}$ -dimethyl- $\text{N}^1, \text{N}^{2'}$ -diphenyl- $\text{N}^{1'}, \text{N}^{2'}$ -di(4-tolyl)ethanedimidamide (**309**; 0.5 g, 1.1 mmol) was dissolved in THF (ca. 30 mL) under argon and Li (0.3 g, 4.3 mmol) was added. The reaction was initiated by means of an ultrasonic bath. After 3 h, a clear red soln was obtained, from which excess Li was removed by filtration. To a soln of dianion **310** (1.1 mmol), thiophosgene (1.1 mmol) was added with stirring at -78°C . After completion of the addition, the mixture was allowed to warm to rt and stirring was continued until the soln was almost colorless. The solvent was then removed in vacuo, the residue was taken up in toluene, and the lithium salt was removed by filtration. The product **311** was purified by column chromatography (silica gel, toluene) or by recrystallization (heptane) to give colorless crystals; yield: 0.42 g (77%); mp 112°C .

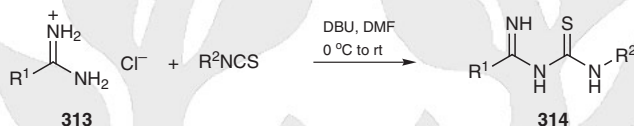
18.10.8.1.3

**Method 3:
From Isothiocyanates**

Isothiocyanates are the most powerful starting materials for preparing thioureas and their derivatives. In general, alkyl and aryl isothiocyanates react with ammonia and primary and secondary amines to give 1-, 1,3-, or trisubstituted thioureas **312**, respectively (Scheme 122). These reactions generally takes place in good yield and work better in polar solvents such as diethyl ether, ethanol, water, or acetone. One of the main advantages of this method is its versatility. A wide range of substituents can be attached to both the amine and in the isothiocyanate components.^[444]

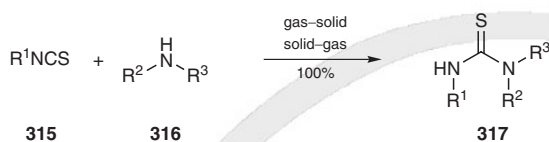
Scheme 122 General Procedure for the Synthesis of Thiourea from Isothiocyanates

The reaction of amidiniums **313** in dry dimethylformamide with an isothiocyanate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene or *N,N*-diisopropylethylamine affords the corresponding (iminomethyl)thiourea derivatives **314** in good yields (Scheme 123).^[445]

Scheme 123 Synthesis of (Iminomethyl)thiourea Derivatives^[445]

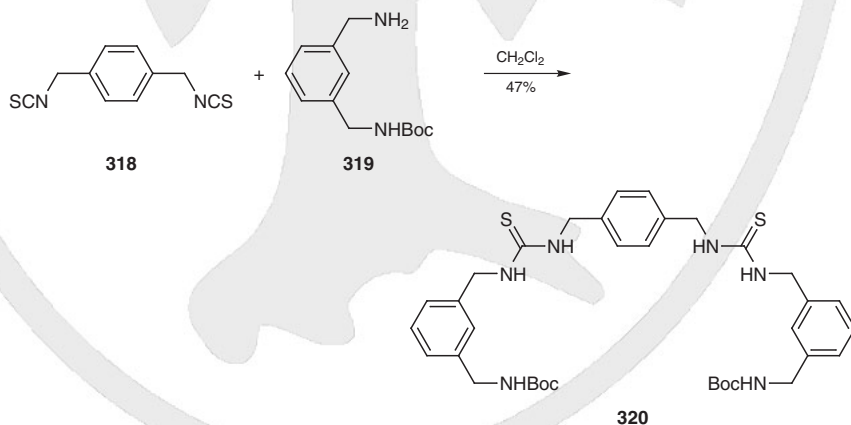
R ¹	R ²	Yield (%)	Ref
Ph	Ph	91	[445]
2-thienyl	Ph	61	[445]
3-NCC ₆ H ₄ CH ₂ S	2-ClC ₆ H ₄	70	[445]
3-NCC ₆ H ₄ CH ₂ S	Ph	86	[445]
4-ClC ₆ H ₄ CH ₂ S	Ph	84	[445]

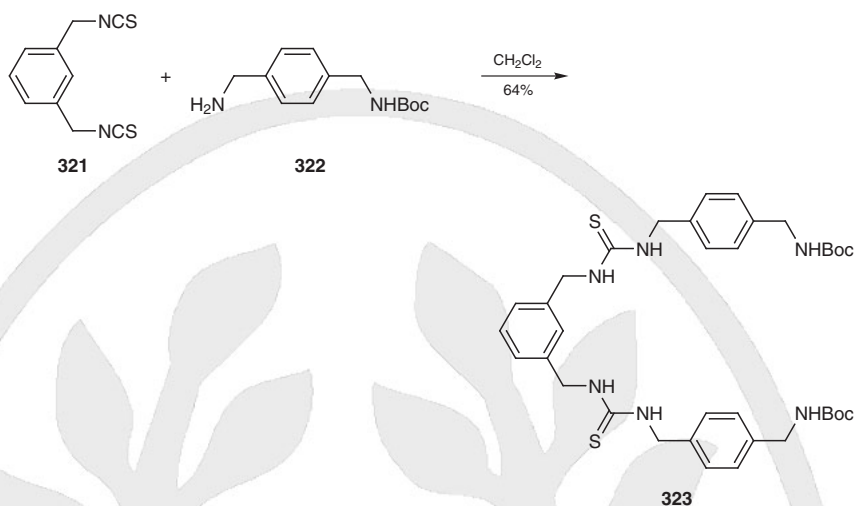
Thioureas **317** are prepared in quantitative yield from the reaction of solid isothiocyanates **315** with gaseous amines or solid anilines **316** without solvent at a suitable temperature. The solid-state techniques add to the value of this important path to thioureas without waste formation. Liquid phases are not involved in these gas–solid reactions. However, the solid–solid reactions of methyl isothiocyanate with solid anilines are so efficient that 100% yields of the crystalline arylthioureas are also obtained by grinding in a mortar, when intermediate melting occurs. Generally, solid-state transformations require low temperatures, but in this case they can be avoided (Scheme 124).^[446]

Scheme 124 Quantitative Gas–Solid and Solid–Solid Synthesis of Thioureas from Isothiocyanates and Amines^[446]

R ¹	R ²	R ³	mp (°C) of 315	Reaction Conditions	mp (°C) of 317	Ref
Ph	H	H	–21	–30 °C, 300 Torr	154	[446]
4-BrC ₆ H ₄	Me	H	60–61	rt, 750 Torr	60	[446]
4-BrC ₆ H ₄	Me	Me	60–61	rt, 750 Torr	163	[446]
1-naphthyl	Me	H	56	rt, 750 Torr	197	[446]
1-naphthyl	Me	Me	56	rt, 750 Torr	161	[446]
4-O ₂ NC ₆ H ₄	Me	H	112–113	rt, 750 Torr	216	[446]
4-O ₂ NC ₆ H ₄	Me	Me	112–113	rt, 750 Torr	182	[446]
Me	H	H	30	0 °C, 375 Torr	121	[446]
Me	Me	H	30	0 °C, 375 Torr	62	[446]
Me	Me	Me	30	0 °C, 375 Torr	88	[446]
Me	4-MeOC ₆ H ₄	H	30	rt	170	[446]
Me	4-BrC ₆ H ₄	H	30	rt	150	[446]
Me	4-ClC ₆ H ₄	H	30	rt	–	[446]

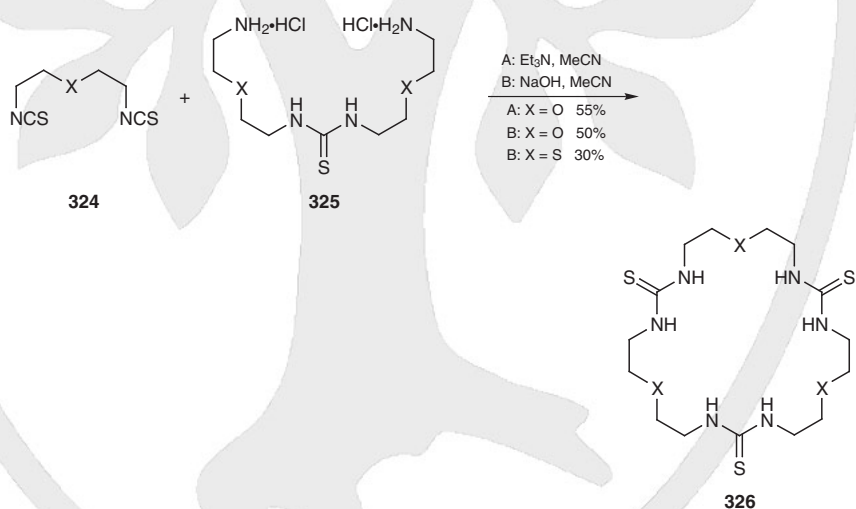
The dithiourea derivatives **320** and **323** are obtained by reaction of 1,4- (**318**) or 1,3-bis(isothiocyanatomethyl)benzene (**321**) with the corresponding mono-*tert*-butoxycarbonyl-protected diamine **319** or **322**, respectively (Scheme 125).^[447]

Scheme 125 Synthesis of Bis-thiourea Derivatives^[447]

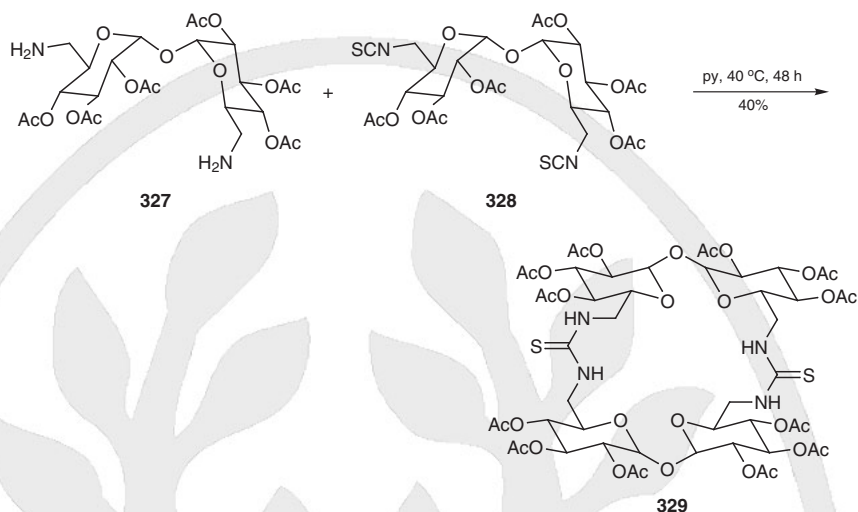


Macrocyclic neutral ionophores containing a thiourea subunit are prepared from the reaction of a thiourea unit bearing two terminal amines with a diisothiocyanate in the final macrocyclization step. Macrocyclization is performed by dissolving the dihydrochloride salt of **325** with triethylamine or sodium hydroxide and addition of the diisothiocyanate **324** in acetonitrile at room temperature. The target compound **326** is obtained in 30–55% yield (Scheme 126).^[448]

Scheme 126 Synthesis of Macrocyclic Ionophores^[448]



Replacement of the classical *O*-glycosidic intersaccharide linkages in cycloglucans with achiral thiourea functional groups permits a convergent retrosynthetic analysis of cyclo-trehaloses, involving the coupling reaction of C2-symmetric diamine and diisothiocyanate precursors. Dimer **329** is prepared from reaction of hexa-*O*-acetylated derivatives **327** and **328** (Scheme 127). A linear pseudotetrasaccharide and a cyclic pseudohexa-saccharide have also been prepared by this route.^[449]

Scheme 127 Synthesis of a Pseudotetrasaccharide^[449]**Thioureas 317 by Solid-State Reactions of Isothiocyanates with Amines;****General Procedure:**^[446]

Crystalline isothiocyanates **315** (2.0 mmol, 250-mL flask; overnight) were, depending on their mps and eutectics, reacted with the basic gases or with the solid anilines **316** (2.0 mmol) in a mortar (occasional grinding and standing for 1 d). Excess gases were recovered by condensation at -196°C . The yields were 100% in all cases.

1,3-Bis[3-(4-[[*tert*-butoxycarbonylamino)methyl]phenyl)methyl]thioureidomethyl]benzene (323):^[447]

A soln of 1,3-bis(isothiocyanoatomethyl)benzene (**321**; 125 mg, 0.6 mmol) in CH_2Cl_2 (5 mL) was added to a soln of the mono-Boc-protected diamine **322** (280 mg, 1.2 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 h, concentrated and purified by column chromatography (EtOAc/petroleum ether 1:1 then MeOH), to give an amorphous solid; yield: 250 mg (64%).

1,9,17-Trioxa-4,6,12,14,20,22-hexaazacyclotetracosane-5,13,21-trithione (326, X = O):^[448]

Method A: 1,3-Bis[2-(2-aminoethoxy)ethyl]thiourea dihydrochloride (**325**, 107 mg, 0.62 mmol) was added to a stirred soln of Et_3N (1.9 g, 2.6 mL, 18.6 mmol) in MeCN (250 mL). The resulting suspension was sonicated for 30 min until it completely dissolved, and bis(2-isothiocyanoethoxy) ether (**324**, 1 equiv) was then added by syringe. The mixture was stirred for 16 h and the solvent and Et_3N were then removed in vacuo to afford a white solid. The solid was dried under high vacuum for several hours. Flash chromatography (MeOH/EtOAc 1:4) afforded the desired product as a white solid; yield: 220 mg (55%).

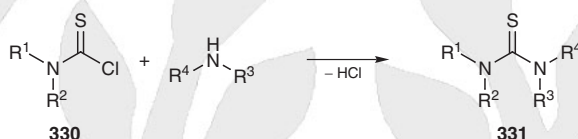
Method B: 1,3-Bis[2-(2-aminoethoxy)ethyl]thiourea dihydrochloride (**325**; 107 mg, 0.62 mmol) was added to a stirred soln of NaOH (74 mg, 1.86 mmol) in MeCN (250 mL). The resulting suspension was sonicated for 30 min, and H_2O (5.0 mL) was added to dissolve all reagents. Bis(2-isothiocyanoethoxy) ether (**324**; 300 mg, 0.93 mmol) was added to this soln by syringe. The mixture was stirred vigorously for 16 h and the solvent was removed in vacuo to yield a white solid. Flash chromatography (MeOH/EtOAc 1:4) gave the desired product as a white solid; yield: 210 mg (50%); mp $231\text{--}232^{\circ}\text{C}$.

18.10.8.1.4

**Method 4:
From Thiocarbamoyl Chloride**

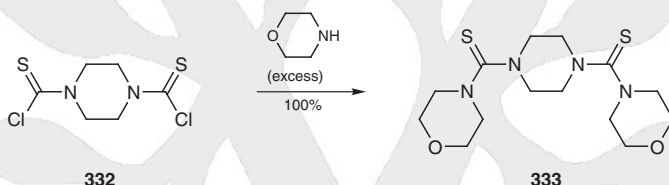
Thiocarbamoyl chlorides (chlorothioformamides) **330** are good precursors of thiourea derivatives such as **331**. These species are readily converted into symmetrical and unsymmetrical thioureas by the treatment with ammonia and primary or secondary amines (Scheme 128).

Scheme 128 General Procedure for the Synthesis of Thioureas from Thiocarbamoyl Chlorides



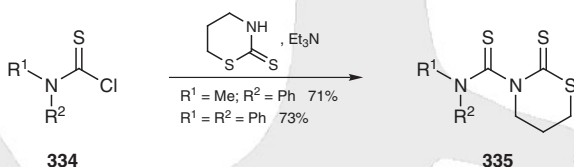
Compound **332** containing two thiocarbamoyl chloride subunits reacts with morpholine to give the corresponding bithiourea derivatives **333** in quantitative yield (Scheme 129).^[450]

Scheme 129 Synthesis of Bithioureas from Thiocarbamoyl Chlorides^[450]

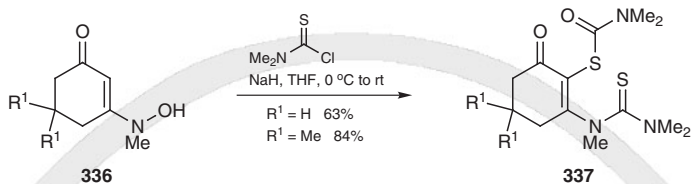


N,N-Disubstituted thiocarbamoyl chlorides **334** are treated with tetrahydro-2H-1,3-thiazine-2-thione in the presence of triethylamine to give the 2-thioxotetrahydro-2H-1,3-thiazine-3-carbothioamide **335** (Scheme 130).^[451]

Scheme 130 Synthesis of a Thiocarbamoyl-Substituted Tetrahydro-2H-1,3-thiazine-2-thione^[451]



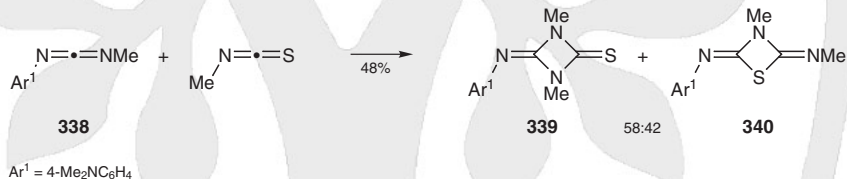
Dimethylthiocarbamoyl chloride reacts smoothly with enehydroxylamines **336** in the presence of base, and affords products **337** in good to excellent yields via a [3,3]-sigmatropic rearrangement to α -substituted products (Scheme 131).^[452]

Scheme 131 Synthesis of a Thiourea via a [3,3]-Sigmatropic Rearrangement^[452]**1,4-Bis[(morpholino)thiocarbonyl]piperazine (333):**^[450]

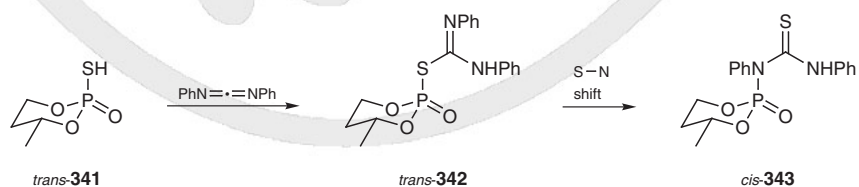
To excess morpholine was added to a soln of **332** in small portions with stirring. When the addition was complete, the mixture was clarified by gentle heating, filtered warm, and poured into H_2O . The crude product **333** precipitated in quantitative yield. It could be recrystallized (MeCN); mp 209–210 $^\circ\text{C}$.

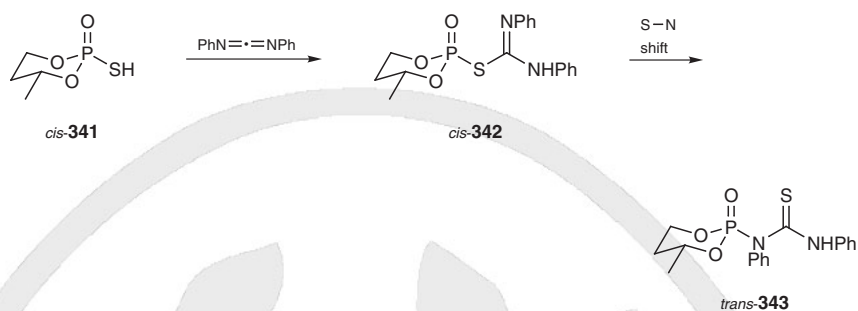
18.10.8.1.5**Method 5:
From Carbodiimides**

The reaction of *N*-[4-(dimethylamino)phenyl]-*N'*-methylcarbodiimide (**338**) with methyl isothiocyanate at room temperature afford a mixture of the two isomeric [2+2] cycloadducts **339** and **340** with a four-membered ring in 58:42 ratio, both of which have been isolated in pure form and analyzed by X-ray crystallography (Scheme 132). When an aryl isothiocyanate is used instead of the alkyl isothiocyanate, the corresponding 1,3-thiazetidine derivatives are obtained.^[453]

Scheme 132 Reaction of a Carbodiimide with Methyl Isothiocyanate^[453]

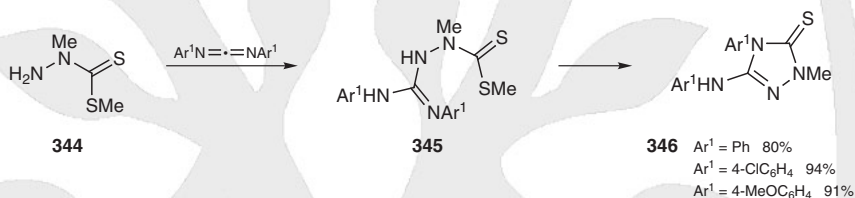
The reaction of carbodiimides with thiophosphoric **341**, dithiophosphoric, and selenophosphoric acids affords, in the first step, 2-phosphorylthio- or -selenoureas that undergo facile rearrangement to the stable and isolatable *N*-phosphorylthio- or -selenoureas. The stereochemistry of the rearrangement of 2-phosphorylthioureas **342** into *N*-phosphorylthioureas **343** has been investigated using two chiral thiophosphoric acids (Scheme 133). The stereochemistry of the rearrangement has been explained in terms of a mechanism involving pseudorotation of the pentavalent phosphorus intermediate.^[454]

Scheme 133 Synthesis of *N*-Phosphorylthioureas^[454]



Heterocyclic thiourea derivatives **346** are synthesized from the reaction of methyl 2-methyldithiocarbazate (**344**) with diarylcarbodiimides and are isolated as a crystalline solids in moderate yields (Scheme 134). The conversion from **344** to **346** involves the initial formation of the aminoguanidine derivative **345** which undergoes ring closure to give **346**. In only one case, the aminoguanidine **345** ($\text{Ar}^1 = 4\text{-ClC}_6\text{H}_4$) was isolated as a crystalline product in 76% yield.^[455]

Scheme 134 Synthesis of 2,4-Dihydro-3H-1,2,4-triazole-3-thione Derivatives^[455]



4-[4-(Dimethylamino)phenylimino]-1,3-dimethyl-1,3-diazetidine-2-thione (**339**).^[453]

A mixture of *N*-[4-(dimethylamino)phenyl]-*N'*-methylcarbodiimide (**338**; 10.86 g, 62 mmol) and methyl isothiocyanate (4.53 g, 62 mmol) was kept for 13 d at rt, while progress of the reaction was monitored by IR. The mixture, consisting of **339** and **340**, was triturated. Recrystallization of this mixture from isooctane (2.5 g in 300 mL of solvent) gave pure product **339** as yellow needles; mp 124–125 °C. The isomeric 2-[4-(dimethylamino)phenylimino]-3-methyl-4-(methylimino)-1,3-thiazetidine (**340**) was isolated on concentration of the isooctane filtrate and recrystallizing the residue (MeCN); yellow crystals; mp 131–132 °C.

4-Aryl-5-(arylamino)-2-methyl-2,4-dihydro-3H-1,2,4-triazole-3-thiones **346**;

General Procedure:^[455]

To a soln of the appropriate diarylcarbodiimide (10 mmol) in dry benzene (40 mL) (**CAUTION: carcinogen**), methyl 2-methyldithiocarbazate (**344**; 1.36 g, 10 mmol) was added and the mixture was stirred at reflux temperature under N_2 for 18 h. After cooling, the separated solid was collected by filtration, washed with hexane (2×15 mL), and recrystallized (CHCl_3) to give **346** as colorless prisms.

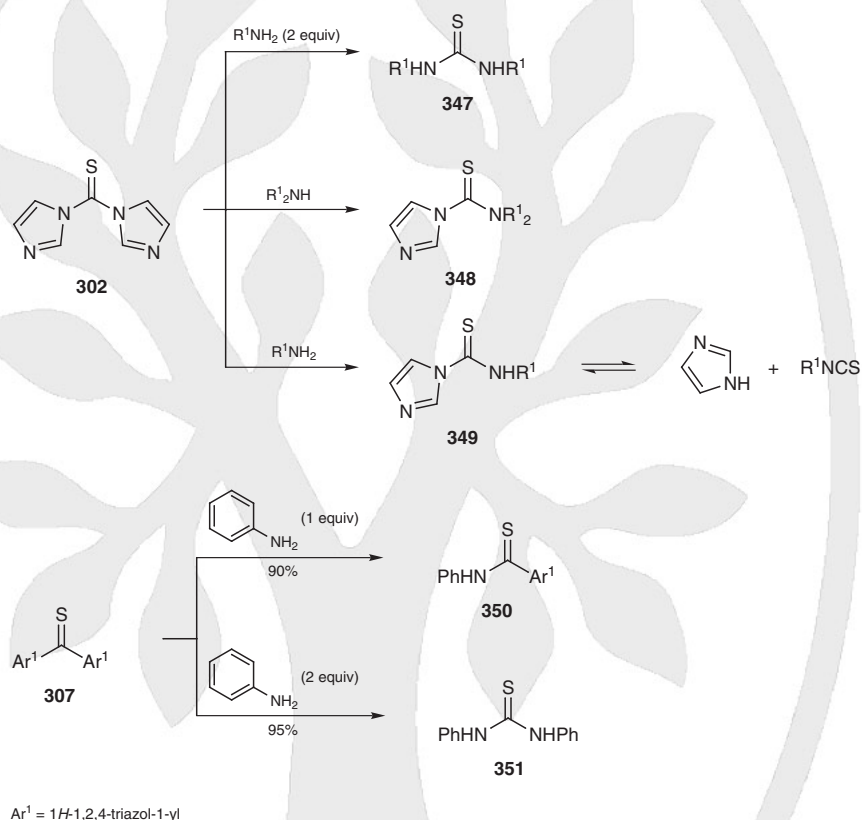
18.10.8.1.6

Method 6: From Thiocarbonyl Transfer Reagents

Reactions of primary or secondary amines with thiophosgene or isothiocyanates are used widely as a synthetic method for the synthesis of thiourea derivatives. However, these methods are hazardous due to the toxic properties of both thiophosgene and isothiocyanates. Despite their toxicity, these reagents continue to be widely used due to the importance of symmetrical and unsymmetrical thioureas. On the other hand, preparative methods involving the use of thiocarbonyl transfer reagents are more efficient and safer.

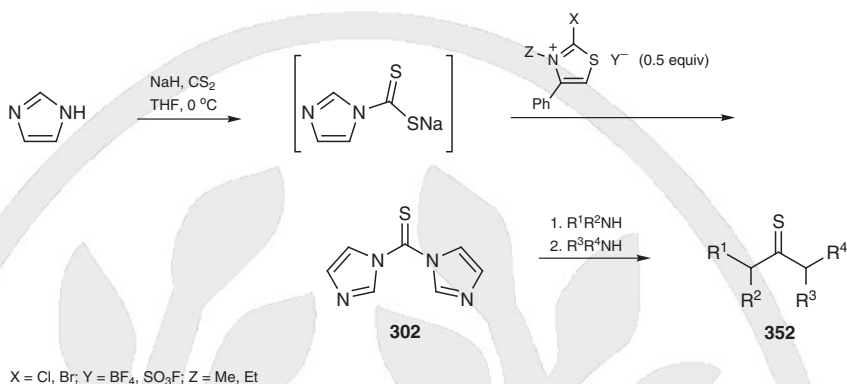
Thiocarbonyl transfer reagents have found several important applications in the synthesis of new compounds. 1,1'-Thiocarbonyldiimidazole (**302**) (see Section 18.10.8.1.2) generally reacts with 2 molar equivalents of an aliphatic or aromatic primary amine, forming 1,3-disubstituted thioureas **347**. The corresponding reaction with 1 molar equivalent of primary amine results in the formation of an isothiocyanate, due to dissociation of the unstable *N*-alkylimidazole-1-carbothioamide **349**. With a 1 equivalent of a secondary amine, the *N,N*-disubstituted imidazole-1-carbothioamide **348** is formed (Scheme 135).^[124,456–461]

Scheme 135 Reaction of 1,1'-Thiocarbonyldiimidazole with Amines^[124,456–461]

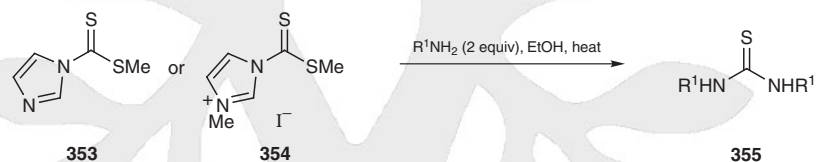


Furthermore, 1,1'-thiocarbonyldi(1,2,4-triazole) (**307**) reacts instantaneously with 1 molar equivalent of amine to produce the *N*-alkyl-1,2,4-triazole-1-carbothioamide (e.g., **350**). The reaction has been carried out with both aliphatic and aromatic amines. If more than 1 equivalent of amine is added to the solution, 1,3-disubstituted thioureas (e.g., **351**) are formed (Scheme 135). This is advantageous as it is possible to produce unsymmetrically substituted thioureas directly.^[124]

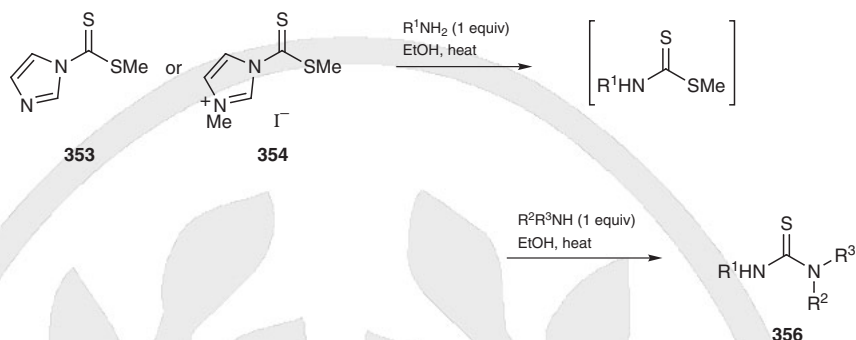
A particularly useful preparation of thiourea derivatives **352** takes advantage of the in situ formation of 1,1'-thiocarbonyldiimidazole (**302**) from 1*H*-imidazole, carbon disulfide, and a 2-halothiazolium salt, thus avoiding the use of thiophosgene. The utility of this in situ generated 1,1'-thiocarbonyldiimidazole (**302**) is demonstrated in the preparation of unsymmetrical thioureas **352** by stepwise addition of two different amines (Scheme 136).^[462]

Scheme 136 Preparation of an Unsymmetrical Thiourea Using 1,1'-Thiocarbonyldiimidazole^[462]

Methyl 1*H*-imidazole-1-carbodithioate (**353**) and its *N*-methyl salt **354** are new useful thiocarbonyl transfer reagents for synthesis of substituted thioureas **355** (Scheme 137). These reagents can be used for the synthesis of symmetrical and unsymmetrical mono-, di-, and trisubstituted thioureas **356** in high yields under mild and simple nonhazardous reaction conditions (Scheme 138).^[463]

Scheme 137 Synthesis of Symmetrical Disubstituted Thioureas^[463]

R ¹	Yield (%)		Ref
	From 353	From 354	
<i>t</i> -Bu	40	60	[463]
CH ₂ CH=CH ₂	75	90	[463]
(CH ₂) ₁₅ Me	78	86	[463]
Bn	79	92	[463]
(CH ₂) ₂ Ph	80	91	[463]
Cy	82	94	[463]
Ph	86	96	[463]
4-MeOC ₆ H ₄ (CH ₂) ₂	75	89	[463]
2-pyridyl	70	80	[463]
cyclopropyl	79	91	[463]

Scheme 138 Unsymmetrical Di- and Trisubstituted Thioureas^[463]

R ¹	R ²	R ³	Yield (%)		Ref
			From 353	From 354	
Ph	Bn	H	75	92	[463]
Ph	(CH ₂) ₂ Ph	H	73	93	[463]
Ph	4-MeOC ₆ H ₄	H	74	86	[463]
Ph	2-pyridyl	H	89	91	[463]
Ph	Me	H	65	94	[463]
Ph	Cy	H	65	82	[463]
Bn	Cy	H	61	96	[463]
Ph	Me	Me	79	94	[463]
Bn	(CH ₂) ₅		87	96	[463]
Ph	(CH ₂) ₂ O(CH ₂) ₂		88	90	[463]
Ph	H	H	66	94	[463]
Bn	H	H	66	84	[463]
H	Ph	Me	72	78	[463]
H	(CH ₂) ₅		76	87	[463]

N-Phenyl-1H-1,2,4-triazole-1-carbothioamide (352):^[124]

To a soln of 1,1'-thiocarbonyldi(1,2,4-triazole) (**307**; 225 mg, 1.25 mmol) in acetone (25 mL) was added aniline (116 mg, 1.25 mmol). The orange color of the soln disappeared immediately. Addition of H₂O and subsequent cooling afforded a slightly yellow precipitate which was collected by filtration to give crystals; yield: 230 mg (90%); mp 80–81 °C. Recrystallization [benzene (**CAUTION: carcinogen**)/hexane] did not increase the melting point.

1,3-Diphenylthiourea (351):^[124]

To a soln of 1,1'-thiocarbonyldi(1,2,4-triazole) (**307**; 450 mg, 2.5 mmol) in CH₂Cl₂ (10 mL) was added aniline (465 mg, 5 mmol). The orange color of the soln disappeared, and at the same time a precipitate formed. Filtration and concentration of the solvent and recrystallization (EtOH/H₂O) gave the product; yield: 540 mg (95%); mp 154–155 °C.

1-Benzyl-1-methylthiourea (352, R¹ = Bn; R² = Me; R³ = R⁴ = H); Typical Procedure:^[462]**N-Benzyl-N-methyl-1H-imidazole-1-carbothioamide:**

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

NaH (110 mg) was washed with hexane and then suspended in THF (5 mL), and the mixture was cooled to 0 °C. To this was added 1H-imidazole (156 mg, 2.29 mmol) and CS₂ (0.2 mL) followed by stirring for 25 min at 0 °C. Then, 2-halothiazolium salt (1.15 mmol) was added and the orange mixture was stirred at rt for 1 h. N-Benzylmethylamine (0.30 mL) was added and the mixture was stirred for 1 h. The solvent was removed in vacuo, and separation of the residue by column chromatography (EtOAc) gave the product as an oil; yield: 170 mg (64%). This oil was used for subsequent reaction without further purification.

1-Benzyl-1-methylthiourea (352, R¹ = Bn; R² = Me; R³ = R⁴ = H):

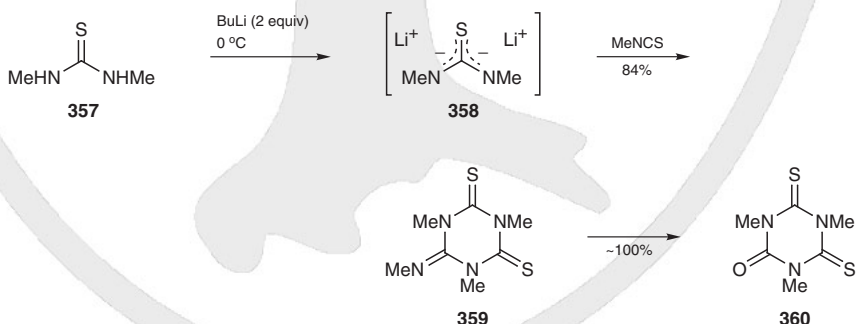
A mixture of N-benzyl-N-methyl-1H-imidazole-1-carbothioamide (120 mg, 0.52 mmol) in 11% NH₃ in EtOH (5 mL) was stirred overnight at rt. The solvent was removed in vacuo and the residue chromatographed (EtOAc) to give O-methyl benzyl(methyl)thiocarbamate as an oil; yield: 31 mg (31%) and **352** (R¹ = Bn; R² = Me; R³ = R⁴ = H); yield: 54 mg (58%); mp 144–145 °C.

18.10.8.1.7

**Methods 7:
Miscellaneous Methods**

The reaction of methyl isothiocyanate with dianion **358**, which is derived from the reaction of 1,3-dimethylthiourea (**357**) with butyllithium, is carried out at room temperature for 24 hours under argon and gives 1,3,5-trimethyl-6-(methylimino)-5,6-dihydro-1,3,5-triazine-2,4-(1H,3H)-dithione (**359**) as the crude product in 84% yield. When crude **359** is chromatographed by preparative thin-layer chromatography, it is converted into 1,3,5-trimethyl-4,6-dithioxo-3,4,5,6-tetrahydro-1,3,5-triazin-2(1H)-one (**360**) in quantitative yield (Scheme 139).^[464]

Scheme 139 Synthesis of 1,3,5-Trimethyl-4,6-dithioxo-3,4,5,6-tetrahydro-1,3,5-triazin-2(1H)-one^[464]



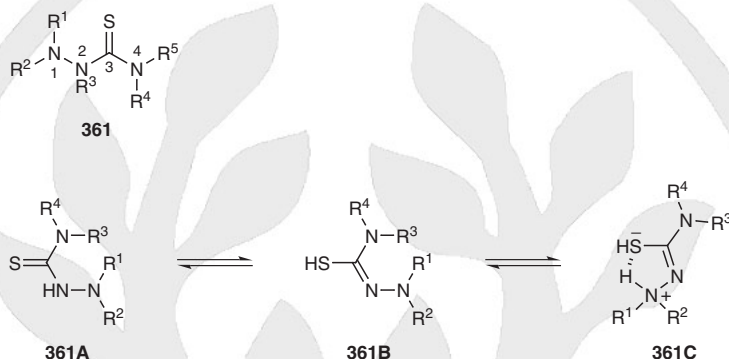
18.10.9

**Product Subclass 9:
Thiosemicarbazides**

This product subclass, thiosemicarbazides, is discussed in *Houben–Weyl*, Vol. E 4, p 506. In general, thiosemicarbazides, represented by the common structure **361**, are stable and highly crystalline compounds except for a few tetra- and pentasubstituted compounds

that are liquids. In naming the thiosemicarbazides, substituents are numbered as shown in Scheme 140. 2-Unsubstituted thiosemicarbazides may exist in the three tautomeric equilibrium states with the thioacyl form **361A**, imide–thiol form **361B**, and betaine form **361C**, the site of the tautomeric equilibrium is determined by steric and electronic substituent effects.

Scheme 140 Thiosemicarbazides and Their Three Tautomeric Forms



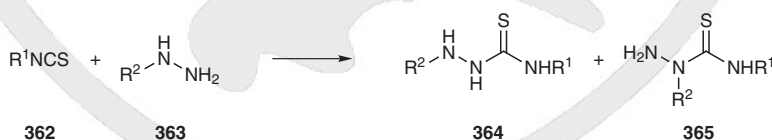
These species are important starting materials in the syntheses of a variety of heterocyclic compounds. In harmony with their highly polarized molecular structures and consistent lack of color, neither thioureas nor thiosemicarbazides exhibit IR or UV-vis spectral properties that unambiguously class these compounds as thiocarbonyl compounds.

18.10.9.1 Synthesis of Product Subclass 9

18.10.9.1.1 Method 1: Using Isothiocyanates and Hydrazine Derivatives

Thiosemicarbazides **361** are prepared in a general manner from isothiocyanates and hydrazines. Thus, alkyl and aryl isothiocyanates **362** react exothermically with mono-, di-, or trisubstituted hydrazines, as well as with hydrazine itself, to give thiosemicarbazides in good yields. When unsymmetrical mono- **363** and disubstituted hydrazines are employed, both of the two possible regioisomers, e.g. **364** and **365**, are obtained, although the thiosemicarbazides resulting from the attack of the less-substituted nitrogen, **364**, predominate in the case of monosubstituted hydrazines (Scheme 141).

Scheme 141 General Procedure of Thiosemicarbazides from Isothiocyanates and Monosubstituted Hydrazines



Functionalized hydrazines are also suitable precursors of thiourea derivatives. In these cases, the free amino group preferentially attacks the isothiocyanate, in ethanol, to give thiosemicarbazides regioselectively in good yields.^[1]

The reaction of semicarbazide hydrochloride **366** with an aryl or alkyl isothiocyanate in the presence of anhydrous sodium acetate in dry acetonitrile affords the corresponding thiourea **367** in good yields (62–78%) (Scheme 142).^[465]

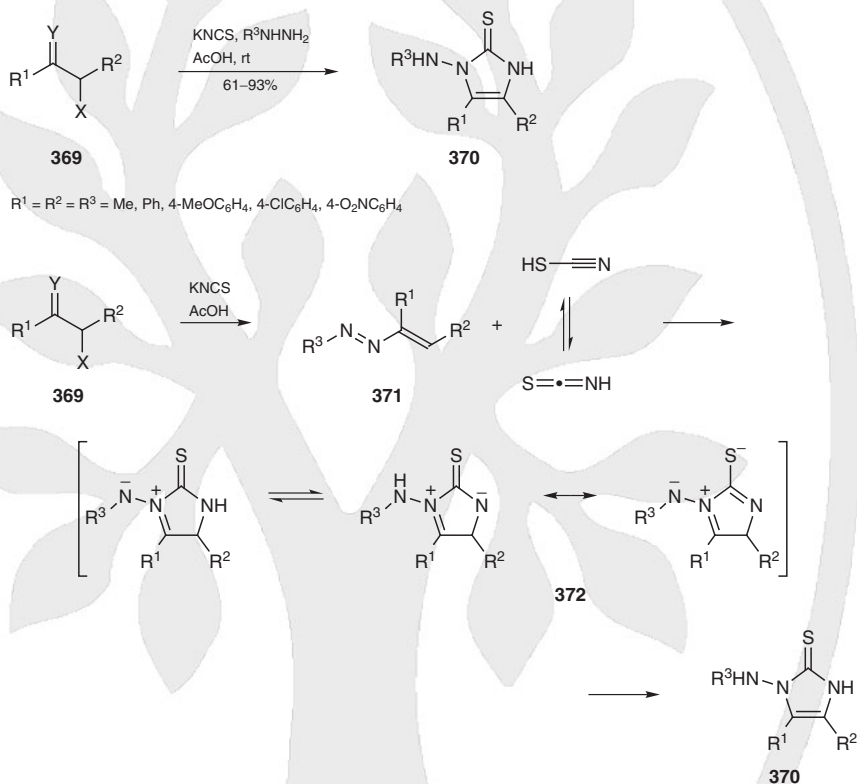
18.10.9.1.1.1

Variation 1:

[3+2]-Cycloaddition Reactions

1-Amino-1,3-dihydro-2*H*-imidazole-2-thiones **370** are obtained in an efficient one-pot procedure by reaction of α -halo ketones **369** with potassium isothiocyanate and mono-substituted hydrazines. This reaction is considered to proceed via the formation of azoalkenes **371** and thiocyanic acid. These intermediates, in turn, undergo a [3+2]-cycloaddition reaction; the resultant azomethine imine cycloadducts **372** are transformed into the final products **370** (Scheme 144).^[477,478]

Scheme 144 Synthesis of 1-Amino-1,3-dihydro-2*H*-imidazole-2-thiones^[477,478]



1-Anilino-1,3-dihydro-2*H*-imidazole-2-thione (370, $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{H}$); Typical Procedure.^[477]

To a stirred soln of **369** ($\text{Y} = \text{O}$; $\text{X} = \text{Cl, Br}$) (1.0 g, 2.95 mmol) in dry DMF (20 mL) under N_2 was added finely ground KNCS (1.0 g, 10.3 mmol). Stirring was continued at 90°C for 2 h, and after cooling to rt H_2O (150 mL) was added. The mixture was extracted with Et_2O ($4 \times 50\text{ mL}$) and the combined Et_2O extracts were washed with H_2O ($2 \times 30\text{ mL}$), dried (MgSO_4) and concentrated. The residue upon recrystallization ($\text{EtOH}/\text{H}_2\text{O}$) furnished slightly yellow crystals; yield: 0.37 g (66%).

1-Substituted-amino 1,3-Dihydro-2*H*-imidazole-2-thiones 370; General Procedure:^[478]

Method A: To a stirred soln of the α -halo ketone **369** ($\text{X} = \text{Cl, Br}$) (2.5 mmol) in AcOH (10 mL) was added finely ground KNCS (0.37 g, 3.8 mmol) at rt. After 1 h, phenylhydrazine (0.27 g, 2.5 mmol) was added dropwise. The mixture turned red and the temperature rose and after 1–2 h the product began to separate. Stirring was continued for another 2 h, Et_2O (15 mL) was added to complete the precipitation of the product **370**, which was collected by filtration and washed with H_2O ($2 \times 20\text{ mL}$). Recrystallization (EtOH) afforded colorless

crystals of **370** the purity was checked by TLC. In order to remove colored impurities the crude product was dissolved in 5% NaOH and extracted with CH_2Cl_2 . Neutralization of the aqueous layer with 10% HCl induced precipitation of the pure (TLC) product **370**.

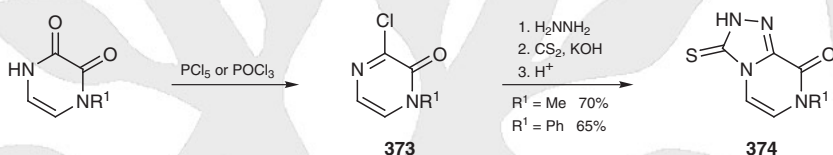
Method B: To a stirred soln of the α -halo ketone **369** ($\text{X} = \text{Cl}, \text{Br}$) (2.5 mmol) in DMF (10 mL) was added finely ground KNCS (0.37 g, 3.8 mmol) at rt. After stirring for 1 h, hydrazine or hydrazine hydrochloride (2.5 mmol) dissolved in DMF (3 mL) was added dropwise. Stirring was continued for 5 h and upon addition of H_2O the resultant precipitate was collected by filtration. Recrystallization (EtOH) afforded the pure (TLC) product **370**.

18.10.9.1.1.2

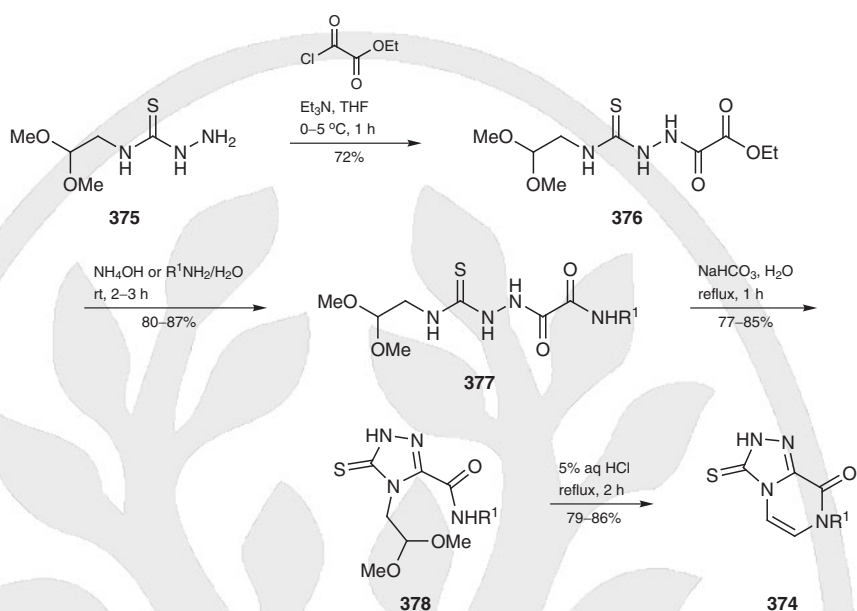
Variation 2: Intramolecular Cyclization Reactions

The 3-thioxo-2,3-dihydro-1,2,4-triazolo[4,3-*a*]pyrazin-8(7*H*)-one ring system is prepared by the reaction of 3-chloropyrazin-2(1*H*)-one **373** with hydrazine to give the 3-hydrazinopyrazin-2(1*H*)-one, further treatment with carbon disulfide under basic conditions gives the corresponding 3-thioxo-2,3-dihydro-1,2,4-triazolo[4,3-*a*]pyrazin-8(7*H*)-ones **374** (Scheme 145).^[479]

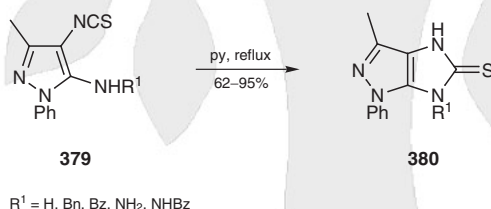
Scheme 145 Synthesis of 3-Thioxo-2,3-dihydro-1,2,4-triazolo[4,3-*a*]pyrazin-8(7*H*)-ones^[479]



An alternative, convenient synthesis of 3-thioxo-2,3-dihydro-1,2,4-triazolo[4,3-*a*]pyrazin-8(7*H*)-ones **374** is shown in Scheme 146. The reaction of dithiocarbamate with hydrazine monohydrate is carried out in ethanol at reflux temperature to give a 4-(2,2-dimethoxyethyl)thiosemicarbazide **375** in good yield. The reaction of thiosemicarbazide **375** with ethyl oxalyl chloride in the presence of triethylamine in tetrahydrofuran affords the product **376** in 72% yield. Reactions of 1-(2-ethoxy-1,2-dioxoethyl)thiosemicarbazide **376** with excess ammonia or primary amines gives the corresponding amides **377** in good yields (80–87%). The cyclization reaction of **377** is carried out in water using 1 molar equivalent of sodium hydrogen carbonate and yields 1,3-dihydro-2*H*-1,2,4-triazole-2-thiones **378** in good yields (77–85%). Intramolecular condensation reaction of **378** with 5% hydrochloric acid at reflux temperature gives **374** in good yields (79–86%). Attempts to achieve a one-pot synthesis of **374** from **376** in water are also very successful (64–69%).^[480]

Scheme 146 Synthesis of 3-Thioxo-2,3-dihydro-1,2,4-triazolo[4,3-*a*]pyrazin-8(7*H*)-ones^[480]

6-Substituted 4,6-dihydroimidazo[4,5-*c*]pyrazole-5(1*H*)-thiones **380** are prepared by the intramolecular cyclization of isothiocyanates **379** by refluxing in pyridine. The yields of **380** range from good to quantitative (Scheme 147).^[481]

Scheme 147 Synthesis of 6-Substituted 4,6-Dihydroimidazo[4,5-*c*]pyrazole-5(1*H*)-thiones^[481]

6-Substituted 3-Methyl-1-phenyl-4,6-dihydroimidazo[4,5-*c*]pyrazole-5(1*H*)-thiones 380;
General Procedure:^[481]

A soln of each 4-isothiocyanato-3-methyl-1-phenyl-1*H*-pyrazol-5-amine **379** (1 mmol) in pyridine (35 mL) was refluxed until the intramolecular cyclization was completed. The solvent was removed under reduced pressure to give solid **380** that was purified either by flash chromatography or by recrystallization from an appropriate solvent.

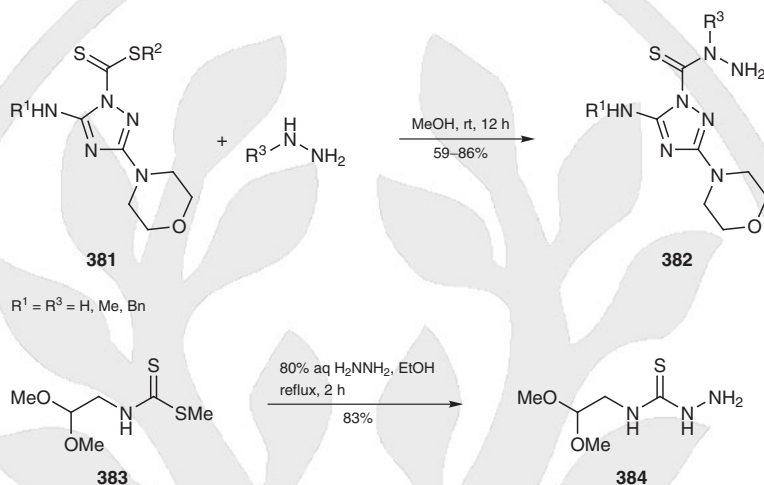
18.10.9.1.2

Method 2:
From Compounds Containing the Thiocarbamoyl Moiety

Compounds **381** and **383** containing a thiocarbamoyl group are readily converted into the corresponding thiosemicarbazides **382** and **384** by using hydrazine derivatives as the nucleophilic reagent. The reactions of thiocarbamoyl chlorides and tetraalkylthiuram sulfides with hydrazines are of importance for the preparation of 1,1,4,4-tetrasubstituted and 1,1,2,4,4-pentasubstituted thiosemicarbazides. Alkyl dithiocarbamates and alkyl dithiocarbazates react with monosubstituted hydrazines to form thiosemicarbazides and

thiocarbonohydrazides, respectively, having the hydrazine substituent located at the nitrogen atom attached to the thiocarbonyl group (Scheme 148). A satisfactory synthetic route to thiosemicarbazide **382** ($R^1 = R^3 = \text{Ph}$) is to treat thiocarbonyl-substituted 1,2,4-triazole **381** ($R^1 = \text{Ph}$) with phenylhydrazine and ammonia.^[462,480,482–484]

Scheme 148 Synthesis of Thiosemicarbazides^[462,480,482–484]



4-(2,2-Dimethoxyethyl)thiosemicarbazide (**384**):^[480]

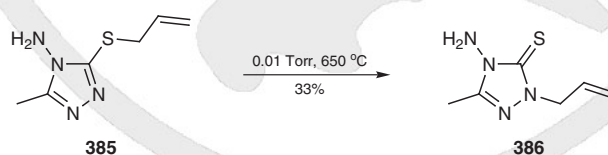
To a stirred soln of methyl (2,2-dimethoxyethyl)dithiocarbamate (**383**; 19.5 g, 100 mmol) in EtOH (100 mL) was added 80% aq H_2NNH_2 (6.9 g, 110 mmol). The mixture was heated at reflux temperature for 2 h, then concentrated under reduced pressure. The residual material was treated with EtOAc (30 mL) and Et_2O (100 mL). The precipitated crystalline solid was separated by filtration and recrystallized ($\text{EtOAc}/\text{Et}_2\text{O}$) to give the product as colorless crystals; yield: 14.9 g (83%).

18.10.9.1.3

Methods 3: Miscellaneous Methods

2-Allyl-4-amino-5-methyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (**386**) is formed by rearrangement 3-(allylsulfanyl)-4-amino-5-methyl-4H-1,2,4-triazole (**385**) under flash-vacuum pyrolysis (650 °C, 0.01 Torr) conditions (Scheme 149).^[485]

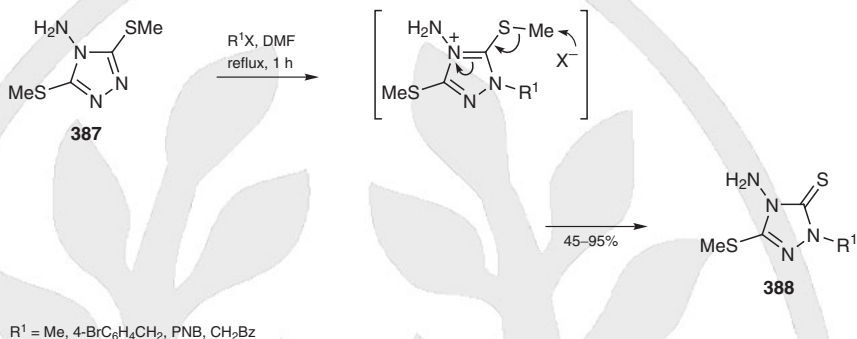
Scheme 149 Synthesis of 2-Allyl-4-amino-5-methyl-2,4-dihydro-3H-1,2,4-triazole-3-thione^[485]



Two methods for the preparation of 2-substituted 4-amino-5-(methylsulfanyl)-2,4-dihydro-3H-1,2,4-triazole-3-thiones **388** are available. The first involves sequential treatment of alkylhydrazines with carbon disulfide, iodomethane, hydrazine, and carboxylic acids; however, limited availability of substituted hydrazine reagents severely restricts the scope of

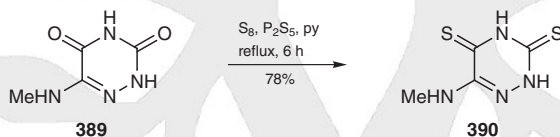
this process. The second method involves alkylation of 4-amino-3,5-bis(methylsulfanyl)-4*H*-1,2,4-triazole **387** followed by treatment with elemental sulfur in presence of triethylamine (Scheme 150).^[486–489]

Scheme 150 Synthesis of 2-Substituted 4-Amino-5-(methylsulfanyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones^[487]



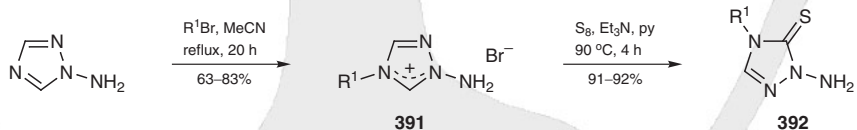
Thiosemicarbazides **390** are synthesized by the thionation of semicarbazides **389** with phosphorus pentasulfide or Lawesson's reagent (Scheme 151).^[490]

Scheme 151 Synthesis of Thiosemicarbazides by Thionation of Semicarbazides^[490]



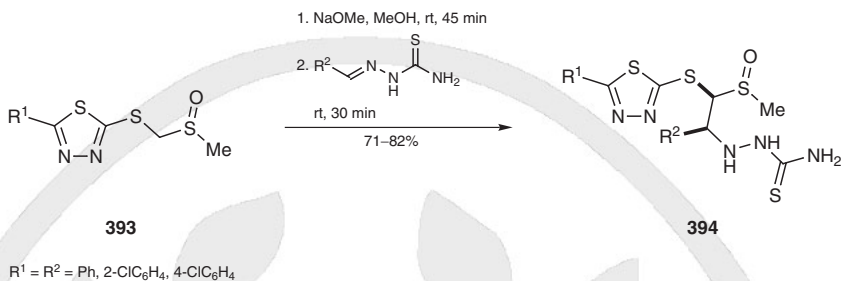
4-Amino-1,2,4-triazolium salts **391** react with sulfur in pyridine in the presence of triethylamine to give 2-amino-4-(arylalkyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **392** (91–92%) (Scheme 152).^[491]

Scheme 152 Synthesis of 2-Amino-4-(arylalkyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones^[491]

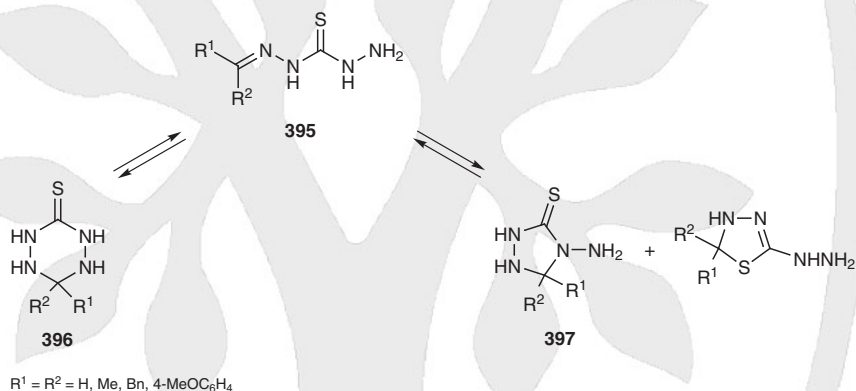


Thiosemicarbazides are also synthesized by the nucleophilic substitution reaction or reduction of the $C=N$ group in thiosemicarbazones.

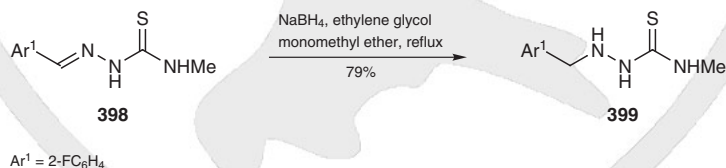
1-[1-Aryl-2-(5-aryl-1,3,4-thiadiazol-2-ylsulfanyl)-2-(methylsulfinyl)ethyl]thiosemicarbazides **394** are formed by the reaction of thiadiazole derivatives **393** with a semicarbazone in methanol (Scheme 153).^[492,493]

Scheme 153 Synthesis of Thiosemicarbazides^[492,493]

Thiocarbonohydrazones **395** undergo intramolecular ring closure in solution to give both tetrahydro-1,2,4,5-tetrazine-3(2*H*)-thiones **396** and 4-amino-1,2,4-triazolidine-3-thiones **397**. This equilibrium is the first example of the tautomerism of nitrogen heterocycles involving five- and six-membered rings at the same time, similar to the formation of pyranose and furanose forms of carbohydrates (Scheme 154).^[494]

Scheme 154 Equilibrium between Thiocarbonohydrazones and Five- and Six-Membered Heterocycles^[494]

Reduction of thiosemicarbohydrazones **398** using sodium borohydride gives thiosemicarbazides **399** (Scheme 155).^[495]

Scheme 155 Synthesis of Thiosemicarbazides^[495]

2-Allyl-4-amino-5-methyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**386**):^[485]

When 3-(allylsulfanyl)-4-amino-5-methyl-4*H*-1,2,4-triazole (**385**; 0.30 g, 1.8 mmol) was sublimed at 120 °C over a period of 1.5 h into a furnace tube at a temperature of 650 °C a mixture of products was obtained, which was separated by dry flash chromatography (silica gel, hexane/EtOAc 6:1), to give **386** as a pale yellow liquid; yield: 0.10 g (33%).

2-Substituted 4-Amino-5-(methylsulfanyl)-2,4-dihydro-3H-1,2,4-triazole-3-thiones 388;**General Procedure:**^[487]

A mixture of 3,5-bis(methylsulfanyl)-1,2,4-triazol-4-amine (**387**; 1.76 g, 10 mmol), the appropriate alkylating reagent (12 mmol), and dry DMF (20 mL) was refluxed for 1 h. After cooling, the mixture was poured into ice water (30 mL), the precipitate was collected by filtration, washed with additional H₂O, dried, and recrystallized from an appropriate solvent to give products **388** as crystalline solids; yield: 45–95%.

6-(Methylamino)-1,2,4-triazine-3,5(2H,4H)-dithione (390):^[490]

6-(Methylamino)-1,2,4-triazine-3,5(2H,4H)-dione (**389**; 5.68 g, 40 mmol), flowers of sulfur (S₈) (2.56 g, 10 mmol), P₂S₅ (17.8 g, 80 mmol), and pyridine (350 mL) were refluxed for 6 h with vigorous stirring. The mixture was allowed to cool and stand at rt for 16 h. The clear, reddish-brown soln was decanted from the reaction flask and the pyridine removed under reduced pressure (water bath, 60 °C), the residue which remained was covered with distilled H₂O (200 mL), boiled for 10 min, and allowed to stand at rt for 18 h. The precipitate was collected by filtration, resuspended in distilled H₂O (200 mL) and basified to pH 10 with concd NH₄OH. The mixture was treated with Norit and filtrated through a Celite pad, and was washed with basic H₂O (pH 10) (2 × 20 mL). The combined filtrate and washings were carefully acidified with 6 M HCl to pH 4 and the product precipitated. The solid was collected by filtration, washed with cold, distilled H₂O (3 × 50 mL), and air dried to provide product **390**; yield: 5.5 g (79%).

2-Amino-4-(arylalkyl)-2,4-dihydro-3H-1,2,4-triazole-3-thiones 392; General Procedure:^[491]

A soln of the appropriate 1-amino-4-(arylalkyl)-1,2,4-triazolium bromide **391** (5.0 mmol), S₈ (160 mg), and Et₃N (0.5 g, 5.0 mmol) in pyridine (50 mL) was heated at 90 °C for 4 h. The mixture was poured into H₂O (100 mL) and set aside at 0 °C for 12 h. The crystals were collected by filtration, washed with H₂O (20 mL) and EtOH (20 mL), and dried. Recrystallization (hot EtOH) gave the pure product; yield: 91–92%.

1-[1-Aryl-2-(5-aryl-1,3,4-thiadiazol-2-ylsulfanyl)-2-(methylsulfinyl)ethyl]thiosemicarbazides 394; General Procedure:^[492]

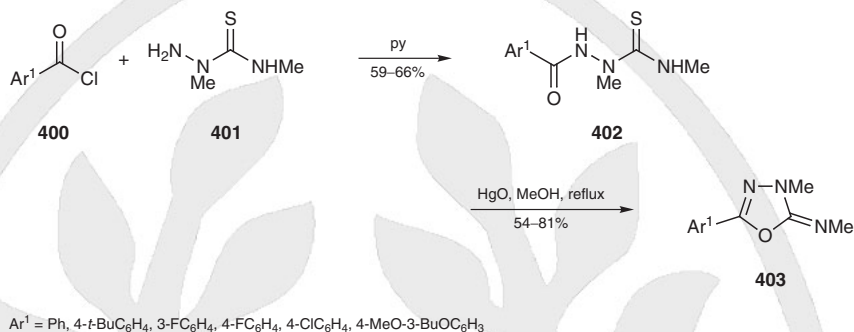
To a soln of NaOMe (1.08 g, 20 mmol) in MeOH (50 mL) was added **393** (10 mmol), and after stirring the mixture at rt for 45 min, the semicarbazone (10 mmol) was added. The mixture was further stirred at rt for 1 h followed by stirring at 50–60 °C for 30 min, then it was quenched with H₂O (50 mL) and acidified with 5 M HCl (4.4 mL) just to neutrality. The product thus precipitated was recrystallized (EtOH) to give a diastereomeric mixture which was again recrystallized (EtOH) to obtain an analytical sample of a single diastereomer **394**; yield: 71–82%.

18.10.9.2 Applications of Product Subclass 9 in Organic Synthesis**18.10.9.2.1 Method 1:
Cyclization of 1-Acylthiosemicarbazides**

It is well known that 1-acylthiosemicarbazides, depending on the reaction conditions, can be cyclized to either 1,2,4-triazoles, 1,3,4-oxadiazoles, or 1,3,4-thiadiazoles; see *Science of Synthesis*, Vol. 13 (Five-Membered Hetarenes with Three or More Heteroatoms). Thus, utilizing the sodium hydrogen carbonate induced cyclization of 1-benzoyl-2,4-dimethylthiosemicarbazides, a series of 5-aryl-2,4-dimethyl-3H-1,2,4-triazole-3-thiones can be prepared. Furthermore, a number of 5-aryl-3-methyl-2-(methylimino)-2,3-dihydro-1,3,4-oxadiazoles **403** can be synthesized in moderate yields by the mercury(II) oxide induced cyclization of 1-benzoyl-2,4-dimethylthiosemicarbazides **402**. The starting thio-

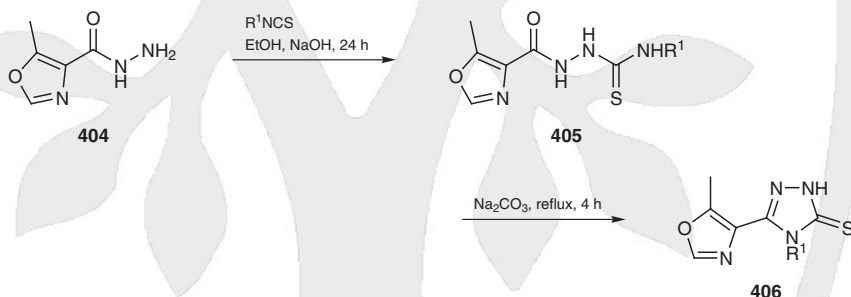
semicarbazides are readily prepared by the reaction of benzoyl chlorides **400** and 2,4-dimethylthiosemicarbazide (**401**) in pyridine (Scheme 156).^[496]

Scheme 156 Synthesis of 5-Aryl-3-methyl-2-(methylimino)-2,3-dihydro-1,3,4-oxadiazoles^[496]



Cyclization of 1-acylthiosemicarbazide derivatives is used to produce 2,4-dihydro-1,2,4-triazole-3-thiones, cyclic thiosemicarbazides. Reaction of carbohydrazide **404** with a substituted isothiocyanate yields 1-acylthiosemicarbazides **405** which are cyclized in basic medium to the corresponding 2,4-dihydro-1,2,4-triazole-3-thione **406** (Scheme 157).^[497]

Scheme 157 Cyclization of 1-Acylthiosemicarbazides to 2,4-Dihydro-1,2,4-triazole-3-thiones^[497]



R ¹	Yield (%)		Ref
	405	406	
Me	72	80	[497]
Bu	75	85	[497]
Cy	72	83	[497]
Ph	85	89	[497]

1-Benzoyl-2,4-dimethylthiosemicarbazides (402, Ar¹ = Ph); General Procedure:^[496]

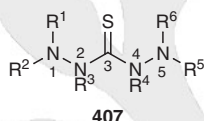
To a stirred soln of 2,4-dimethylthiosemicarbazide (**401**) and pyridine was added portionwise the benzoyl chloride. After 24 h the pyridine was concentrated under reduced pressure. The concentrate was treated with H₂O and the crude product was collected by filtration. Recrystallization (EtOH) afforded a colorless solid.

4-Methyl-5-(5-methyloxazol-4-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (406, R¹ = Me);**Typical Procedure:**^[497]

A mixture of compound **405** (R¹ = Me; 214 mg, 1 mmol) and 5% aq Na₂CO₃ (10 mL) was stirred and refluxed for 4 h. After cooling, the soln was acidified with HCl and the precipitate was collected by filtration. The precipitate was recrystallized (EtOH); yield: 157 mg (80%).

**18.10.10 Product Subclass 10:
Thiocarbonohydrazides**

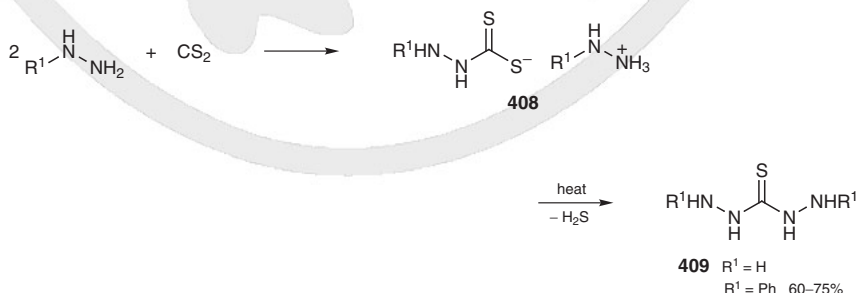
This product subclass of compounds, thiocarbonohydrazides, has the structure shown **407** (Scheme 158) and are described in *Houben-Weyl*, Vol. E 4, p 518. The organization of this subclass is according to the principal reagents used as primary sources for the synthesis of these compounds.

Scheme 158 Thiocarbonohydrazides


Thiocarbonohydrazides are thiocarbonyl derivatives with two hydrazide groups. They are both thioureas and thiosemicarbazides, and have close links with thiocarbamic and thiocarbamic acids as well as with aminoguanidines. The chemical behavior of thiocarbonohydrazides is similar to the oxygen analogue, carbonohydrazides. In general, these species are prepared by the reaction of carbon disulfide or thiophosgene with two equimolar amounts of a hydrazine derivative.

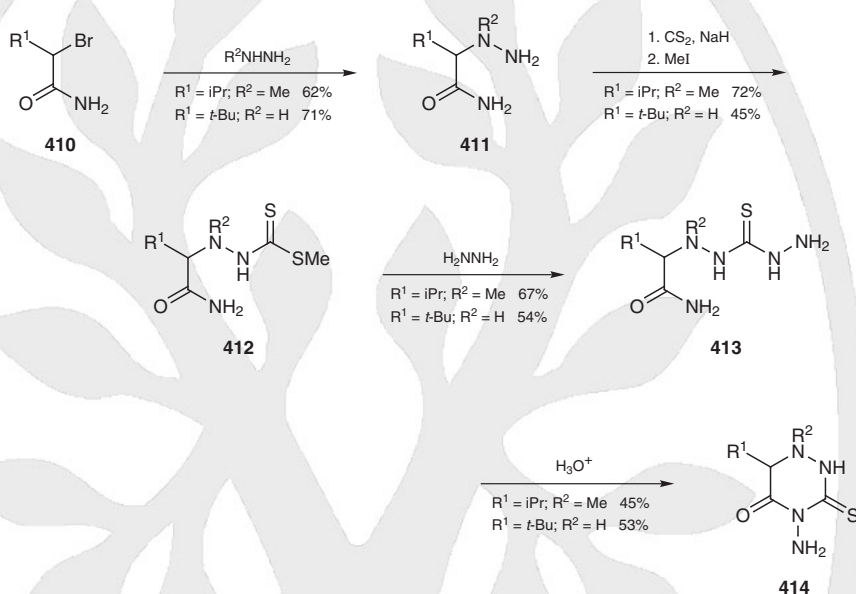
18.10.10.1 Synthesis of Product Subclass 10
**18.10.10.1.1 Method 1:
From Carbon Disulfide**

Thiocarbonohydrazide (**409**, R¹ = H) is prepared as a colorless crystalline solid, by refluxing a mixture of carbon disulfide and hydrazine hydrate at 90 °C for 1 hour, and is formed via dithiocarbazic salt **408** (R¹ = H) (Scheme 159).^[498] 1,5-Diphenylthiocarbazine (**409**, R¹ = Ph) is also prepared by the pyrolysis of the phenylhydrazine salt of 3-phenyldithiocarbamic acid **408** (R¹ = Ph), which is synthesized from phenylhydrazine and carbon disulfide.^[499,500]

Scheme 159 Synthesis of Thiocarbonohydrazides^[498–500]


4-Amino-3-thioxotetrahydro-1,2,4-triazin-5(2H)-ones **414** are synthesized from bromoacetamides **410** by four synthetic steps. Starting with **410**, hydrazinoacetamides **411** are obtained upon treatment with hydrazines. When **411** is reacted with carbon disulfide in the presence of sodium hydride followed by S-methylation with iodomethane, **412** is obtained. It is noteworthy that when $R^2 = \text{H}$ and $R^1 = t\text{-Bu}$, thiocarbonylation occurs at N2 due to the bulkiness of the R^1 substituent. Hydrazinolysis of **412** effects the removal of the methylsulfanyl group to give **413**. Cyclization of **413** in hydrochloric acid under reflux results in the formation of **414** (Scheme 160).^[501]

Scheme 160 Synthesis of 4-Amino-3-thioxotetrahydro-1,2,4-triazin-5(2H)-ones^[501]



1,5-Diphenylthiocarbonohydrazide (409, $R^1 = \text{Ph}$):^[499]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

In a 1-L three-necked flask, fitted with a mechanical stirrer, a condenser, and a dropping funnel, was placed a soln of pure redistilled phenylhydrazine (128 mL, 1.3 mol) in Et_2O (600 mL). To the vigorously stirred mixture, CS_2 (52 mL, 0.86 mol) was added over the course of 30 min. After the mixture had been stirred for an additional 30 min, the precipitate was filtered with suction, washed with Et_2O (50 mL), and spread on filter paper for 15–20 min to allow evaporation of Et_2O . The yield of the 3-phenyldithiocarbazic salt **408** ($R^1 = \text{Ph}$) was 181–185 g (96–98%). This salt was transferred to 1-L beaker, and while being continuously stirred by hand, it was heated in a water bath maintained at 96–98 °C. After about 20–30 min NH_3 was evolved. When a distinct odor of ammonia was first detected, the beaker was removed from the bath, placed in a pan of cold H_2O for 1 min, and then surrounded immediately by crushed ice. Abs EtOH (ca. 150 mL) was added, and the mixture was warmed slightly to loosen the mass, and the taffylike material was stirred until it was transformed into a granular precipitate. After the mixture had stood at rt for 1 h, the precipitate was collected on a Buchner funnel and washed with abs EtOH (50 mL) to give crude product; yield: 100–125 g (60–75% based on phenylhydrazine).

Methyl 3-(1-Carbamoyl-2-methylpropyl)-3-methylcarbazate (412, R¹ = iPr; R² = Me);**Typical Procedure:**^[501]**CAUTION:** Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.**CAUTION:** Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

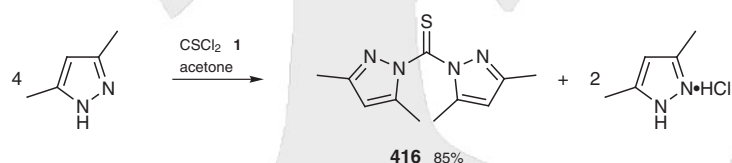
To a soln of 62.7% NaH (284 mg, 7.43 mmol) in THF (5 mL) was added a soln of **411** (980 mg, 6.75 mmol) in THF (15 mL) at rt and the resultant mixture was stirred for 20 min. CS₂ was added to the mixture, which was stirred for an additional 1 h. To the mixture were added H₂O (5 mL) and, 5 min later, MeI (506 µL). The mixture was stirred for 1 h and then the usual extractive workup with EtOAc provided crude **412** (R¹ = iPr; R² = Me) which was purified by column chromatography (silica gel, hexane/Et₂O) to give pure product; yield: 979 mg (72%). An analytically pure sample was obtained by recrystallization (hexane/EtOH); mp 147.2 °C.

18.10.10.1.2**Method 2:
From Thiophosgene**

2,4-Disubstituted thiocarbonohydrazides **415** are prepared by reaction of thiophosgene (**1**) with 4 equivalents of alkylhydrazines (Scheme 161).^[502]

Scheme 161 Preparation of 2,4-Disubstituted Thiocarbonohydrazides^[502]

1,1'-Thiocarbonylbis(3,5-dimethylpyrazole) (**416**) is prepared in an analogous way from 3,5-dimethyl-1H-pyrazole and thiophosgene (**1**) (Scheme 162).^[430]

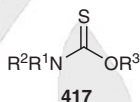
Scheme 162 Synthesis of 1,1'-Thiocarbonylbis(3,5-dimethylpyrazole)^[430]**1,1'-Thiocarbonylbis(3,5-dimethylpyrazole) (416):**^[430]**CAUTION:** Thiophosgene (CSeCl₂) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

To a stirred soln of 3,5-dimethyl-1H-pyrazole (96 g, 1 mol) in acetone (400 mL), a soln of thiophosgene (**1**; 28.5 g, 0.25 mol) in acetone (30 mL) was added dropwise. The color of soln turned to deep yellow. After removal of 3,5-dimethyl-1H-pyrazole hydrochloride by filtration, the soln was stirred as a further 30 min. After concentration of the soln, crystals of the crude product were obtained at low temperature. The product **416** was recrystallized (cyclohexane); yield: 85%.

18.10.11 **Product Subclass 11:**
Thiocarbamate O-Esters

This product subclass of compounds, thiocarbamate *O*-esters, has the structure **417** (Scheme 163) and is described in *Houben-Weyl*, Vol. E 4, p 434. This section is organized according to the principal reagents used as primary sources for the synthesis of these compounds.

Scheme 163 Thiocarbamate *O*-Esters



In general, thiocarbamate *O*-ester derivatives (thiocarbamic *O*-acid esters) are frequently treated as intermediates of Newman-Kwart thermal rearrangement and as a protecting group for alcohols.

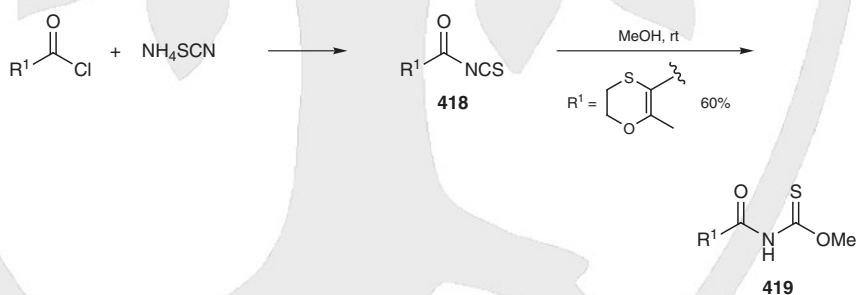
18.10.11.1 **Synthesis of Product Subclass 11**

18.10.11.1.1 **Method 1:**
From Isothiocyanates

There is a large number of well-known methods for the synthesis of thiocarbamate *O*-esters from isothiocyanate derivatives. Thiocarbamate *O*-esters are formed when isothiocyanates are treated with alcohols.

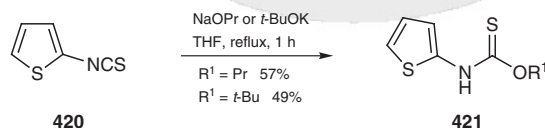
O-Methyl acylthiocarbamates **419** are readily obtained through the reaction of acid chlorides with ammonium thiocyanate, and addition of methanol to the resulting acyl isothiocyanates **418** (Scheme 164).^[503]

Scheme 164 Synthesis of *O*-Methyl Acylthiocarbamates^[503]



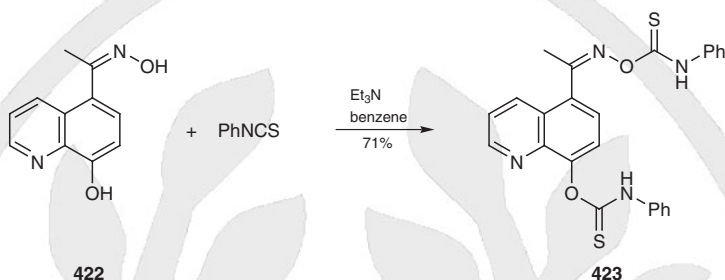
2-Thienyl isothiocyanate (**420**) reacts with alkoxides to afford *O*-alkyl 2-thienylthiocarbamates **421** in dry tetrahydrofuran. 2-Thienyl isothiocyanates are readily available by Curtius rearrangement of 2-thienylcarbonyl azides (Scheme 165).^[504]

Scheme 165 Synthesis of *O*-Alkyl 2-Thienylthiocarbamates^[504]



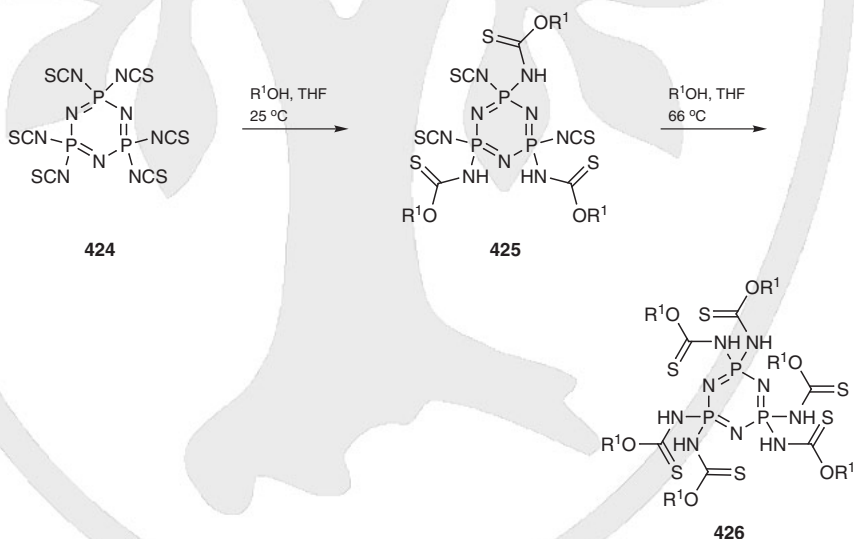
Phenyl isothiocyanate reacts readily with oximes **422** in boiling dry benzene in the presence of triethylamine to afford the corresponding thiocarbamates **423** in good yields (Scheme 166).^[505]

Scheme 166 Synthesis of a Bis(thiocarbamate)^[505]

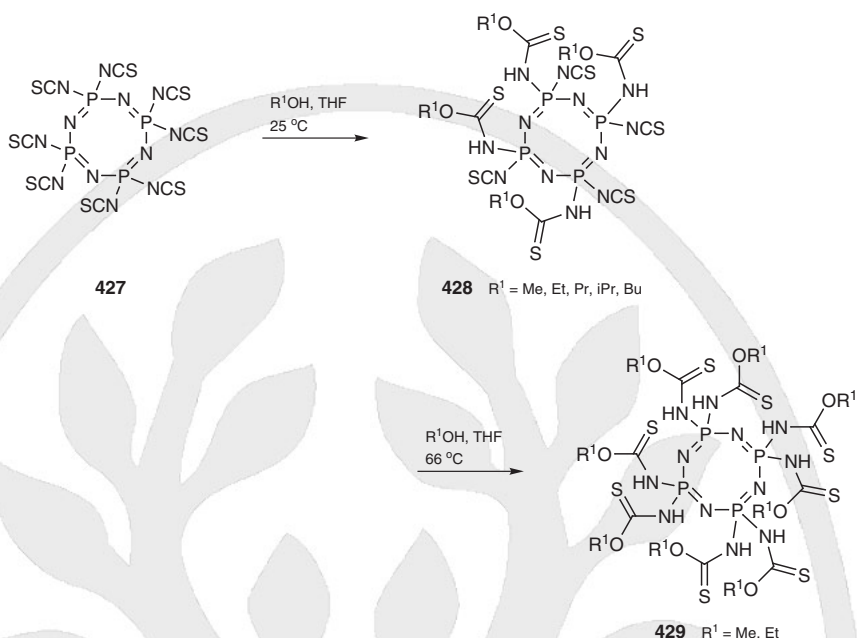


Reaction of a cyclic trimeric phosphazene **424** with alcohols (e.g., MeOH, EtOH, PrOH, iPrOH, BuOH) in tetrahydrofuran results in the formation of thiocarbamate derivatives **426** quantitatively via the nongeminal products **425** (Scheme 167). On the other hand, reaction of the corresponding tetramer **427** with alcohols under the same conditions proceeds in a nongeminal pattern to give products **428** as primary reaction intermediates. With methanol and ethanol the corresponding octakis(thiocarbamate) derivatives **429** ($R^1 = \text{Me, Et}$) are formed from **428** in tetrahydrofuran at 66 °C, but reaction of **428** with propanol, propan-2-ol, or butanol under the same conditions did not give the corresponding tetrakis(thiocarbamate) derivatives **429** (Scheme 167).^[506]

Scheme 167 Synthesis of Thiocarbamate-Substituted Phosphazenes^[506]

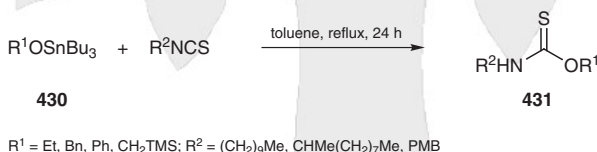


$R^1 = \text{Me, Et, Pr, iPr, Bu}$

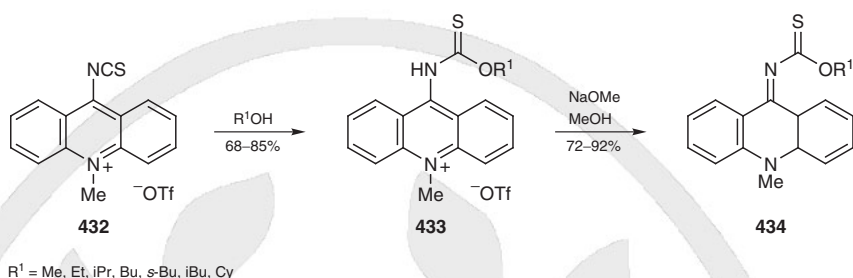


The thiocarbamate *O*-esters **431** are also synthesized by the reaction of 2 equivalents of isothiocyanate derivatives with the corresponding tin alkoxides **430**, which are prepared by the treatment of alcohols with 1 equivalent of bis(tributyltin) oxide in refluxing toluene. The products **431** are obtained by column chromatography on silica gel in excellent yields. This addition reaction is not promoted by an acid, which is necessary to catalyze the addition of an alcohol to an isocyanate. The addition can be applied to both primary and secondary alcohols (Scheme 168).^[507]

Scheme 168 Synthesis of Thiocarbamate O-Esters^[507]



Derivatives based on 9-isothiocyanatoacridine are a potential new source of fluorogens. Acridine derivatives have been synthesized with 10-methylacridinium-9-yl and 10-methyl-10*H*-acridin-9-ylidene skeletons derivatized with substituted amino and imino groups. The increased reactivity of the 9-isothiocyanato group in 9-isothiocyanato-10-methylacridinium trifluoromethanesulfonate (**432**) allows it to undergo nucleophilic addition reactions with various types of alcohols at room temperature, whereas the analogous reaction of phenyl isothiocyanate requires higher temperatures and longer reaction times. 9-[(Alkoxy)thiocarbonyl]amino-10-methylacridinium trifluoromethanesulfonates **433** are prepared in >80% yields. After addition of powdered sodium methoxide to a methanolic solution of **433**, trifluoromethanesulfonic acid is lost to give *O*-alkyl (10-methyl-9,10-dihydroacridin-9-ylidene)thiocarbamates **434** (Scheme 169).^[508]

Scheme 169 Synthesis of *O*-Alkyl (10-Methyl-9,10-dihydroacridin-9-ylidene)-thiocarbamates^[508]***O*-Methyl [(2-Methyl-5,6-dihydro-1,4-oxathiin-3-yl)carbonyl]thiocarbamate (419, $R^1 = 2\text{-Methyl-5,6-dihydro-1,4-oxathiin-3-yl}$):^[503]**

2-Methyl-5,6-dihydro-1,4-oxathiin-3-ylcarbonyl isothiocyanate (**418**), prepared from 2-methyl-5,6-dihydro-1,4-oxathiin-3-carbonyl chloride (40 g, 0.25 mol) and ammonium thiocyanate was treated with MeOH (100 mL) and then allowed to stand at rt overnight. The excess MeOH was distilled off in vacuo, the residue dissolved in toluene (500 mL), and the soln washed with H₂O. Concentration of the toluene soln in vacuo and allowing the concentrate to cool yielded light-yellow crystals; yield: 35 g (60%); mp 86–88 °C.

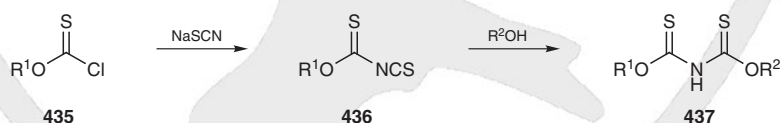
***O*-tert-Butyl 2-Thienylthiocarbamate (**421**, $R^1 = t\text{-Bu}$):^[504]**

A stirred slurry of *t*-BuOK (895 mg, 7.1 mmol) in Na-dried THF was refluxed with **420** (1.0 g, 7.1 mmol) for 1 h under anhydrous conditions, H₂O (0.25 mL) was added, and heating was continued for 15 min. The mixture was cooled to rt and 6 M HCl (1 mL) was added with stirring. The precipitate of KCl was filtered and the soln was concentrated to a small volume. Upon adding distilled H₂O, an oil separated and crystallized on standing. The product **421** ($R^1 = t\text{-Bu}$) was recrystallized (petroleum ether) to give light brown crystals; yield: 760 mg (49%); mp 95–96 °C.

18.10.11.1.2

**Method 2:
From Chlorothioformate *O*-Esters**

Symmetrical and unsymmetrical *O,O*-dialkyl dithioimidodicarbonates **437** are prepared by reaction of *O*-alkyl chlorothioformates **435** with sodium thiocyanate and treatment of the resultant alkoxythiocarbonyl isothiocyanates **436** with alcohols (Scheme 170).^[509]

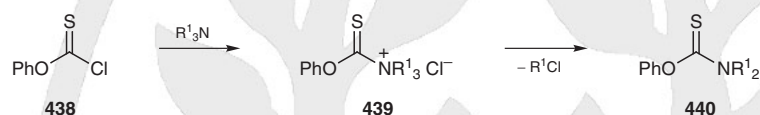
Scheme 170 Synthesis of *O,O*-Dialkyl Dithioiminodicarbonates^[509]

R^1	R^2	Yield (%)	Ref
Et	Et	67	[509]
Et	Me	74	[509]
Et	Pr	75	[509]
Et	iPr	70	[509]
Et	Bu	72	[509]
Bu	Et	41	[509]

R ¹	R ²	Yield (%)	Ref
Et	iBu	71	[509]
iBu	Et	45	[509]
Et	Cy	73	[509]
Et	Bn	48	[509]
iBu	iPr	85	[509]

O-Phenyl chlorothioformate (**438**) reacts rapidly with aliphatic tertiary amines at room temperature to give thiocarbamates **440** and alkyl chlorides via an intermediate ammonium species **439** (Scheme 171).^[510,511]

Scheme 171 Synthesis of a Thiocarbamate^[510,511]



Amine R ¹ ₃ N	Conditions	Products 440	R ¹ Cl	Yield(%)	Ref
Et ₃ N	CH ₂ Cl ₂ , 20 °C, 1 h		EtCl	93	[510]
Et ₂ NBn	CH ₂ Cl ₂ , 20 °C, 1 h		BnCl	97	[510]
4-methylmorpholine	CH ₂ Cl ₂ , 20 °C, 1 h		MeCl	73	[510]
quinuclidine	CH ₂ Cl ₂ , 20 °C, 1 h			95	[510]
tropine acetate	CH ₂ Cl ₂ , 20 °C, 1 h		MeCl	95	[510]
bicuculline	CH ₂ Cl ₂ , 20 °C, 1 h			87	[510]
Me ₂ NPh	neat, 130 °C, 24 h		MeCl	75	[510]

O,O-Dialkyl Dithioiminodicarbonates 437; General Procedure:^[509]

A mixture of powdered dry NaSCN (0.65 g, 8 mmol), CCl₄ (4 mL) (**CAUTION: toxic**), the *O*-alkyl chlorothioformate **435** (4 mmol), and 3-methylpyridine (1 drop) was vigorously stirred at rt for 4 h under N₂. An excess of the respective anhyd alcohol (5 mL) was added and the mixture was refluxed for 1 h under N₂. The mixture was then shaken with H₂O (10 mL) and extracted with CHCl₃ (4 × 4 mL). The product **437** was extracted from the CHCl₃ soln with 5% NaOH (10 mL), and then precipitated by the addition of 5% HCl. The suspension was extracted with CHCl₃ (4 × 4 mL), the solvent concentrated, and the residue recrystallized (EtOH or EtOH/H₂O).

18.10.11.1.3

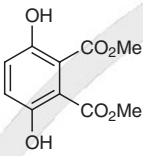
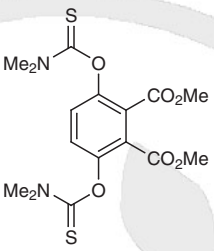
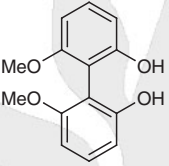
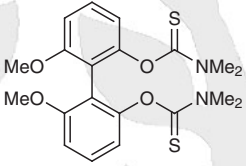
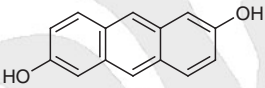
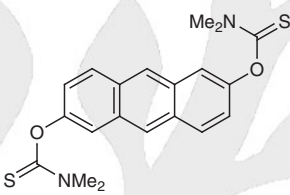

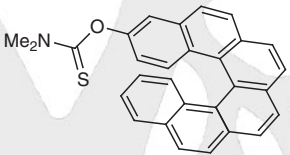
Method 3:**From N,N-Disubstituted Thiocarbamoyl Chlorides**

Thiocarbamoyl chloride derivatives **441** react with alcohols or phenols **442** to afford the corresponding N,N-disubstituted thiocarbamate *O*-esters **443**. Typical examples are shown in Table 6.^[51,512–522]

Table 6 Synthesis of N,N-Disubstituted Thiocarbamate *O*-Esters^[51,512–522]

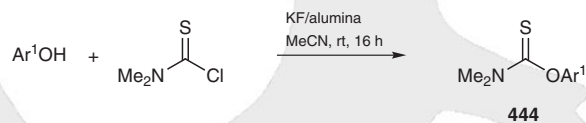
$\text{R}^2\text{R}^1\text{N}-\text{C}(=\text{S})\text{Cl} \quad \text{441} + \quad \text{R}^3\text{OH} \quad \text{442} \xrightarrow{-\text{HCl}} \text{R}^2\text{R}^1\text{N}-\text{C}(=\text{S})\text{OR}^3 \quad \text{443}$			
R ³ OH	Products	Yield (%)	Ref
		95	[51]
		92	[512]
		90, 94	[513,516]
		43, 55	[514,515]
		98 (R ¹ = H) 91 (R ¹ = OMe)	[517,518] [517,518]

Table 6 (cont.)

R ³ OH	Products	Yield (%)	Ref
		97	[519]
		80	[520]
		59	[521]
		83	[522]

A series of *O*-aryl dimethylthiocarbamates **444** have been also prepared by the reaction of dimethylthiocarbamoyl chloride with phenols absorbed on potassium fluoride on alumina as a solid base (Scheme 172).^[523]

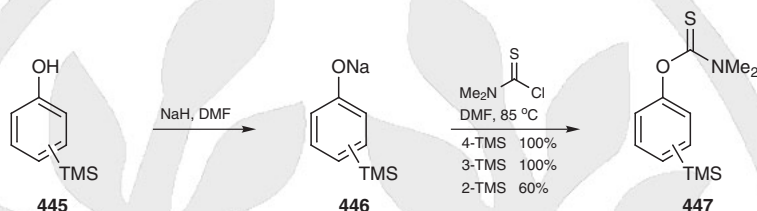
Scheme 172 Synthesis of *O*-Aryl Dimethylthiocarbamates with Potassium Fluoride on Alumina^[523]



Ar ¹	Yield (%)	Ref
Ph	80	[523]
4-Tol	88	[523]
4-O ₂ NC ₆ H ₄	64	[523]
4-AcOC ₆ H ₄	98	[523]
2-MeO ₂ CC ₆ H ₄	83	[523]
3,4-(OCH ₂ O)C ₆ H ₃	75	[523]
1-naphthyl	58	[523]
2-naphthyl	70	[523]
3-(methoxycarbonyl)-2-naphthyl	82	[523]

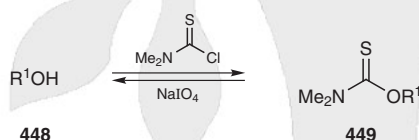
In the reaction of phenols with dimethylthiocarbamoyl chloride, substituent effects have been noted in the phenols. The trimethylsilyl substituent has a remarkable activating effect on the phenols. Trimethylsilyl-substituted phenols **445** are treated with sodium hydride in dry dimethylformamide to give the corresponding sodium phenolates **446**. The O-aryl dimethylthiocarbamates **447** are prepared by the reaction of the produced sodium phenolate **446** with dimethylthiocarbamoyl chloride (Scheme 173).^[524]

Scheme 173 Synthesis of O-Aryl Dimethylthiocarbamates^[524]



Dimethylthiocarbamates **449** are used as an alcohol protecting group. Dimethylthiocarbamates **449**, prepared from the corresponding alcohols **448** using commercial dimethylthiocarbamoyl chloride, are spectrally simple, achiral, and nonpolar. These compounds are moderately to highly stable to a wide range of reagents and conditions including metal hydrides, hydroboration, ylides, sodium hydroxide, hydrochloric acid, organolithiums, Grignard reagents, 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone, pyridinium chlorochromate, Swern oxidation, tetrabutylammonium fluoride, chromium(II) chloride, heat, and Lewis acids. They are readily removed by sodium periodate or hydrogen peroxide in the presence of other common alcohol protecting groups (Scheme 174).^[525]

Scheme 174 Synthesis of Dimethylthiocarbamates^[525]



O-(6-Acetyl-2-naphthyl) Dimethylthiocarbamate (443, R¹ = R² = Me; R³ = 6-Acetyl-2-naphthyl):^[512]

6-Acetyl-2-naphthol (**442**, R³ = 6-acetyl-2-naphthyl; 27.9 g, 0.15 mol) was added to an ice-cooled soln of KOH (10.1 g, 0.18 mol) in MeOH (150 mL). The soln was stirred for 0.25 h and dimethylthiocarbamoyl chloride (**441**, R¹ = R² = Me; 22.1 g, 0.18 mol) was added. A mildly exothermic reaction was observed after a short time. The mixture was stirred for 0.5 h and the precipitated white solid was collected by filtration and washed with ice-cold MeOH/H₂O (1:1, 150 mL). Drying of the solid in vacuo (50 °C/150 Torr) afforded the product; yield: 37.8 g (92%). The product was found to be 97% pure as determined by HPLC. Recrystallization of a small sample with (abs EtOH) furnished white crystals; mp 164–165 °C.

2,2'-Bis[[(dimethylamino)thiocarbonyl]oxy]-1,1'-binaphthyl (443, R¹ = R² = Me; R³ = 1,1'-Binaphthyl-2,2'-diyl):^[516]

NaH was added in small portions over 2 h to a stirred soln of 1,1'-binaphthalene-2,2'-diol (60 g, 210 mmol) in dry DMF (450 mL) at 0 °C under N₂. After the addition was complete, dimethylthiocarbamoyl chloride (52 g, 420 mmol) was added in one portion and the mixture was stirred at 85 °C under N₂ for 1 h. The resulting brown suspension was cooled and shaken with 1% aq KOH (1.5 mL). The precipitate was collected by filtration and dried in air at 25 °C overnight. Crude product (110 g) was dissolved in hot toluene (250 mL) and the

H₂O which separated was removed by decantation. The organic soln was cooled in an ice bath to give a powder; yield: 91 g (94%); mp 208 °C.

O-(2,2-Dimethyl-4-oxo-3,4-dihydro-2H-1-benzopyran-7-yl) Dimethylthiocarbamates (443):^[518]

A mixture of 2,2-dimethyl-7-hydroxy-2,3-dihydro-4H-1-benzopyran-4-one (10 mmol), dimethylthiocarbamoyl chloride (2.48 g, 20 mmol), DABCO (2.24 g, 20 mmol), and abs DMF (30 mL) was stirred at rt for 2 h, and then it was poured onto crushed ice (200 g). The separated solid was collected by filtration, washed with 10% aq HCl (50 mL) and H₂O, and treated with cold MeOH to afford the product: yield: 95–99%. Analytical samples were recrystallized (MeOH).

O-Aryl Dimethylthiocarbamates 444; General Procedure:^[523]

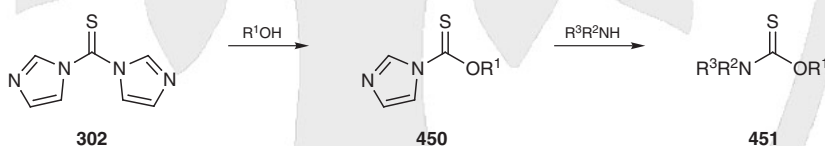
To a soln of phenol (10 mmol) in MeCN (10 mL) was added dimethylthiocarbamoyl chloride (10 mmol). Following this, KF on alumina (6 g) was added with stirring. After 16 h at rt, the mixture was filtered and the solvent was concentrated. The products **444** were purified by recrystallization or distillation.

18.10.11.1.4

**Method 4:
From 1,1'-Thiocarbonyldiimidazole and Related Compounds**

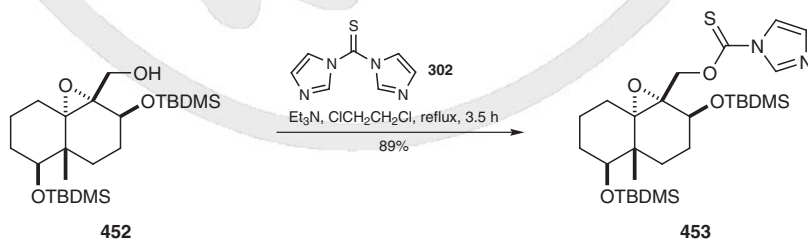
1,1'-Thiocarbonyldiimidazole (**302**) is very useful as a thiocarbonyl transfer reagent. This reagent reacts with one equimolar amount of an alcohol or phenol derivatives to give the 1H-imidazole-1-carbothioate O-ester **450**, a thiocarbamate O-ester. These reactions are frequently employed in the syntheses of natural products since the thiocarbamate O-esters are reduced by tributyltin hydride to the corresponding deoxygenated products. The 1H-imidazole-1-carbothioate O-esters **450** are also precursors of thiocarbamate O-esters **451**, by reaction with one equimolar amount of amine derivatives (Scheme 175).^[129,137,526–543]

Scheme 175 Synthesis of Thiocarbamate O-Esters^[129,137,526–543]



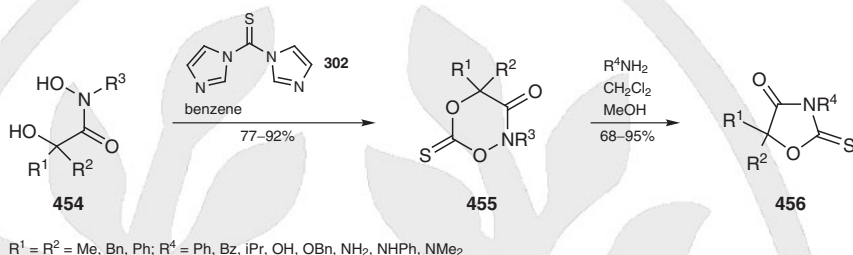
For example, epoxy alcohol **452** reacts with 1,1'-thiocarbonyldiimidazole (**302**) to give the 1H-imidazole-1-carbothioate O-ester **453** (Scheme 176).^[541]

Scheme 176 Synthesis of the 1H-Imidazole-1-carbothioate O-Ester of an Epoxy Alcohol Using 1,1'-Thiocarbonyldiimidazole^[541]



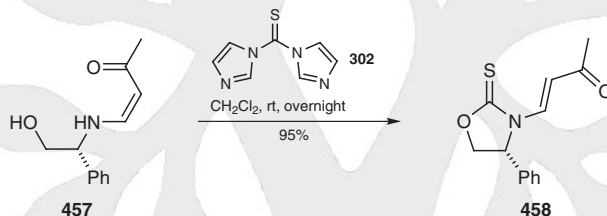
1,1'-Thiocarbonyldiimidazole (**302**) converts N-substituted glycolhydroxamic acids **454** into 6-thioxo-2H-1,5,2-dioxazin-3(4H)-ones **455** at room temperature, which are highly reactive heterocyclic compounds. In the presence of primary amines (benzyloxyamine, hydroxylamine, hydrazines) **455** undergoes ring contraction yielding 2-thioxooxazolidin-4-ones **456** (Scheme 177).^[544]

Scheme 177 Synthesis of 2-Thioxooxazolidin-4-ones^[544]



Amino alcohols such as **457** react with 1,1'-thiocarbonyldiimidazole (**302**) to give the corresponding heterocyclic products, in this case oxazolidine-2-thione **458**, containing a thiocarbamate O-ester moiety (Scheme 178).^[545,546]

Scheme 178 Synthesis of an Oxazolidine-2-thione^[545,546]



(1R*,2S*,4aR*,5S*,8aS*)-2,5-Bis(tert-butoxydimethylsiloxy)-1,8a-epoxy-4a-methyl-1-(((1H-imidazol-1-yl)thiocarbonyl)oxy)methyl)decahydronaphthalene (453):^[541]

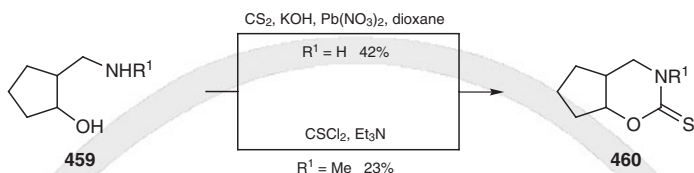
To a soln of **452** (87.4 mg, 0.19 mmol) in anhyd 1,2-dichloroethane (1.2 mL), was added 1,1'-thiocarbonyldiimidazole (**302**; 90%, 76.0 mg, 0.38 mmol). After refluxing for 80 min, the soln was then diluted with H₂O and extracted with CH₂Cl₂. The combined organic layers were washed successively with cold 1 M HCl, sat. NaHCO₃, and brine. The solvent was dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc 5: 1) to give a yellow oil; yield: 97.0 mg (89%).

18.10.11.1.5

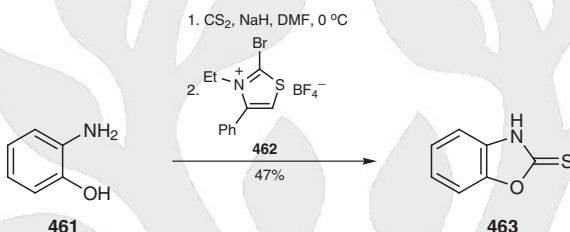
Method 5:

From Amino Alcohols and Carbon Disulfide and Related Methods

Hexahydrocyclopenta[*c*]-1,3-oxazine-2(3*H*)-thiones **460** are prepared from 2-(aminomethyl)cyclopentanol **459** and carbon disulfide or thiophosgene (Scheme 179).^[547] A variety of oxazine-2-thiones **460** are prepared similarly from amino alcohols.^[548-550]

Scheme 179 Synthesis of Hexahydrocyclopenta[e]-1,3-oxazine-2(3H)-thiones^[547]

2-Aminophenol (**461**) affords a thiocarbonyl-transfer product **463** in 47% yield upon treatment with carbon disulfide and 2 equivalents of sodium hydride followed by reaction with 2-bromo-3-ethyl-4-phenylthiazolium tetrafluoroborate (**462**) (Scheme 180).^[462]

Scheme 180 Synthesis of Benzoxazole-2(3H)-thione^[462]

Benzoxazole-2(3H)-thione (463):^[462]

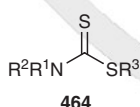
CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

NaH (250 mg) was washed with hexane and suspended in DMF (6 mL), and the mixture was cooled to 0 °C. 2-Aminophenol (**461**; 273 mg, 2.50 mmol) was added portionwise at 0 °C, and the red mixture was stirred for 5 min, then CS₂ (0.5 mL) was added at -10 °C. The mixture was stirred for 15 min and then 2-bromo-3-ethyl-4-phenylthiazolium tetrafluoroborate (**462**; 890 mg, 2.50 mmol) was added and the cooling bath was removed. After the resulting mixture was stirred at rt for 2 h, it was diluted with excess EtOAc and H₂O. The organic layer was separated, dried, and concentrated. Chromatography of the residue (CHCl₃) gave **463**; yield: 176 mg (47%); mp 189–190 °C.

18.10.12

Product Subclass 12:**Dithiocarbamic Acid Esters**

This product subclass, dithiocarbamic acid esters, has the structure **464** (Scheme 181) and are discussed in *Houben–Weyl*, Vol. E 4 p 461. This section is organized according to the principal reagents used as primary sources for the synthesis of these compounds.

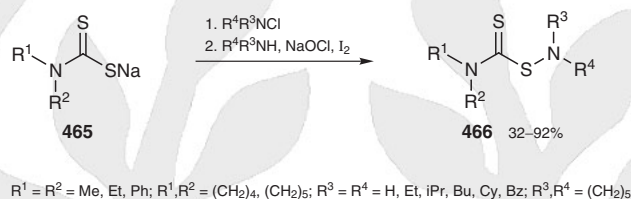
Scheme 181 Dithiocarbamate Esters

18.10.12.1 Synthesis of Product Subclass 12

18.10.12.1.1 Method 1:
From Sodium Dithiocarbamates

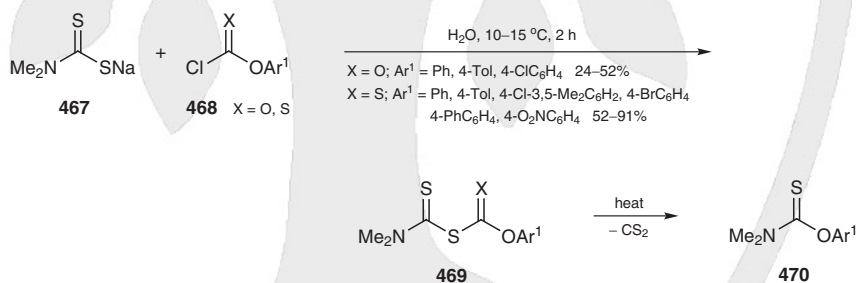
[(Dialkylamino)thiocarbonyl]sulfenamides **466** are prepared by reaction of amines and sodium dialkyldithiocarbamates **465** (Scheme 182).^[551]

Scheme 182 Synthesis of [(Dialkylamino)thiocarbonyl]sulfenamides^[551]



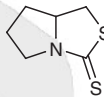
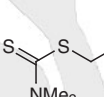
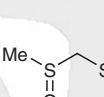
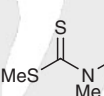
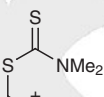
Aryl chloroformates **468** (X = O) react with sodium dimethyldithiocarbamate (**467**) in acetone to give *O*-aryl *S*-[(dimethylamino)thiocarbonyl]thiocarbonates **469** (X = O). These esters are unstable and decompose, even at room temperature, within a few weeks. *O*-Aryl chlorothioformates **468** (X = S), however, react with sodium dimethyldithiocarbamate (**467**) or ammonium dimethyldithiocarbamate to give various *O*-aryl *S*-[(dimethylamino)thiocarbonyl] dithiocarbonates **469** (X = S) in good yields (Scheme 183). *O*-Aryl *S*-[(dimethylamino)thiocarbonyl] dithiocarbonates **469** (X = S) decompose when heated at their melting point for long periods to give carbon disulfide and *O*-aryl dimethylthiocarbamates **470** (Scheme 183).^[552]

Scheme 183 Synthesis of *O*-Aryl Dimethylthiocarbamates^[552]

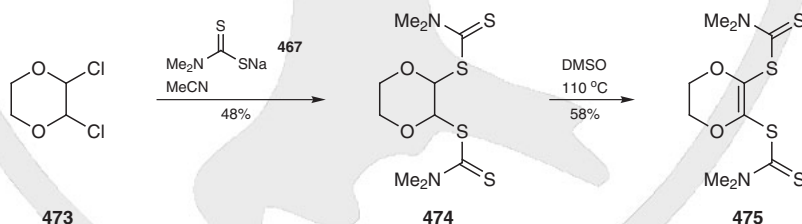


Alkyl dithiocarbamates **472** are also prepared by the reaction of sodium dialkyldithiocarbamates (**471**) with alkyl halides (Scheme 184).^[299,553–556]

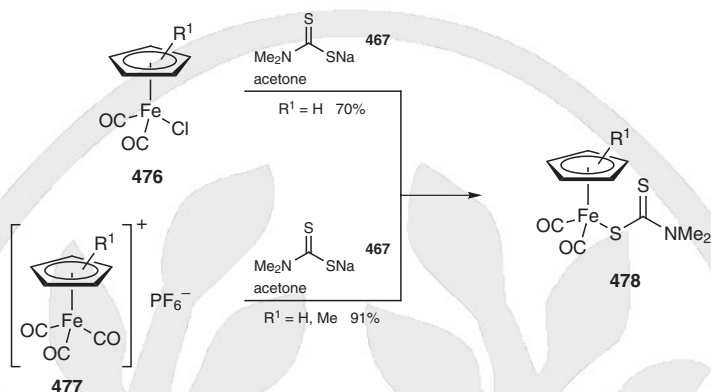
Scheme 184 Synthesis of Alkyl Dithiocarbamates^[299,553–556]

$\text{R}^2\text{R}^1\text{N}-\text{C}(=\text{S})\text{SNa} \quad \text{471} + \text{R}^3\text{Cl} \longrightarrow \text{R}^2\text{R}^1\text{N}-\text{C}(=\text{S})\text{SR}^3 \quad \text{472}$						
R ¹	R ²	R ³ Cl	Conditions	Product	Yield (%)	Ref
Me	Me	2-chloromethylpyrrolidine	DMF, rt, 1 h		15	[553]
Me	Me	ClCH ₂ CH ₂ Cl	THF, 60 °C, 6 h		67.5	[554]
Me	Me	CH ₂ S(O)Me	EtOH, 50–60 °C, 5 h		80	[555]
Me	CH(NMe ₂) ₂	Me	Et ₂ O, 0 °C		87	[556]
Me	Me	Ph ₃ P ⁺ CH ₂ I [−]	CHCl ₃ , reflux, 6 h		84.6	[299]

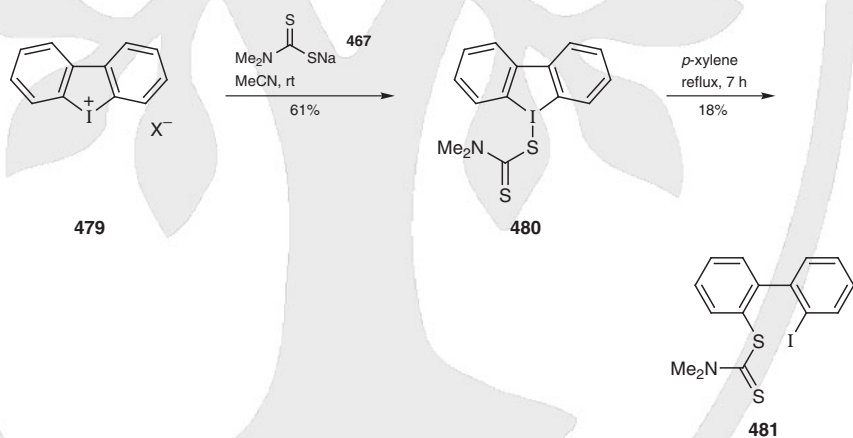
1,4-Dioxane-2,3-diyl bis[dimethyl(dithiocarbamate)] (**474**) and 5,6-dihydro-1,4-dioxin-2,3-diyl bis[dimethyl(dithiocarbamate)] (**475**) are prepared by reaction of 2,3-dichlorodioxane (**473**) with sodium dimethyldithiocarbamate (**467**) (Scheme 185). The product **475** is a precursor of an oxygen-substituted tetrathiafulvalene.^[557,558]

Scheme 185 Synthesis of 5,6-Dihydro-1,4-dioxin-2,3-diyl Bis[dimethyl(dithiocarbamate)]^[557,558]

Tricarbonyl(η^5 -cyclopentadienyl)iron hexafluorophosphate (**477**) or dicarbonylchloro(η^5 -cyclopentadienyl)iron (**476**) react with sodium dimethyldithiocarbamates (**467**) to give the corresponding monodentate (η^5 -cyclopentadienyl)iron–dimethyldithiocarbamate complex **478** (Scheme 186).^[559,560]

Scheme 186 Synthesis of a (η^5 -Cyclopentadienyl)iron–Dimethyldithiocarbamate Complex^[559,560]

Diaryl{[(dialkylamino)thiocarbonyl]sulfanyl}- λ^3 -iodanes are prepared in 48–91% yield by the reaction of diaryliodonium halides with sodium dialkyldithiocarbamates in acetonitrile or water in the dark. The product decomposes on heating to give the corresponding aryl dithiocarbamate and aryl iodide. The reaction using biphenyl-2,2'-diyliodonium salt **479** as a substrate gives (biphenyl-2,2'-diyl){[(dimethylamino)thiocarbonyl]sulfanyl}- λ^3 -iodane (**480**) which decomposes on heating to 2'-iodobiphenyl-2-yl dimethyldithiocarbamate (**481**) (Scheme 187).^[553,561]

Scheme 187 Synthesis of (Biphenyl-2,2'-diyl){[(dimethylamino)thiocarbonyl]sulfanyl}- λ^3 -iodane and 2'-Iodobiphenyl-2-yl Dimethyldithiocarbamate^[553,561]

O-(4-Chloro-3,5-dimethylphenyl) S-[(Dimethylamino)thiocarbonyl] Dithiocarbonate (469, Ar¹ = 4-Cl-3,5-Me₂C₆H₂; X = S); Typical Procedure:^[552]

To a soln of sodium dimethyldithiocarbamate (**467**; 14.3 g, 0.1 mol) in H₂O (100 mL) was added gradually *O*-(4-chloro-3,5-dimethylphenyl) chlorothioformate (**468**, Ar¹ = 4-Cl-3,5-Me₂C₆H₂; X = S; 23.5 g, 0.1 mol) keeping the temperature at 10–15°C during the reaction period of 2 h. The mixture was filtered to give the product as yellow crystals; yield: 27.2 g (85%). Recrystallization (acetone/EtOH) gave yellow prisms; mp 113–114.5°C.

O-(4-Tolyl) Dimethylthiocarbamate (470, Ar¹ = 4-Tol); Typical Procedure:^[552]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

In an oil bath, S-[(dimethylamino)thiocarbonyl] O-(4-tolyl) dithiocarbonate (**469**, Ar¹ = 4-Tol; X = S; 0.45 g, 1.56 mmol) was kept at 160 °C for 1 h. After the evolution of CS₂ had subsided, the mixture was cooled to rt. Recrystallization (2 ×) of the mixture from EtOH (0.5 mL) gave the product; yield: 0.2 g (62%); mp 95–96 °C.

**18.10.12.1.2 Method 2:
From Carbon Disulfide**

In principle, dithiocarbamates **482** can be formed by reaction of carbon disulfide with an amine in the presence of a base. The resulting nucleophilic dithiocarbamates **482** can be converted into dithiocarbamate derivatives **483** by reaction with a suitable electrophile (Table 7).

Table 7 Synthesis of Dithiocarbamic Acid Esters Using Carbon Disulfide and an Amine^[368,462,480,562–572]

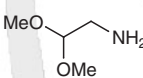
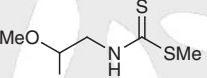
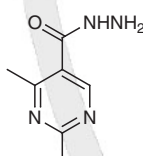
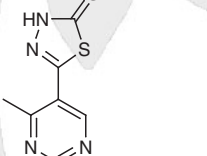
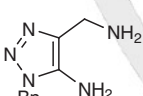
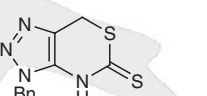
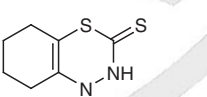
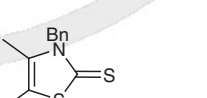
$\begin{array}{c} R^1 \\ \\ NH \\ \\ R^2 \end{array} + CS_2 \xrightarrow{\text{base}} \begin{array}{c} S \\ \\ R^1-N-R^2 \\ \\ S^- \end{array} \xrightarrow{R^3X} \begin{array}{c} S \\ \\ R^1-N-R^2 \\ \\ SR^3 \end{array}$					
		482	483		
Amine	Base	Conditions	Product 483	Yield (%)	Ref
	Et ₃ N	1. EtOH, H ₂ O, 0–5 °C, 1 h 2. MeI, rt, 1 h		95	[480]
	KOH	EtOH, 20–25 °C, 1 h		5	[563]
	Et ₃ N	pyridine, reflux, 6 h		63	[562]
H ₂ NNH ₂	KOH	1. iPrOH, 15 min 2. 2-chlorocyclohexanone		30	[564]
BnNH ₂	–	1. EtOH, 0 °C 2. AcCHClMe		77	[565]

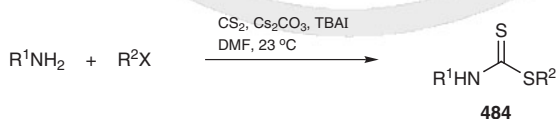
Table 7 (cont.)

Amine	Base	Conditions	Product 483	Yield (%)	Ref
BnNHMe	Et ₃ N	MeCN 0 °C		75	[462]
BuNHMe	BuLi	1. THF 0 °C 2. 2-bromo-3-methyl-4-phenylthiazolium salt, Mel		95	[566]
morpholine	NaOH	1. DMF, 0–60 °C, 3 h 2. <i>trans</i> -2,3-dichloro-1,4-dioxane		78 ^a	[368]
1 <i>H</i> -1,2,4-triazol-5-amine	KOH	1. DMF, <15 °C to rt, 2 h 2. Mel		67	[567]
	Et ₃ N	1. CHCl ₃ , rt, 1 h 2. Mel		88	[568]
piperidine	NaOH	1. EtOH, rt, 5 h, then reflux, 24 h 2. (EtO) ₂ CHCH ₂ Br		76	[569]
MeNHOH•HCl	Et ₃ N	1. CH ₂ Cl ₂ , 0 °C to rt 2. Mel		95	[570]
	Et ₃ N	1. MeCN, 0 °C to reflux 2. HC(O)CH ₂ Cl		66	[571,572]

^a NR¹R² = morpholino.

The presence of cesium carbonate and tetrabutylammonium iodide facilitates efficient dithiocarbonylation of amines using carbon disulfide with alkyl halides to give dithiocarbamates **484**. This protocol is mild, chemoselective, and efficient when compared to existing methods (Scheme 188).^[210]

Scheme 188 Efficient Dithiocarbonylation of Amines Using Carbon Disulfide with Alkyl Halides^[210]



R ¹	R ²	X	Time (h)	Yield (%)	Ref
Bn	Bn	Cl	5	96	[210]
CH ₂ CH ₂ Ph	Bn	Cl	6	88	[210]
(CH ₂) ₅ Me	Bn	Cl	10	93	[210]
tetrahydro-2-furylmethyl	Bn	Cl	6	93	[210]
cyclooctyl	Bn	Cl	6	78	[210]
4-benzylpiperazin-1-yl	Bn	Cl	12	85	[210]
2-furfuryl	(CH ₂) ₃ Ph	Br	6	82	[210]
CHPhMe	(CH ₂) ₃ Ph	Br	7	93	[210]
4-MeOC ₆ H ₄ CH ₂	(CH ₂) ₃ Ph	Br	6	85	[210]
2-thienylmethyl	(CH ₂) ₃ Ph	Br	5	90	[210]
2-(1 <i>H</i> -indol-3-yl)ethyl	(CH ₂) ₃ Ph	Br	8	89	[210]

Secondary amines **485** are successively treated with butyllithium and carbon disulfide and then with iodomethane to give the corresponding dithiocarbamates **486** in high yields (Scheme 189).^[573]

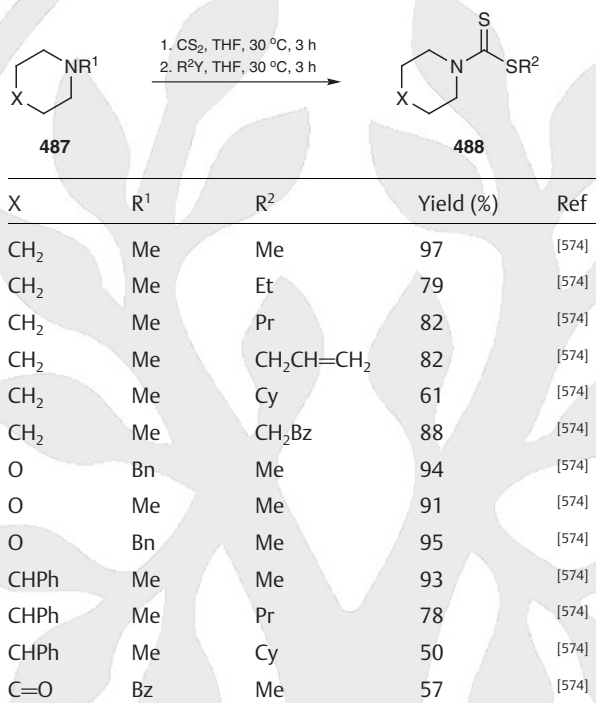
Scheme 189 Synthesis of Dithiocarbamates from Secondary Amines, Carbon Disulfide, and Iodomethane^[573]



R ¹	R ²	Yield (%)	Ref
Ph	Ph	83	[573]
4-MeOC ₆ H ₄	Bn	97	[573]
4-ClC ₆ H ₄	Bn	86	[573]
4-FC ₆ H ₄	Bn	90	[573]
4-NCC ₆ H ₄	Bn	88	[573]
4-MeOC ₆ H ₄	Me	68	[573]
4-O ₂ NC ₆ H ₄	Me	79	[573]
3-Tol	3-Tol	82	[573]
4-Br-2-FC ₆ H ₃	Me	90	[573]
4-Br-2-FC ₆ H ₃	Et	87	[573]
4-Br-2-FC ₆ H ₃	(CH ₂) ₅ Me	74	[573]
Ph	Me	96	[573]
Ph	Et	86	[573]
Ph	Pr	96	[573]
Ph	(CH ₂) ₅ Me	100	[573]
Ph	(CH ₂) ₇ Me	92	[573]
Bn	Bn	99	[573]
Bn	Pr	96	[573]

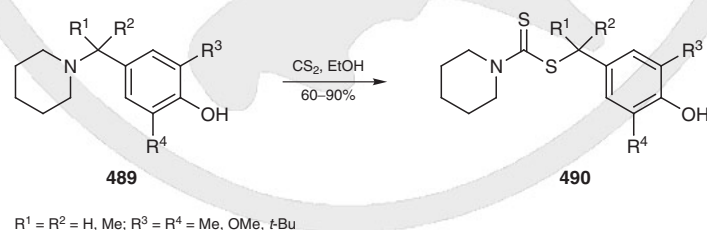
Dithiocarbamates are also prepared in two steps from tertiary amines by treatment with carbon disulfide followed by addition of an electrophile (alkyl halide) in tetrahydrofuran solution. The reaction with tertiary *N*-methyl- or *N*-benzylamines **487** allows the formation of a wide range of dithiocarbamates **488** in good to excellent yields, frequently better than those afforded by classical methods (Scheme 190).^[574]

Scheme 190 Synthesis of Dithiocarbamates from Tertiary *N*-Methyl- or *N*-Benzylamines^[574]



Dithiocarbamates are prepared by the reaction of disubstituted 1-benzylpiperidines with carbon disulfide. When the benzyl group possesses a 4-hydroxy substituent together with 3,5-substituents such as alkyl and methoxy groups, e.g. **489**, these reactions lead to dithiocarbamates **490** formed by insertion of carbon disulfide between the benzylic carbon atom and nitrogen (Scheme 191).^[575,576]

Scheme 191 Synthesis of Dithiocarbamates from 1-Benzylpiperidines^[575,576]



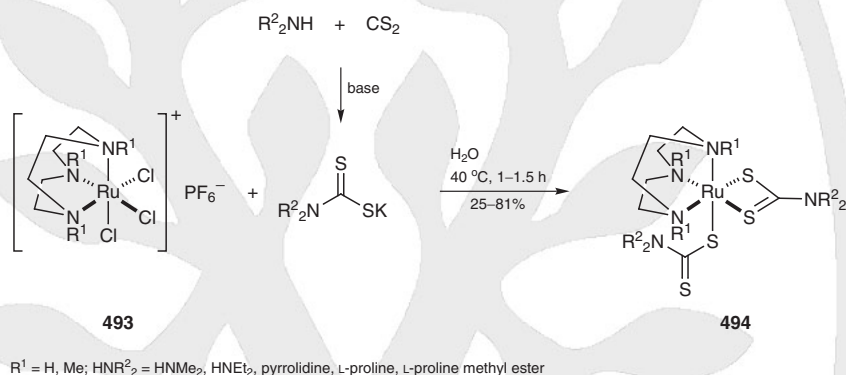
Thiocarbamoyl disulfides **492** are prepared by the insertion of carbon disulfide into the N–S bond of simple sulfenamides **491** containing a secondary amine (Scheme 192).^[577]

$\text{R}^1\text{-N}(\text{R}^1)\text{-S-R}^2 \xrightarrow[\text{36-98\%}]{\text{CS}_2, \text{Et}_2\text{O}, \text{rt, 5 min}} \text{R}^1\text{-N}(\text{R}^1)\text{-C(=S)-S-R}^2$

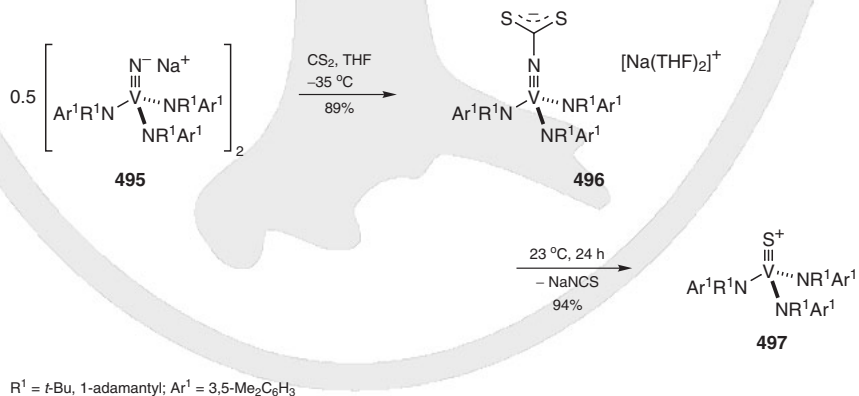
491 **492**

$\text{NR}^1_2 = \text{NMe}_2, \text{NEt}_2, \text{morpholino, piperazin-1-yl}; \text{R}^2 = \text{Me, CH}_2\text{CH=CH}_2, \text{Ph, CH}_2\text{CH}_2\text{SMe}$

Scheme 193 Synthesis of Ruthenium Complexes Containing Dithiocarbamate Ligands^[578]



Scheme 194 Synthesis of Vanadium–Dithiocarbamate Complexes^[579]



Methyl (2,2-Dimethoxyethyl)dithiocarbamate [483, $R^1 = \text{CH}_2\text{CH}(\text{OMe})_2$; $R^2 = \text{H}$; $R^3 = \text{Me}$]:^[480]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

To a stirred soln of aminoacetaldehyde dimethyl acetal (21.0 g, 200 mmol) in EtOH (150 mL) and water (10 mL) was added Et_3N (24.3 g, 240 mmol) and CS_2 (16.8 g, 220 mmol) in a dropwise manner at 0–5 °C. The mixture was stirred at rt for 1 h, then MeI (31.2 g, 220 mmol) was added, and stirring was continued at rt for 1 h. The mixture was concentrated under reduced pressure, and the residue was treated with Et_2O (200 mL). The precipitated crystalline solid ($\text{Et}_3\text{N}\cdot\text{HI}$) was removed by filtration, and the filtrate concentrated under reduced pressure to give the product as a slightly yellow liquid that was subjected to the next reaction without further purification; yield 36.9 g (95%). An analytical sample was prepared by column chromatography (silica gel, hexane/ EtOAc 2:1).

Dithiocarbamates 486; General Procedure:^[573]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

BuLi (12 mmol) was slowly added dropwise to a stirred soln of a secondary amine **485** (10 mmol) in THF (20 mL) at –10 °C. After the soln was allowed to warm to 0 °C over 1 h, CS_2 (20 mmol) was added dropwise to this mixture at 0 °C. The mixture was stirred for 12 h at rt, and MeI (20 mmol) was added dropwise to the mixture at 0 °C. The mixture was stirred at rt for 3–5 h and was then treated with sat. NaHCO_3 . The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 ×). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography or recrystallization to give the desired dithiocarbamates **486**.

Dithiocarbamates 488; General Procedure:^[574]

CAUTION: Carbon disulfide is extremely flammable and toxic by inhalation, skin absorption, and ingestion.

To a soln of the amine **487** (1 mmol) in THF (20 mL) was added CS_2 (1.2 mmol). The resulting mixture was stirred and heated at 30 °C for 3 h, then the alkyl bromide or alkyl iodide (1.2 mmol) was added and stirring was continued at 30 °C for 3 h. The soln was cooled to rt and the volatiles were carefully removed under reduced pressure. The residue was extracted with CH_2Cl_2 (4 ×) and the combined organic layers washed with H_2O , dried (MgSO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, petroleum ether/ CH_2Cl_2) to afford the pure dithiocarbamates **488**.

18.10.12.1.3 Method 3: From Isothiocyanates

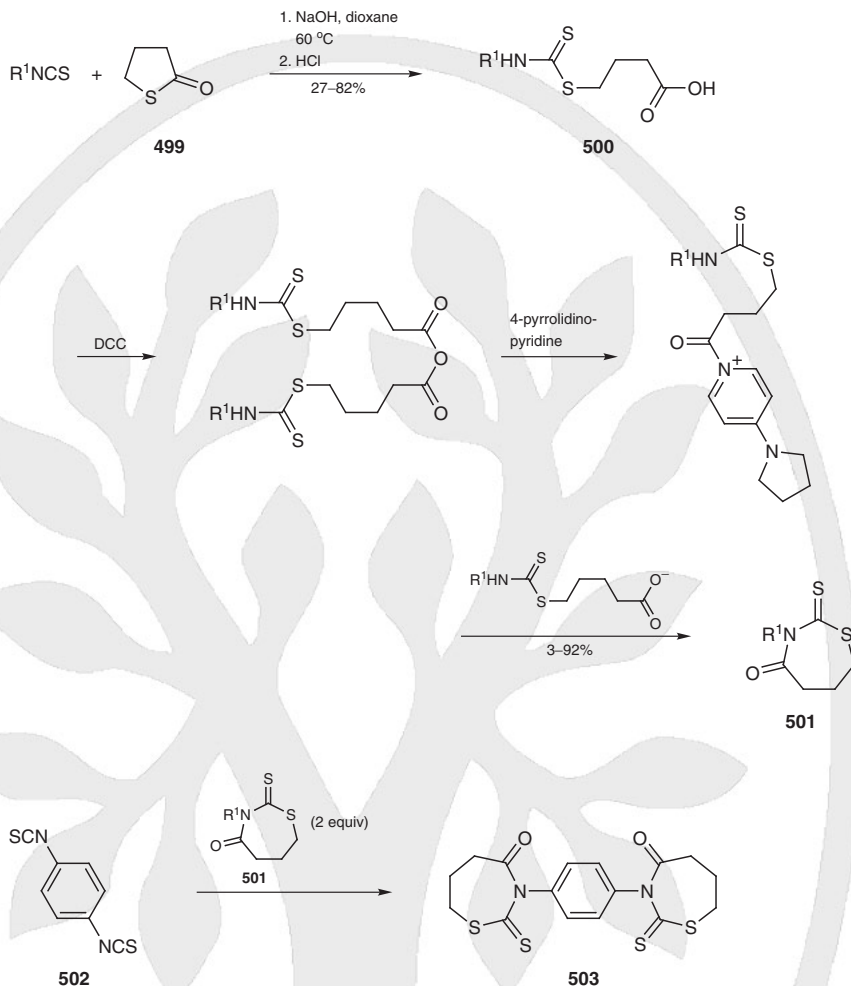
The synthesis of dithiocarbamate ester derivatives **498** is achieved directly by the reaction of isothiocyanates with thiols or related compounds (Table 8).

Table 8 Synthesis of Dithiocarbamate Ester^[504,580–585]

$\text{R}^1\text{NCS} + \text{R}^2\text{SH} \longrightarrow \text{R}^1\text{HN}-\text{C}(=\text{S})\text{SR}^2$ <p style="text-align: center;">498</p>					
R ¹	R ²	Conditions	Product	Yield (%)	Ref
Me	CH ₂ CH ₂ NH ₂	NaOH, H ₂ O, 33–75 °C		74	[580]
Bn	CH ₂ CH ₂ CO ₂ H	NaOH, pyridine, 40 °C, 2 h		55	[581]
2-thienyl	<i>t</i> -Bu	<i>t</i> -BuSH, rt, 20 h		86	[504]
Me		rt		80	[582]
Me		pyridine, reflux, 1.5 h		43	[583]
	Na	H ₂ O, CHCl ₃ , 40 °C		86 ^a	[584]
Ph	CH ₂ P(O) <i>i</i> Pr ₂	NaH, THF, rt		60	[585]

^a Ar¹ = 2,6-Me₂C₆H₃.

Reaction of isothiocyanates with dihydrothiophen-2(3*H*)-one (**499**) in alkaline medium yields 3-carboxypropyl dithiocarbamates **500** after acidification, which are converted into the 2-thioxo-1,3-thiazepan-4-ones **501**. In addition, 1,4-diisothiocyanatobenzene (**502**) reacts with **501** to give the 1,4-bis(4-oxo-2-thioxo-1,3-thiazepan-3-yl)benzene **503** (Scheme 195).^[586]

Scheme 195 Synthesis of 2-Thioxo-1,3-thiazepan-4-ones^[586]***tert*-Butyl 2-Thienyldithiocarbamate (498, $R^1 = 2\text{-Thienyl}$; $R^2 = t\text{-Bu}$):^[504]**

A slurry of *t*-BuSLi (682 mg, 7.1 mmol), 2-thienyl isothiocyanate (1.0 g, 7.1 mmol), and *t*-BuSH (10 mL) was refluxed for 5 min and then stirred at rt in a foil-covered flask for 20 h under anhydrous conditions. The thiol was evaporated under a stream of N_2 and the pasty residue was neutralized with HCl. The resultant oil was extracted with Et_2O and concentration of the Et_2O gave a crystalline product. This was chromatographed [dry-packed silica gel 60, 40 g, CCl_4 (**CAUTION: toxic**)], Unreacted 2-thienyl isocyanate ran with the solvent front and the product ran a little later. The product was recrystallized (petroleum ether, acid-washed Norit A charcoal) to give yellow needles; yield: 1.42 g (86%); mp 87.5–88.5 °C (dec).

N-Substituted 3-Carboxypropyl Dithiocarbamates 500; General Procedure:^[586]

Equimolar quantities of the appropriate isothiocyanate and dihydrothiophen-2(3H)-one (499) were dissolved in dioxane (50 mL) and heated to 60 °C. An equimolar amount of NaOH, dissolved in the minimum amount of H_2O was added with stirring. The reaction started spontaneously and was stopped after 20 min of stirring by pouring the soln onto crushed ice. After acidification to pH 2 by addition of concd HCl the acid 500 in some case separated in crystalline form and could be collected by filtration with suction, washed

with a small amount of H₂O, dried, and recrystallized. If **500** did not crystallize, the whole soln was concentrated to dryness. Acetone was added to the residue and after 1 h of cooling in ice the precipitated NaCl was removed by filtration. The acetone solution was dried (Na₂SO₄), filtered, and concentrated in vacuo to yield **500**, which was purified by recrystallization.

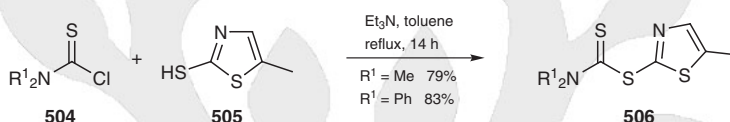
18.10.12.1.4

Method 4:
From Thiocarbamoyl Chlorides

Dithiocarbamates are produced directly by the reaction of thiocarbamoyl chlorides with thiolates in the presence of base.

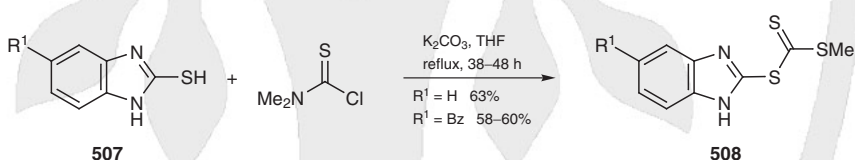
5-Methyl-1,3-thiazole-2-thiol (**505**), which is prepared by the reaction of prop-2-ynylamine with carbon disulfide, reacts with thiocarbamoyl chlorides **504** to afford N,N-disubstituted 5-methylthiazol-2-yl dithiocarbamates **506** in high yield (Scheme 196).^[587]

Scheme 196 Synthesis of N,N-Disubstituted 5-Methylthiazol-2-yl Dithiocarbamates^[587]



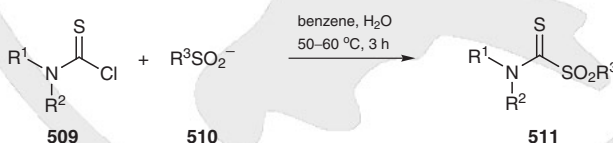
1H-Benzimidazole-2-thiol (**507**, R¹ = H) or 5-benzoyl-1H-benzimidazole-2-thiol (**507**, R¹ = Bz) react with dimethylthiocarbamoyl chloride in the presence of potassium carbonate to give the corresponding benzimidazol-2-yl dimethyldithiocarbamates **508** (Scheme 197).^[588]

Scheme 197 Synthesis of Benzimidazol-2-yl Dimethyldithiocarbamates^[588]



Sulfonylthioformamides **511** are synthesized from the reaction of thiocarbamoyl chloride **509** with sulfonate **510** (Scheme 198).^[450,589]

Scheme 198 Synthesis of Sulfonylthioformamides^[450,589]



R¹, R² = Me, Bn, Ph, (CH₂)₄; R³ = Me, Ph, 1-adamantyl, 4-Tol

1H-Benzimidazol-2-yl Dimethyldithiocarbamate (508, R¹ = H); Typical Procedure:^[588]

Dimethylthiocarbamoyl chloride (15 mmol) was added dropwise to a cold stirred mixture of 1H-benzimidazole-2-thiol (**507**, R¹ = H; 10 mmol) and anhyd K₂CO₃ (5 mmol) in dry THF (30 mL). The resulting mixture was stirred at reflux temperature for 36–48 h and then cooled; the dimethylthiocarbamoyl derivative precipitated from the mixture upon stirring for 2–3 d at rt. The precipitate was collected by filtration. The solid was redissolved

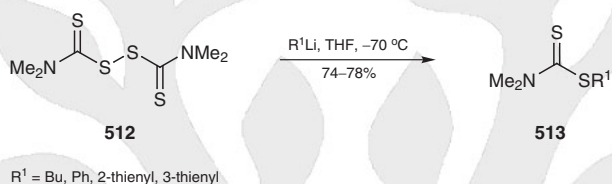
in EtOAc and was washed with H₂O. The organic layer was dried (anhyd Na₂SO₄), filtered, and concentrated to dryness to afford the product. Purification was accomplished either by recrystallization (EtOAc) or by column chromatography (silica gel, CHCl₃/MeOH).

18.10.12.1.5 Method 5: From Thiuram Disulfides

Dithiocarbamates are prepared directly by the reaction of thiuram disulfides with nucleophilic reagents. Thiuram disulfides are attacked at sulfur rather than at carbon by nucleophilic reagents.

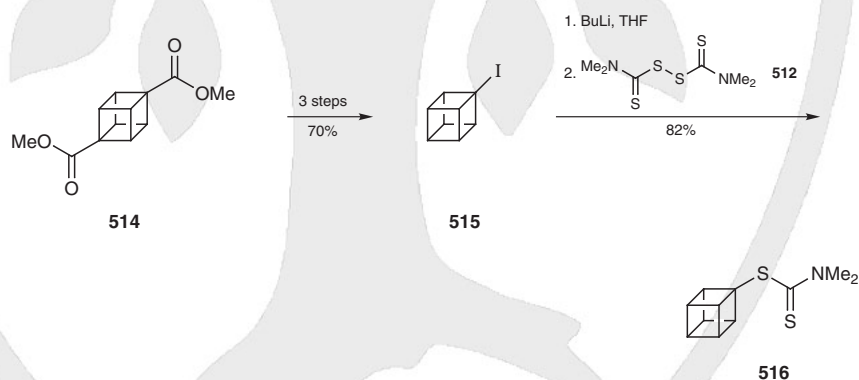
The reaction of organolithium derivatives with tetramethylthiuram disulfide (thiuram) (**512**) is a convenient method for the synthesis of dithiocarbamates **513** that does not produce any of the corresponding thioamides (Scheme 199).^[590–592]

Scheme 199 Synthesis of Dithiocarbamates Using Tetramethylthiuram Disulfide^[590]

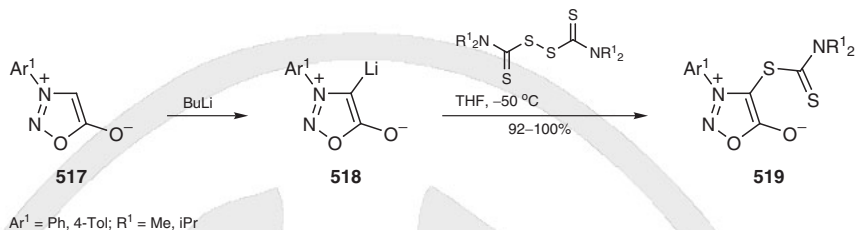


Commercially available dimethyl cubane-1,4-dicarboxylate (**514**) provides 1-iodocubane (**515**) in three steps in 70% yield.^[593,594] Lithium–halogen exchange of the monoiodide **515** followed by reaction with tetramethylthiuram disulfide (**512**) at low temperature yields cuban-1-yl dimethyldithiocarbamate (**516**) (Scheme 200).^[593–597]

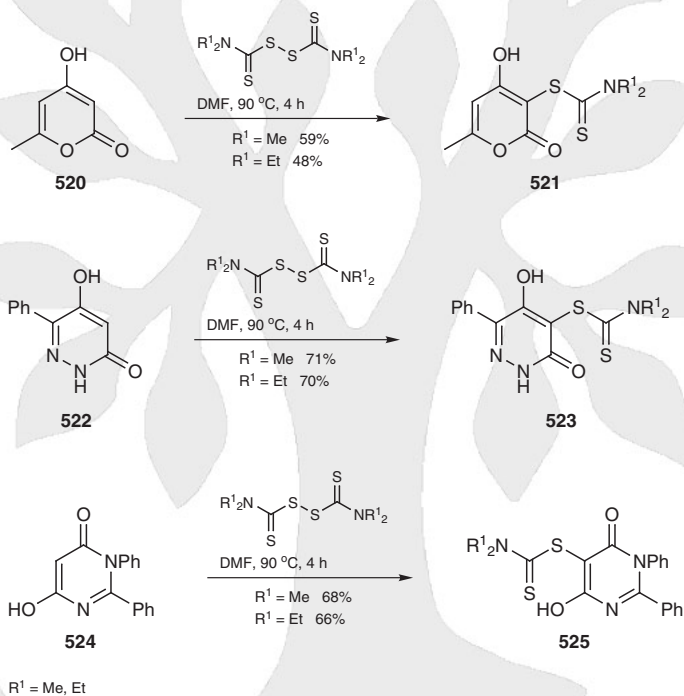
Scheme 200 Synthesis of Cuban-1-yl Dimethyldithiocarbamate^[593–597]



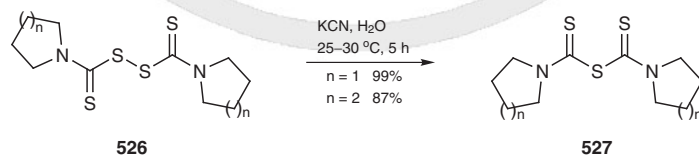
Sydnon-4-yl dithiocarbamates **519** are prepared in excellent yields by the reaction of 4-lithiosydnone **518** with tetraalkylthiuram disulfides in tetrahydrofuran at temperatures below –50 °C. 4-Lithiosydnone **518** is synthesized from the sydnone **517** by treatment with butyllithium (Scheme 201).^[598]

Scheme 201 Synthesis of Sydnon-4-yl Dithiocarbamates^[598]

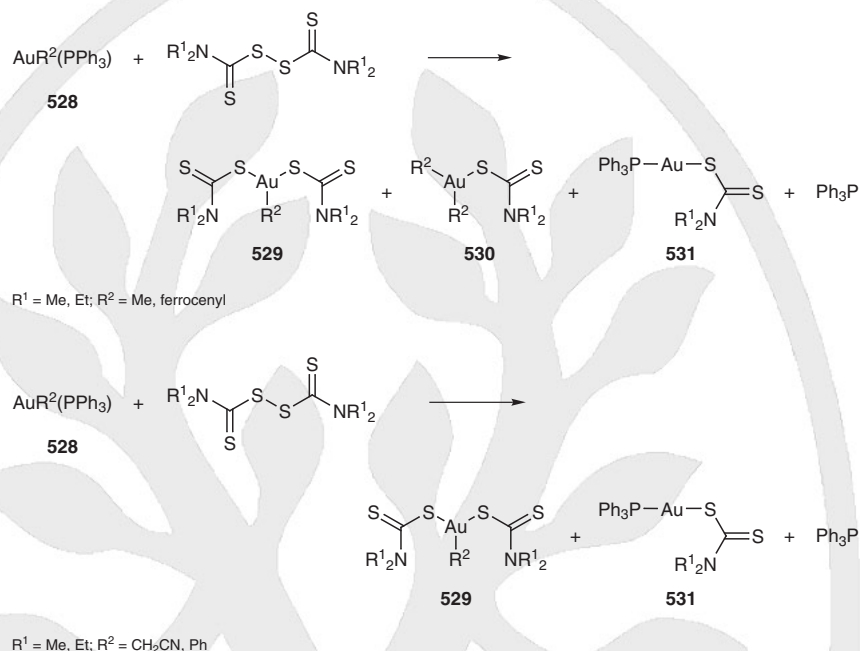
Anions of enolized heteroaromatic 1,3-dicarbonyl systems, 4-hydroxy-2H-pyran-2-one **520**, 5-hydroxypyridazin-3(2H)-one **522**, and 6-hydroxypyrimidin-4(3H)-ones **524**, react in dimethylformamide in the presence of potassium carbonate with tetraalkylthiuram disulfides to yield the corresponding dialkyl dithiocarbamic derivatives **521**, **523**, and **525** (Scheme 202).^[599]

Scheme 202 Synthesis of Dialkyl Dithiocarbamic Derivatives^[599]

Bis(pyrrolidinothiocarbonyl) sulfide (**527**, *n* = 1) and bis(piperidinothiocarbonyl) sulfide (**527**, *n* = 2) are prepared by the reaction of the corresponding thiuram disulfide **526** with potassium cyanide in water (Scheme 203).^[600]

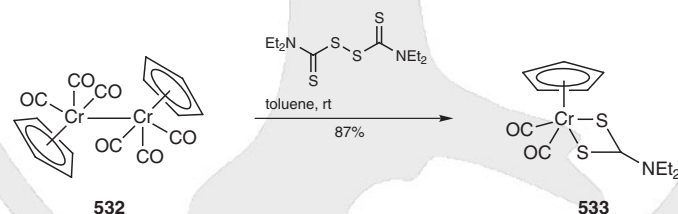
Scheme 203 Synthesis of Bis(thiocarbonyl) Sulfide Derivatives^[600]

Scheme 204 Synthesis of Gold(III)–Dialkyldithiocarbamate Complexes^[601,602]



The reaction of organochromium complex **532** with one molar equivalent of tetraethylthiuram disulfide in toluene at room temperature gives a dark red solution, which upon concentration yielded air-stable deep red crystals of chromium–dithiocarbamate complex **533** (Scheme 205).^[603] Organocobalt(III)–phosphine complexes containing a dithiocarbamate ligand have also been prepared.^[604,605]

Scheme 205 Synthesis of an Organocobalt–Dithiocarbamate Complex^[603]



The lithium compounds were prepared from the corresponding bromoaryl derivative (20 mmol) and 2.0 M BuLi in hexane (11 mL, 0.22 mmol) in THF (150 mL) under N₂ at -70°C. 1.9 M PhLi in cyclohexane (11.5 mL, 0.22 mmol) or 2.0 M BuLi in cyclohexane (11.5 mL, 0.22 mmol), which are both available commercially, were diluted with THF (150 mL) and cooled to -70°C. To this soln, tetramethylthiuram disulfide (**512**; 1 equiv) was added in one portion. After stirring at -70°C for 2 h, (when Et₂O was used as solvent the reaction was left overnight) the mixture was allowed to reach rt and poured into cold

sat. aq NH_4Cl . The phases were separated and the organic phase dried (Na_2SO_4) and concentrated. The residue was chromatographed (silica gel 60, heptane/EtOAc 95:5).

3-Phenylsydnnon-4-yl Dimethyldithiocarbamate (519, $\text{R}^1 = \text{Me}$; $\text{Ar}^1 = \text{Ph}$):^[598]

To a stirred suspension of 3-phenylsydnnone (**517**, $\text{Ar}^1 = \text{Ph}$; 1.00 g, 6.2 mmol) in anhyd THF (10 mL), under dry N_2 , was added dropwise a solution of 15% BuLi in hexane (4.0 mL, 6.5 mmol) below -50°C . After ca. 1 h of stirring, a soln of tetramethylthiuram disulfide (1.48 g, 6.2 mmol) in THF (7 mL) was added dropwise to the resulting brown soln below -50°C . After an additional 8 h of stirring, the yellow-brown mixture was poured into ice water. The precipitated yellow solid was collected by filtration, washed with H_2O , and dried: yield 1.71 g (99%); mp $145\text{--}147^\circ\text{C}$. Recrystallization (EtOH) provided the pure product as yellow plates; yield: 1.55 g (89%); mp $148\text{--}150^\circ\text{C}$.

4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl Dimethyldithiocarbamate (521, $\text{R}^1 = \text{Me}$):^[599]

A mixture of **522** (1.26 g, 10 mmol), tetramethylthiuram disulfide (2.65 g, 11 mmol), K_2CO_3 (2.76 g, 20 mmol), and DMF (30 mL) was heated with stirring at 90°C for 4 h. After removing half of the solvent in vacuo, the soln was poured into ice water. After standing for 3 h it was filtered and the filtrate was slowly acidified with dil HCl. The resulting precipitate was collected by filtration with suction; yield: 1.45 g (59%); mp $196\text{--}198^\circ\text{C}$.

Bis(pyrrolidinothiocarbonyl) Sulfide (527, $n = 1$) and Bis(piperdinothiocarbonyl) Sulfide (527, $n = 2$):^[600]

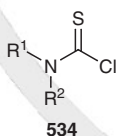
CAUTION: Cyanide salts can be absorbed through the skin and are extremely toxic.

A slurry containing bis(pyrrolidinothiocarbonyl) disulfide or bis(piperdinothiocarbonyl) disulfide **526** (0.1 mol), 96% KCN (7.4 g, 0.11 mol), and H_2O (600 mL) was stirred at $25\text{--}30^\circ\text{C}$ for 5 h. The solid was collected by filtration, washed with H_2O (1 L) and air-dried at $25\text{--}30^\circ\text{C}$ to give crude **527** ($n = 1$); yield: 99%; mp $114\text{--}116^\circ\text{C}$, or crude **527** ($n = 2$); yield: 87%; mp $115\text{--}117^\circ\text{C}$, respectively. After recrystallization (EtOAc) **527** ($n = 1$) and **527** ($n = 2$) melted at $117\text{--}118^\circ\text{C}$ and $121\text{--}122^\circ\text{C}$, respectively.

**18.10.13 Product Subclass 13:
Thiocarbamoyl Chlorides**

This product subclass, thiocarbamoyl chlorides, had the structure **534** (Scheme 206), and is discussed in *Houben–Weyl*, Vol. E 4, p 415. This section is organized according to the principal reagents used as primary sources for the synthesis of these compounds.

Scheme 206 Thiocarbamoyl Chlorides



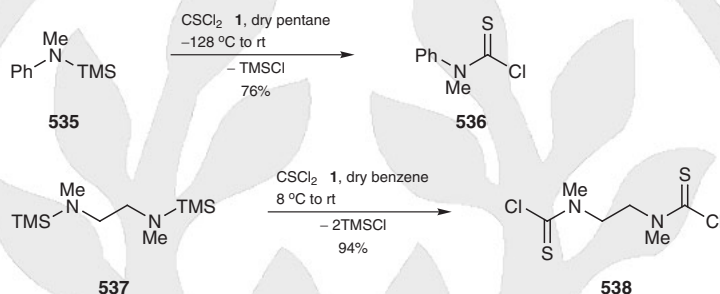
18.10.13.1 Synthesis of Product Subclass 13

**18.10.13.1.1 Method 1:
From Thiophosgene and Primary or Secondary Amines**

In general, thiocarbamoyl chloride derivatives are synthesized by reaction of an equimolar amount of a primary or secondary amine with thiophosgene (**1**), however this results in

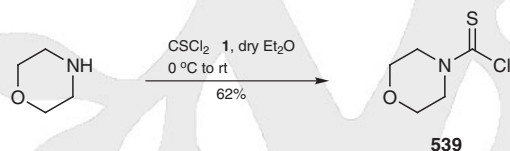
the product being contaminated by the corresponding thiourea as an impurity. Treatment of an *N*-silylamine with excess thiophosgene (**1**) affords thiocarbamoyl chlorides in good yields and excellent purity, e.g., *N*-silylamine **535** gives methyl(phenyl)thiocarbamoyl chloride (**536**) in 76% yield (Scheme 207). This method is also suitable for the preparation of bis(thiocarbamoyl chlorides), e.g. *N,N'*-dimethyl-*N,N'*-bis(trimethylsilyl)ethylenediamine (**537**) gives bis(thiocarbamoyl chloride) **538** in 94% yield (Scheme 207).^[450]

Scheme 207 Synthesis of Thiocarbamoyl Chlorides from *N*-Silylamines and Thiophosgene^[450]



The morpholine-4-thiocarbonyl chloride (**539**) is prepared in 62% yield by reaction of morpholine with thiophosgene (**1**) at 0 °C (Scheme 208).^[377]

Scheme 208 Synthesis of Morpholine-4-thiocarbonyl Chloride^[377]



Methyl(phenyl)thiocarbamoyl Chloride (**536**):^[450]

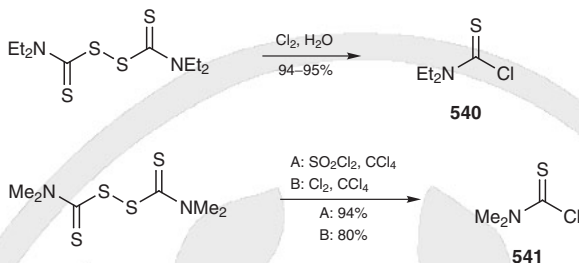
CAUTION: Thiophosgene (CSCl_2) is an intravenous poison. It is moderately toxic upon ingestion and is a skin, mucous membrane, and eye irritant. This reagent should be handled with care.

A stirred soln of thiophosgene (**1**; 2.1 g, 18 mmol) in dry pentane (50 mL) was kept at -128°C (pentane/liq N_2 bath). With a syringe *N*-methyl-*N*-(trimethylsilyl)aniline (**535**; 2.2 g, 12 mmol) was slowly injected through a rubber septum. After the addition the mixture was allowed to warm to rt. The precipitated product was collected by filtration and recrystallized (CHCl_3 /petroleum ether); yield: 1.7 g (76%); mp $37\text{--}38^\circ\text{C}$.

18.10.13.1.2

Method 2: From Thiuram Disulfides

N,N-Dialkylthiocarbamoyl chlorides are synthesized by the reaction of the corresponding tetraalkylthiuram disulfide with chlorine gas or sulfuryl chloride, for example, diethylthiocarbamoyl chloride (**540**) is synthesized by reaction of tetraethylthiuram sulfide with chlorine gas,^[606] while dimethylthiocarbamoyl chloride (**541**) is synthesized by reaction of tetramethylthiuram disulfide with sulfuryl chloride in 94% yield^[607] or with chlorine gas in 80% yield (Scheme 209).^[608]

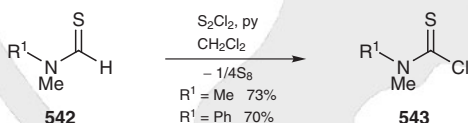
Scheme 209 Synthesis of N,N-Disubstituted Thiocarbamoyl Chlorides^[606–608]**Diethylthiocarbamoyl Chloride (540):**^[606]

A 200-mL three-necked flask, equipped with a mechanical stirrer arranged to permit the escape of gas, a thermometer, and a gas inlet tube 10 mm in diameter, was placed in a vessel to which cooling H_2O may be added. The entire apparatus was placed in a well-ventilated hood. The flask was charged with dry molten tetraethylthiuram disulfide (74 g, 0.25 mol). The molten mass was stirred vigorously, and Cl_2 was passed through a safety trap and was introduced below the surface of the liquid through the inlet tube. The reaction was exothermic, and the temperature was held at 70–75 °C by adjusting the rate of Cl_2 addition and with cold water cooling. After approximately 84.5 mmol Cl_2 had been absorbed, the temperature was lowered to 50–55 °C and maintained for the remainder of the chlorination. When about 90% of the theoretical amount of Cl_2 had been added, S_8 begun to precipitate and the mixture changed from a clear yellow-red soln to a cloudy yellow mixture. The reaction was complete when Cl_2 (18 g, 0.25 mol) had been absorbed (measured by gain in weight of the mixture). The chlorination time was about 40 min. The crude product, at 50 °C, consisted of a red-yellow upper layer of diethylthiocarbamoyl chloride saturated with S_8 and a viscous lower layer of amorphous S_8 saturated with diethylthiocarbamoyl chloride. The mechanical stirrer was replaced by a 6-inch glass-helix-packed column arranged for distillation. The diethylthiocarbamoyl chloride was distilled under reduced pressure, bp 80–85 °C/1 Torr; yield: 71–72 g (94–95%); mp: 48–51 °C.

18.10.13.1.3

**Method 3:
From Thioformamides**

Thiocarbamoyl chloride derivatives **543** are prepared by reaction of thioformamides **542** with sulfur monochloride in the presence of pyridine (Scheme 210).^[609]

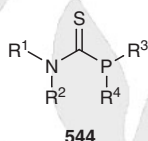
Scheme 210 Synthesis of Thiocarbamoyl Chloride Derivatives^[609]**Dimethylthiocarbamoyl Chloride (543, R¹ = Me); Typical Procedure:**^[609]

To a soln of S_2Cl_2 (27 g, 0.2 mol) and pyridine (15.8 g, 0.2 mol) in CH_2Cl_2 (200 mL) was added dimethylthioformamide (**542**, $\text{R}^1 = \text{Me}$; 17.8 g, 0.2 mol). After refluxing the soln, the mixture was added to either benzene (**CAUTION: carcinogen**) or Et_2O . The precipitate of pyridinium chloride was removed by filtration and the solvent was concentrated. The product was purified by distillation; yield: 73%; mp 40–42 °C.

18.10.14 **Product Subclass 14:**
Phosphinecarbothioamides

This product subclass, phosphinecarbothioamides, have the structure **544** (Scheme 211) and are thiocarbonyl derivatives with one nitrogen and one phosphorus function.^[610] These species also named thiocarbamoylphosphines and phosphinoformamides, are generally used as ligands in organometallic chemistry. This section is organized according to the principal reagents used as primary sources for the synthesis of these compounds.

Scheme 211 Phosphinecarbothioamides

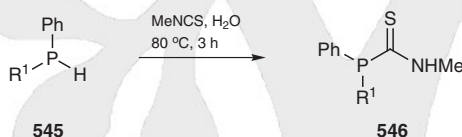


18.10.14.1 **Synthesis of Product Subclass 14**

18.10.14.1.1 **Method 1:**
From Isothiocyanates

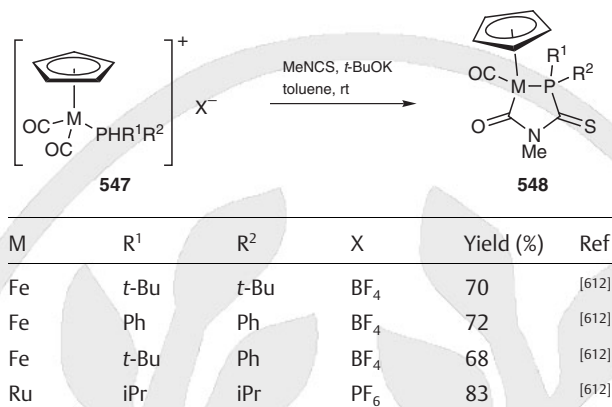
A series of alkylaryl-substituted *N*-methylphosphinecarbothioamides **546** is synthesized from the racemic secondary phosphines **545** and methyl isothiocyanate (Scheme 212).^[611]

Scheme 212 Synthesis of Alkylaryl-Substituted *N*-Methylphosphinecarbothioamides^[611]

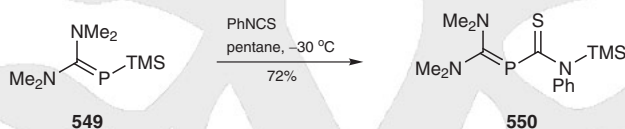


R ¹	Yield (%)	Ref
Me	43	[611]
Et	56	[611]
iPr	58	[611]
<i>t</i> -Bu	35	[611]
Cy	67	[611]
menthyl	52	[611]
neomenthyl	35	[611]

Deprotonation of the cationic phosphine complexes **547** with potassium *tert*-butoxide in the presence of methyl isothiocyanate yields the five-membered phosphametallacycles **548** (Scheme 213).^[612]

Scheme 213 Synthesis of Five-Membered Phosphametallacycles^[612]

Reaction of [bis(dimethylamino)methylene](trimethylsilyl)phosphine (**549**) with phenyl isothiocyanate in pentane at -30°C affords the yellow orange *N*-(trimethylsilyl)-substituted [bis(dimethylamino)methylene]phosphinecarbothioamide **550** in 72% yield (Scheme 214).^[613]

Scheme 214 Synthesis of *N*-(Trimethylsilyl)-Substituted [Bis(dimethylamino)methylene]phosphinecarbothioamide^[613]

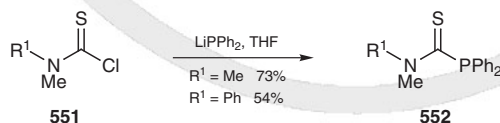
1-[Bis(dimethylamino)methylene]-*N*-phenyl-*N*-(trimethylsilyl)phosphinecarbothioamide (**550**):^[613]

A soln of phenyl isothiocyanate (0.17 g, 1.26 mmol) in pentane (10 mL) was added dropwise to a cold soln (-30°C) of [bis(dimethylamino)methylene](trimethylsilyl)phosphine (**549**; 0.26 g, 1.26 mmol) in pentane (30 mL) to afford pure product as an orange powder; yield: 0.31 g (72%).

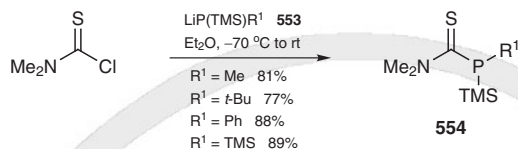
18.10.14.1.2

Method 2: From Halothioamides

The *N*-methyl-1,1-diphenylphosphinecarbothioamides **552** are prepared by reaction of *N,N*-disubstituted thiocarbonyl chlorides **551** with lithium diphenylphosphide (Scheme 215).^[614]

Scheme 215 Synthesis of *N*-Methyl-1,1-diphenylphosphinecarbothioamides^[614]

However, the more nucleophilic lithium (trimethylsilyl)phosphides **553** react with dimethylthiocarbonyl chloride at -70°C to give *N,N*-dimethyl-1-(trimethylsilyl)phosphinecarbothioamides **554** in 77–89% yield (Scheme 216).^[502]

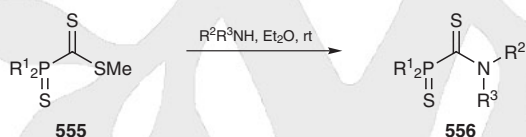
Scheme 216 Synthesis of *N,N*-Dimethyl-1-(trimethylsilyl)phosphinecarbothioamides^[502]***N,N*-1-Trimethyl-1-(trimethylsilyl)phosphinecarbothioamide (554, R¹ = Me);****Typical Procedure:**^[502]

To a suspension of dimethylthiocarbamoyl chloride (5.7 g, 46.1 mmol) in dry Et₂O (50 mL) was added lithium methyl(trimethylsilyl)phosphide (**553**, R¹ = Me; 1 equiv) in Et₂O [prepared from reaction of methyl(trimethylsilyl)phosphine (5.5 g, 45.8 mmol) with 1.6 M MeLi in Et₂O (28.6 mL) at -70 °C]. After the filtration of lithium chloride, the solvent was removed to give the product; yield: 7.7 g (81%).

18.10.14.1.3

**Method 3:
Thiophosphoryldithioformate**

Thiophosphorylthioformamide derivatives **556** are prepared in 30–85% yield by aminolysis of thiophosphoryldithioformates **555** (Scheme 217). Thiophosphoryldithioformates **555** (R¹ = Et, Ph) react readily with ammonia and primary aliphatic amines with moderate steric hindrance.^[615]

Scheme 217 Synthesis of Thiophosphorylthioformamide Derivatives^[615]

R ¹	R ²	R ³	Yield (%)	Ref
Et	H	H	40	[615]
Et	H	Me	85	[615]
Et	H	<i>i</i> Pr	60	[615]
Et	H	Et	30	[615]
Ph	H	H	40	[615]
Ph	H	Me	50	[615]
Ph	H	<i>i</i> Pr	45	[615]
Ph	Me	Me	40	[615]

Thiophosphorylthioformamides 556; General Procedure:^[615]

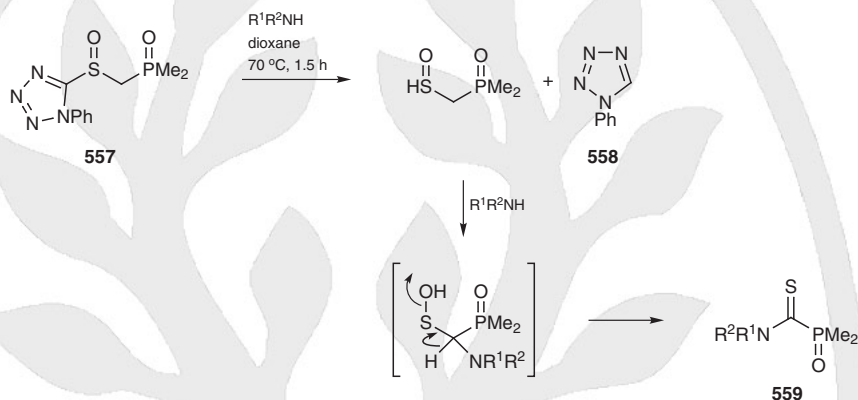
The methyl esters **555** (10 mmol) were dissolved in Et₂O (10 mL) and excess amine was added at rt. In most cases the reaction was complete within 1 min and was accompanied by evolution of MeSH and a change of color from red to yellow. The soln was concentrated to dryness and the product **556** was purified by recrystallization.

18.10.14.1.4

Methods 4:
Miscellaneous Methods

Phosphinecarbothioamides **559** are prepared by the thermolysis of the hetaryl-substituted sulfoxide **557** in the presence of several amines, such as aniline, benzylamine, and morpholine. These products **559** and 1-phenyl-1*H*-tetrazole (**558**) are thought to be formed by the addition of amines to the initially formed sulfine and then elimination of water (Scheme 218).^[616]

Scheme 218 Synthesis of Phosphinecarbothioamides^[616]



R ¹ R ² NH	Time (h)	Yield (%)		Ref
		558	559	
PhNH ₂	1.5	83	50	[616]
BnNH ₂	2.5	99	50	[616]
iPr ₂ NH	1.5	81	0	[616]
piperidine	0.75	99	52	[616]
morpholine	1.0	75	53	[616]
1 <i>H</i> -pyrrole	0.75	82	52	[616]
1 <i>H</i> -imidazole	5.0	99	0	[616]

Phosphinecarbothioamide 559; General Procedure;^[616]

To a stirred soln of **557** (56 mg, 0.2 mmol) in dioxane (1.5 mL) was added aniline (0.042 mL, 0.46 mmol) at 70 °C. This mixture was stirred at 70 °C for 1.5 h. After cooling, the solvent was evaporated and the residual yellow oil was separated by preparative layer chromatography (silica gel, EtOAc/hexane 1:1). Products **559** as a yellow crystals (mp 139–147 °C) and **558** were obtained in 50 and 83% yield, respectively.

References

- [1] Duus, F., In *Comprehensive Organic Chemistry*, Barton, D. H. R.; Ollis, W. D., Eds.; Pergamon: Oxford, (1979); Vol. 3, p 373.
- [2] Kleinpeter, E.; Pihlaja, K., In *Comprehensive Organic Functional Group Transformations*, Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds.; Pergamon: Oxford, UK, (1995); Vol. 6, p 527.
- [3] Reich, H. J.; Trend, J. E., *J. Org. Chem.*, (1973) **38**, 2637.
- [4] Allgeier, H.; Winkler, T., *Tetrahedron Lett.*, (1976), 215.
- [5] Raasch, M. S., *J. Org. Chem.*, (1975) **40**, 161.
- [6] Zwanenburg, B.; Thijs, L.; Strating, J., *Tetrahedron Lett.*, (1969), 4461.
- [7] Middleton, W. J.; Howard, E. G.; Sharkey, W. H., *J. Am. Chem. Soc.*, (1961) **83**, 2588.
- [8] Middleton, W. J.; Howard, E. G.; Sharkey, W. H., *J. Org. Chem.*, (1965) **30**, 1375.
- [9] Einfeld, T. S.; Maul, C.; Chichinin, A.; Gericke, K.-H., *J. Chem. Phys.*, (2002) **117**, 1123.
- [10] Waterfeld, A., *Chem. Ber.*, (1990) **123**, 1635.
- [11] Munavalli, S.; Rossman, D. I.; Rohrbach, D. K.; Ferguson, C. P.; Szafraniec, L. J., *J. Fluorine Chem.*, (1992) **59**, 91.
- [12] Munavalli, S.; Rossman, D. I.; Rohrbach, D. K.; Ferguson, C. P.; Banks, H. D., *J. Fluorine Chem.*, (1993) **60**, 85.
- [13] Brosius, A.; Haas, A.; Pryka, M., *Chem. Ber.*, (1994) **127**, 457.
- [14] Maegerlein, H.; Meyer, G.; Rupp, H. D., *Synthesis*, (1974), 26.
- [15] Kraatz, U., In *Houben-Weyl*, (1983); Vol. E 4, p 409.
- [16] Klabunde, K. J.; White, C. M.; Efner, H. F., *Inorg. Chem.*, (1974) **13**, 1778.
- [17] Steudel, R., *Angew. Chem.*, (1967) **79**, 649; *Angew. Chem. Int. Ed. Engl.*, (1967) **6**, 635.
- [18] Sharma, S., *Sulfur Rep.*, (1986) **5**, 1.
- [19] Sharma, S., *Synthesis*, (1978), 803.
- [20] Dyson, G. M., *Org. Synth., Coll. Vol. I*, (1941), 165.
- [21] Steudel, R., *Z. Anorg. Allg. Chem.*, (1968) **361**, 180.
- [22] Steudel, R., *Z. Naturforsch., B*, (1966) **21**, 1106.
- [23] Yarovenko, N. N.; Vasil'eva, A. S., *Zh. Obshch. Khim.*, (1959) **29**, 3792.
- [24] Henn, R.; Sundermeyer, W.; Pritzkow, H., *Chem. Ber.*, (1987) **120**, 1499.
- [25] Haas, A.; Mikolajczak, J., *Chem. Ber.*, (1981) **114**, 829.
- [26] Henn, R.; Sundermeyer, W., *J. Fluorine Chem.*, (1988) **39**, 329.
- [27] Eschwey, M.; Sundermeyer, W.; Stephenson, D., *Chem. Ber.*, (1983) **116**, 1623.
- [28] Holoch, J.; Sundermeyer, W., *Chem. Ber.*, (1986) **119**, 269.
- [29] Veenstra, G. F.; Zwanenburg, B., *Recl. Trav. Chim. Pays-Bas*, (1976) **95**, 28.
- [30] Senning, A., *Sulfur Lett.*, (1992) **14**, 275.
- [31] Schork, R.; Sundermeyer, W., *Chem. Ber.*, (1985) **118**, 1415.
- [32] Klason, P., *Ber. Dtsch. Chem. Ges.*, (1887) **20**, 2384.
- [33] Delepine, M., *Bull. Soc. Chim. Fr.*, (1911) **9**, 901.
- [34] Kevill, D. N.; D'Souza, M. J., *Can. J. Chem.*, (1999) **77**, 1118.
- [35] Kevill, D. N.; D'Souza, M. J., *J. Chem. Soc., Perkin Trans. 2*, (1997), 1721.
- [36] Kevill, D. N.; D'Souza, M. J.; Anderson, S. W., *J. Org. Chem.*, (1991) **56**, 1845.
- [37] McKinnon, D. M.; Queen, A., *Can. J. Chem.*, (1972) **50**, 1401.
- [38] Ostrogovich, G.; Csunderlik, C.; Bacaloglu, R., *J. Prakt. Chem.*, (1975) **317**, 62.
- [39] Martinez, M. A.; Vega, J. C., *Synthesis*, (1986), 760.
- [40] Martin, D.; Mucke, W., *Chem. Ber.*, (1965) **98**, 2059.
- [41] Strum, B.; Gattow, G., *Z. Anorg. Allg. Chem.*, (1984) **508**, 136.
- [42] Schroll, A. L.; Barany, G., *J. Org. Chem.*, (1986) **51**, 1866.
- [43] Zaim, O., *Tetrahedron Lett.*, (1999) **40**, 8059.
- [44] Garmaise, D. L.; Uchiyama, A.; McKay, A. F., *J. Org. Chem.*, (1962) **27**, 4509.
- [45] Walter, W.; Bode, K. B., *Justus Liebigs Ann. Chem.*, (1966) **692**, 108.
- [46] Walter, W.; Bode, K. B., *Justus Liebigs Ann. Chem.*, (1962) **681**, 64.
- [47] Reich, P.; Martin, D., *Chem. Ber.*, (1965) **98**, 2063.
- [48] Walter, W.; Bode, K. D., *Angew. Chem.*, (1967) **79**, 285; *Angew. Chem. Int. Ed. Engl.*, (1967) **6**, 281.
- [49] Saljoughian, M.; Morimoto, H.; Williams, P. G., *J. Chem. Soc., Perkin Trans. 1*, (1990), 1803.
- [50] Banert, K.; Groth, S., *Angew. Chem.*, (1992) **104**, 865; *Angew. Chem. Int. Ed. Engl.*, (1992) **31**, 866.
- [51] Ponaras, A. A.; Zaim, Ö.; Pazo, Y.; Ohannesian, L., *J. Org. Chem.*, (1988) **53**, 1110.

- [52] Holm, A.; Christophersen, C.; Ottersen, T.; Hope, H.; Christensen, A., *Acta Chem. Scand., Ser. B*, (1977) **31**, 687.
- [53] Barany, G.; Schroll, A. L.; Mott, A. W.; Halsrud, D. A., *J. Org. Chem.*, (1983) **48**, 4750.
- [54] Mott, A.; Barany, G., *J. Chem. Soc., Perkin Trans. 1*, (1984), 2615.
- [55] Barany, G., *Tetrahedron Lett.*, (1983) **24**, 5683.
- [56] Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C., *Tetrahedron*, (1993) **49**, 7193.
- [57] Martineau, E.; Milne, J. B., *J. Chem. Soc. D*, (1971), 1327.
- [58] Lawlor, L.; Passmore, J., *Inorg. Chem.*, (1979) **18**, 2923.
- [59] McMahon, T. B.; Northcott, C. J., *Can. J. Chem.*, (1978) **56**, 1069.
- [60] Strum, B.; Gattow, G., *Z. Anorg. Allg. Chem.*, (1983) **502**, 7.
- [61] Evans, J. A.; Hacker, M. J.; Kemmit, R. D. W.; Russell, D. R.; Stocks, J., *J. Chem. Soc., Chem. Commun.*, (1972), 72.
- [62] Goerdeler, J.; Hohage, H., *Chem. Ber.*, (1973) **106**, 1487.
- [63] Haas, A.; Klug, W.; Marsmann, H., *Chem. Ber.*, (1972) **105**, 820.
- [64] Strum, B.; Gattow, G., *Z. Anorg. Allg. Chem.*, (1984) **508**, 136.
- [65] Nakayama, J.; Dan, S.; Hoshino, M., *J. Chem. Soc., Perkin Trans. 1*, (1981), 413.
- [66] El-Sayed, I.; Abdel-Megeed, M. F.; Yassin, S. M.; Senning, A., *Sulfur Rep.*, (1995) **16**, 235.
- [67] Hawata, M. A.; El-Torgoman, A. M.; El-Kousy, S. M.; Ismail, A. E.; Madsen, J. O.; Sotofte, I.; Lund, T.; Senning, A., *Eur. J. Org. Chem.*, (2000) **14**, 2583.
- [68] El-Sayed, I.; Senning, A., *Sulfur Lett.*, (2002) **25**, 263.
- [69] Strum, B.; Gattow, G., *Z. Anorg. Allg. Chem.*, (1984) **509**, 67.
- [70] Strum, B.; Gattow, G., *Z. Anorg. Allg. Chem.*, (1984) **509**, 61.
- [71] Haas, V. A.; Koch, B.; Welcman, N., *Z. Anorg. Allg. Chem.*, (1976) **427**, 114.
- [72] Moltzen, E. K.; Senning, A.; Kramer, M. P.; Klabunde, K. J., *J. Org. Chem.*, (1984) **49**, 3854.
- [73] Gattow, G.; Behrendt, W., *Top. Sulfur Chem.*, (1977) **2**, 1.
- [74] Klabunde, K. J.; Kramer, M. P.; Senning, A.; Moltzen, E. K., *J. Am. Chem. Soc.*, (1984) **106**, 263.
- [75] Koch, K. N.; Moller, J.; Senning, A., *Sulfur Lett.*, (1998) **21**, 53.
- [76] Viola, H.; Mayer, R., *Z. Chem.*, (1979), 289.
- [77] Haas, A.; Kempf, K. W., *Tetrahedron*, (1984) **40**, 4963.
- [78] Hansen, H. C.; Senning, A.; Hazell, R. G., *Tetrahedron*, (1985) **41**, 5145.
- [79] Braun, J. V.; Schornig, L., *Ber. Dtsch. Chem. Ges.*, (1925) **58**, 2151.
- [80] Al-Kazimi, H. R.; Tarbell, D. S.; Plant, D., *J. Am. Chem. Soc.*, (1955) **77**, 2479.
- [81] Challenger, F.; Masson, E. A.; Holdsworth, E. C.; Emmott, R., *J. Chem. Soc.*, (1953), 292.
- [82] Kim, S.; Yi, K. Y., *Tetrahedron Lett.*, (1985), **26**, 1661.
- [83] Kuroboshi, M.; Hiyama, T., *Synlett*, (1994), 251.
- [84] Krebs, A. W.; Tholke, B.; Pforr, K.-I.; Konig, W.; Scharwachter, K.; Grimme, S.; Vogtle, F.; Sobanski, A.; Schramm, J.; Hormes, J., *Tetrahedron: Asymmetry*, (1999) **10**, 3483.
- [85] Krief, A.; Provins, L.; Froidbise, A., *Tetrahedron Lett.*, (2002) **43**, 7881.
- [86] Nazaré, M.; Waldmann, H., *Angew. Chem.*, (2000) **112**, 1171; *Angew. Chem. Int. Ed.*, (2000) **39**, 1125.
- [87] Kuwatani, M.; Yoshida, T.; Kusaka, A.; Iyoda, M., *Tetrahedron Lett.*, (2000) **41**, 359.
- [88] Kreiser, W.; Korner, F., *Helv. Chim. Acta*, (1999) **82**, 1610.
- [89] Jahnisch, K., *Liebigs Ann./Recl.*, (1997), 757.
- [90] Alcón, M.; Poch, M.; Moyano, A.; Pericàs, M. A., *Tetrahedron: Asymmetry*, (1997) **8**, 2967.
- [91] Canas, M.; Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A., *Tetrahedron Lett.*, (1991) **32**, 6931.
- [92] Alcón, M.; Canas, M.; Poch, M.; Moyano, M.; Pericàs, M. A.; Riera, A., *Tetrahedron Lett.*, (1994) **35**, 1589.
- [93] Dressel, J.; Chasey, K. L.; Paquette, L. A., *J. Am. Chem. Soc.*, (1988) **110**, 5479.
- [94] Lipshutz, B. H.; Nguyen, S. L.; Elworthy, T. R., *Tetrahedron*, (1988) **44**, 3355.
- [95] Augusstyn, K.; Rozenski, J.; van der Aerschot, A.; Janssen, G.; Herdewijijn, P., *J. Org. Chem.*, (1993) **58**, 2977.
- [96] Harusawa, S.; Shibata, N.; Yamazaki, N.; Sakanoue, S.; Ishida, T.; Yoneda, R.; Kurihara, T., *Chem. Pharm. Bull.*, (1989) **37**, 264.
- [97] Narasimhamurthy, N.; Samuelson, A. G., *Tetrahedron Lett.*, (1988) **29**, 827.
- [98] Faure, A.; Decostes, G., *Synthesis*, (1978), 286.
- [99] Decostes, G.; Faure, A.; Martin, J. C., *J. Carbohydr., Nucleosides, Nucleotides*, (1974) **1**, 133.
- [100] Labar, D.; Dumont, W.; Hevesi, L.; Krief, A., *Tetrahedron Lett.*, (1978), 1145.

- [101] Shasha, B. S.; Doane, W. M.; Russell, C. R.; Rist, C. E., *Carbohydr. Res.*, (1966) **3**, 121.
- [102] Tang, R.; Fraser-Reid, B., *J. Org. Chem.*, (1992) **57**, 1065.
- [103] Chu, C. K.; Bhaddi, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; Van Roey, P., *J. Org. Chem.*, (1989) **54**, 2217.
- [104] Neuman, K., *Acta Chem. Scand.*, (1992) **46**, 913.
- [105] Miura, K.; Fujisawa, N.; Saito, H.; Wang, D.; Hosomi, A., *Org. Lett.*, (2001) **3**, 2591.
- [106] Hamada, T.; Mizojiri, R.; Urabe, H.; Sato, F., *J. Am. Chem. Soc.*, (2000) **122**, 7138.
- [107] Castro, E. A.; Santos, J. G.; Tellez, J.; Umana, M., *J. Org. Chem.*, (1997) **62**, 6568.
- [108] Castro, E. A.; Garcia, P.; Leandro, L.; Quesieh, N.; Rebolledo, A.; Santos, J. G., *J. Org. Chem.*, (2000) **65**, 9047.
- [109] Castro, E. A.; Leandro, L.; Quesieh, N.; Santos, J. G., *J. Org. Chem.*, (2001) **66**, 6130.
- [110] Castro, E. A.; Galvez, A.; Leandro, L.; Santos, J. G., *J. Org. Chem.*, (2002) **67**, 4309.
- [111] Castro, E. A., *Chem. Rev.*, (1999) **99**, 3505.
- [112] Gonzalez-Bello, C.; Coggins, J. R.; Hawkins, A. R.; Abell, C., *J. Chem. Soc., Perkin Trans. 1*, (1999), 849.
- [113] Bocquel, P.; Loustau Cazalet, C.; Chapleur, Y.; Samreth, S.; Bellamy, F., *Tetrahedron Lett.*, (1992) **33**, 1997.
- [114] Manna, S.; Yadagirz, P.; Falck, J. R., *J. Chem. Soc., Chem. Commun.*, (1987), 1324.
- [115] Barton, D. H. R.; Blundell, P.; Dorchak, J.; Jang, D. O.; Jaszberenyi, J. Cs., *Tetrahedron*, (1991) **47**, 8969.
- [116] Koreeda, M.; George, I. R., *Chem. Lett.*, (1990), 83.
- [117] Hsu, F.-L.; Zhang, X.; Hong, S.-S.; Berg, F. J.; Miller, D. D., *Heterocycles*, (1994) **39**, 801.
- [118] Millan, D. S.; Prager, R. H., *J. Chem. Soc., Perkin Trans. 1*, (1998), 3245.
- [119] Xi, Z.-F.; Suemune, H.; Sakai, K., *Tetrahedron: Asymmetry*, (1993) **4**, 973.
- [120] Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs., *Tetrahedron*, (1993) **49**, 2793.
- [121] Liu, L.; Postema, M. H. D., *J. Am. Chem. Soc.*, (2001) **123**, 8602.
- [122] Thoma, G.; Magnani, J. L.; Patton, J. T.; Ernst, B.; Jahnke, W., *Angew. Chem.*, (2001) **113**, 1995; *Angew. Chem. Int. Ed.*, (2001) **40**, 1941.
- [123] Staab, H. A., *Angew. Chem.*, (1961) **73**, 148.
- [124] Larsen, C.; Steliou, K.; Harpp, D. N., *J. Org. Chem.*, (1978) **43**, 337.
- [125] Sandris, C., *Tetrahedron*, (1968) **24**, 3589.
- [126] Hauptmann, E.; Fagan, P. J.; Marshall, M., *Organometallics*, (1999) **18**, 2061.
- [127] Kim, S.; Lawson, J. A.; Pratico, D.; Fitzgerald, G. A.; Rokach, J., *Tetrahedron Lett.*, (2002) **43**, 2801.
- [128] De Angelis, F.; Marzi, M.; Minetti, P.; Misiti, D.; Muck, S., *J. Org. Chem.*, (1997) **62**, 4159.
- [129] Goto, M.; Miyoshi, I.; Ishii, Y.; Ogasawara, Y.; Kakimoto, Y.-I.; Nagumo, S.; Nishida, A.; Kawahara, N.; Nishida, M., *Tetrahedron*, (2002) **58**, 2339.
- [130] Zhang, Z.; Xiong, Z.; Zheng, G.; Li, Y., *Tetrahedron: Asymmetry*, (2001) **12**, 2137.
- [131] Voight, E. A.; Rein, C.; Burke, S. D., *J. Org. Chem.*, (2002) **67**, 8489.
- [132] Burke, S. D.; Voight, E. A., *Org. Lett.*, (2001) **3**, 237.
- [133] Lester, M. G.; Giblin, G. M. P.; Inglis, G. G. A.; Procopiou, P. A.; Ross, B. C.; Watson, N. S., *Tetrahedron Lett.*, (1993) **34**, 4357.
- [134] Mills, S.; Desmond, R.; Reamer, R. A.; Volante, R. P.; Schinkai, I., *Tetrahedron Lett.*, (1988) **29**, 281.
- [135] Yoshida, M.; Watanabe, T.; Ishikawa, T., *Tetrahedron Lett.*, (2002) **43**, 6751.
- [136] Rubin, Y.; Knobler, C. B.; Diederich, F., *J. Am. Chem. Soc.*, (1990) **112**, 1607.
- [137] Alibés, R.; Bourdelande, J. L.; Font, J.; Parella, T., *Tetrahedron*, (1996) **52**, 1279.
- [138] Jimenez, J. M.; Rife, J.; Ortuño, R. M., *Tetrahedron: Asymmetry*, (1996) **7**, 537.
- [139] Kato, N.; Nakanishi, K.; Takeshita, H., *Bull. Chem. Soc. Jpn.*, (1986) **59**, 1109.
- [140] Wagaman, M. W.; Bellmann, E.; Cufullu, M.; Grubbs, R. H., *J. Org. Chem.*, (1997) **62**, 9076.
- [141] Adiyaman, M.; Lawson, J. A.; Hwang, S.-W.; Khanapure, S. P.; FitzGerald, G. A.; Rokach, J., *Tetrahedron Lett.*, (1996) **37**, 4849.
- [142] Yu, B.; Yang, Z., *Org. Lett.*, (2001) **3**, 377.
- [143] Manchand, P. S.; Belica, P. S.; Holman, M. J.; Huang, T.-N.; Maehr, H.; Tam, S. Y.-K.; Yang, R. T., *J. Org. Chem.*, (1992) **57**, 3473.
- [144] Buenger, G. S.; Nair, V., *Synthesis*, (1990), 962.
- [145] Crich, D.; Huang, X.; Newcomb, M., *Org. Lett.*, (1999) **1**, 225.
- [146] Lautens, M.; Colucci, J. T.; Hibert, S.; Smith, N. D.; Bouchain, G., *Org. Lett.*, (2002) **4**, 1879.
- [147] Lavyssiere, H.; Dousse, G.; Satge, J., *Recl. Trav. Chim. Pays-Bas*, (1988) **107**, 440.
- [148] Lavyssiere, H.; Dousse, G., *J. Organomet. Chem.*, (1985) **297**, C17.

- [149] Tsuda, Y.; Sato, Y.; Kakimoto, K.; Kanemitsu, K., *Chem. Pharm. Bull.*, (1992) **40**, 1033.
- [150] Haque, M. E.; Kikuchi, T.; Kanemitsu, K.; Tsuda, Y., *Chem. Pharm. Bull.*, (1987) **35**, 1016.
- [151] Haque, M. E.; Kikuchi, T.; Kanemitsu, K.; Tsuda, Y., *Chem. Pharm. Bull.*, (1987) **34**, 430.
- [152] Janssen, M. J., In *The Chemistry of Carboxylic Acids and Esters*, Patai, S., Ed.; Interscience: New York, (1969); chapter 15.
- [153] Bogemann, M.; Petersen, S.; Schultz, O.-E.; Soll, H., In *Houben-Weyl*, (1955); Vol. 9, p 804.
- [154] McKenzie, S., In *Organic Compounds of Sulfur, Selenium, and Tellurium: A Specialist Periodical Report*, Reid, D. H., Ed.; The Chemical Society: London, (1970); Vol. 1, chapter 5.
- [155] Nace, H. R., *Org. React. (N. Y.)*, (1962) **12**, 57.
- [156] Corey, E. J.; Winter, R. A. E., *J. Am. Chem. Soc.*, (1963) **85**, 2677.
- [157] Corey, E. J.; Carey, F. A.; Winter, R. A. E., *J. Am. Chem. Soc.*, (1965) **87**, 934.
- [158] Corey, E. J.; Schulman, J. I., *Tetrahedron Lett.*, (1968), 3655.
- [159] Barton, D. H. R.; McCombie, S. W., *J. Chem. Soc., Perkin Trans. 1*, (1975), 1574.
- [160] Barton, D. H. R.; Motherwell, W. B.; Stange, A., *Synthesis*, (1981), 743.
- [161] Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C., *J. Org. Chem.*, (1993) **58**, 6838.
- [162] Chu, C. K.; Doboszewski, B.; Schmidt, W.; Ullas, G. V.; Van Roey, P., *J. Org. Chem.*, (1989) **54**, 2767.
- [163] Franck-Neumann, M.; Sedrati, M.; Vigneron, J.-P.; Bloy, V., *Angew. Chem.*, (1985) **97**, 995; *Angew. Chem. Int. Ed. Engl.*, (1985) **24**, 996.
- [164] Duboudin, G.; Ratier, M.; Trouve, B., *J. Organomet. Chem.*, (1987) **331**, 181.
- [165] Rao, Y. K.; Nagarajan, M., *Tetrahedron Lett.*, (1988) **29**, 107.
- [166] Clive, D. L. J.; Magnuson, S. R.; Manning, H. W.; Mayhew, D. L., *J. Org. Chem.*, (1996) **61**, 2095.
- [167] Koert, U.; Krauss, R.; Weinig, H.-G.; Heumann, C.; Ziemer, B.; Mugge, C.; Seydack, M.; Bendig, J., *Eur. J. Org. Chem.*, (2001), 575.
- [168] Crimmins, M. T.; DeLoach, J. A., *J. Am. Chem. Soc.*, (1986) **108**, 800.
- [169] Weyerstahl, P.; Brendel, J., *Liebigs Ann. Chem.*, (1992), 669.
- [170] Ferrier, R. J.; Petersen, P., *J. Chem. Soc. Perkin Trans. 1*, (1992), 2023.
- [171] Alibes, R.; Bourdelande, J. L.; Font, J., *Tetrahedron Lett.*, (1994) **35**, 2587.
- [172] Carda, M.; Marco, J. A., *Tetrahedron Lett.*, (1991) **32**, 5191.
- [173] Trost, B. M.; Fray, M. J., *Tetrahedron Lett.*, (1988) **29**, 2163.
- [174] Pettus, T. R. R.; Inoue, M.; Chen, X.-T.; Danishefsky, S. J., *J. Am. Chem. Soc.*, (2000) **122**, 6160.
- [175] Zuurmond, H. M.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H., *Tetrahedron*, (1993) **49**, 6501.
- [176] Zuurmond, H. M.; van der Klein, P. A. M.; van der Marel, G. A.; van Boom, J. H., *Tetrahedron Lett.*, (1992) **33**, 2063.
- [177] Gervay, J.; Danishefsky, S., *J. Org. Chem.*, (1991) **56**, 5448.
- [178] Robins, M. J.; Wilson, J. S., *J. Am. Chem. Soc.*, (1981) **103**, 932.
- [179] Bartlett, P. A.; McLaren, K. L.; Ting, P. C., *J. Am. Chem. Soc.*, (1988) **110**, 1633.
- [180] Calvo-Mateo, A.; Camarasa, M.-J.; Diaz-Ortiz, A.; De las Heras, F. G.; Alemany, A., *Tetrahedron*, (1988) **44**, 4895.
- [181] Robins, M. J.; Madej, D.; Hansske, F.; Wilson, J. C.; Gasselin, G.; Bergogne, M.-C.; Imbach, J.-L., *Can. J. Chem.*, (1988) **66**, 1258.
- [182] Seela, F.; Bourgeois, W., *Synthesis*, (1988), 938.
- [183] Seela, F.; Muth, H.-P., *Liebigs Ann. Chem.*, (1988), 215.
- [184] Chris, M.; Tam, H.-D., *Synlett*, (1991), 227.
- [185] Samano, V.; Robins, M. J., *J. Am. Chem. Soc.*, (1992) **114**, 4007.
- [186] Jones, M. F.; Myers, P. L.; Robertson, C. A.; Storer, R.; Williamson, C., *J. Chem. Soc., Perkin Trans. 1*, (1991) **10**, 2479.
- [187] Sanghvi, Y. S.; Ross, B.; Bharadwaj, R.; Vasseur, J.-T., *Tetrahedron Lett.*, (1994) **35**, 4697.
- [188] Nagashima, S.; Taishi, T.; Kanematsu, K., *Tetrahedron Lett.*, (1994) **35**, 3577.
- [189] Jung, M. E.; Sledeski, A. W., *J. Chem. Soc., Chem. Commun.*, (1993), 589.
- [190] De Almeida, M. V.; Figueiredo, R. M.; Dos Santos, H. F.; Da Silva, A. D.; De Almeida, W. B., *Tetrahedron Lett.*, (2001) **42**, 2767.
- [191] Takamatsu, T.; Maruyama, T.; Katayama, S.; Hirose, N.; Izawa, K., *Tetrahedron Lett.*, (2001) **42**, 2321.
- [192] Maruyama, T.; Takamatsu, S.; Kozai, S.; Satoh, Y.; Izawa, K., *Chem. Pharm. Bull.*, (1999) **47**, 966.
- [193] Wunk, S. F.; Companioni, D. R.; Neschandimenko, V.; Robbins, M. J., *J. Org. Chem.*, (2002) **67**, 8794.
- [194] Lee, A. W. M.; Chang, W. H.; Wong, H. C., *Synth. Commun.*, (1989) **19**, 547.

- [195] Chang, T.-L.; Chow, H.-F.; Fong, S.; Leung, M.-K.; Tu, J., *J. Chem. Soc., Chem. Commun.*, (1994), 1919.
- [196] Diana, M. B.; Marchetti, M.; Melloni, G., *Tetrahedron: Asymmetry*, (1995) **6**, 1175.
- [197] Weinstock, J.; Lewis, S. N., *J. Am. Chem. Soc.*, (1957) **79**, 6243.
- [198] Zweig, A.; Lehnse, J. E., *J. Am. Chem. Soc.*, (1965) **87**, 2647.
- [199] Tanaka, K.; Uneme, H.; Matsui, S.; Kaji, A., *Bull. Chem. Soc. Jpn.*, (1982) **55**, 2965.
- [200] Bordwell, F. G.; Landis, P. S., *J. Am. Chem. Soc.*, (1958) **80**, 6379.
- [201] Askani, R.; Wieduwilt, M., *Liebigs Ann. Chem.*, (1986), 1104.
- [202] Tomita, K.; Nagano, M., *Chem. Pharm. Bull.*, (1968) **16**, 1911.
- [203] Suryawanshi, S. N.; Rani, A.; Bhakuni, D. S., *Synth. Commun.*, (1990) **20**, 625.
- [204] Mortlock, S. V.; Thomas, E. J., *Tetrahedron Lett.*, (1988) **29**, 2479.
- [205] Ziegler, F. E.; Zheng, Z., *Tetrahedron Lett.*, (1987) **28**, 5973.
- [206] De Groot, A.; Evenhuis, B.; Wynberg, H., *J. Org. Chem.*, (1968) **33**, 2214.
- [207] Price, M. F.; Schore, N. E., *J. Org. Chem.*, (1989) **54**, 5662.
- [208] Vincens, M.; Fadel, R.; Vidal, M., *Tetrahedron*, (1988) **44**, 6345.
- [209] Blazewski, J.-C.; Anselmi, E.; Wakselman, C., *J. Org. Chem.*, (2001) **66**, 1061.
- [210] Salvatore, R. N.; Sahab, S.; Jung, K. W., *Tetrahedron Lett.*, (2001) **42**, 2055.
- [211] Horiguchi, T.; Ritner, C. D.; Croteau, R.; Williams, R. M., *J. Org. Chem.*, (2002) **67**, 4901.
- [212] Chaudhary, A. G.; Chordia, M. D.; Kingston, D. G. I., *J. Org. Chem.*, (1995) **60**, 3260.
- [213] Chen, S.-H.; Wei, J.-M.; Vyas, D. M.; Doyle, T. W.; Farina, V., *Tetrahedron Lett.*, (1993) **34**, 6845.
- [214] Chaudhary, A. G.; Kingston, D. G. I., *Tetrahedron Lett.*, (1993) **34**, 4921.
- [215] Chen, S.-H.; Huang, S.; Kant, J.; Fairchild, C.; Wei, J.-M.; Farina, V., *J. Org. Chem.*, (1993) **58**, 5028.
- [216] Chen, S.-H.; Wei, J.-M.; Farina, V., *Tetrahedron Lett.*, (1993) **34**, 3205.
- [217] Srikrishna, A.; Gharpure, S. J., *J. Org. Chem.*, (2001) **66**, 4379.
- [218] Bensasson, C. S.; Cornforth, J.; Du, M.-H.; Hanson, J. R., *Chem. Commun. (Cambridge)*, (1997), 1509.
- [219] Koriyama, Y.; Nozawa, A.; Hayakawa, R.; Shimizu, M., *Tetrahedron*, (2002) **58**, 9621.
- [220] Kadota, I.; Takamura, H.; Yamamoto, Y., *Tetrahedron Lett.*, (2001) **42**, 3649.
- [221] Miyaoka, H.; Honda, D.; Mitome, H.; Yamada, Y., *Tetrahedron Lett.*, (2002) **43**, 7773.
- [222] Gomez, A. M.; Moreno, E.; Valverde, S.; Lopez, T. C., *Synlett*, (2002), 891.
- [223] Hagiwara, H.; Kobayashi, K.; Miya, S.; Hoshi, T.; Suzuki, T.; Ando, M.; Okamoto, T.; Kobayashi, M.; Yamamoto, I.; Ohtsubo, S.; Kato, M.; Uda, H., *J. Org. Chem.*, (2002) **67**, 5969.
- [224] Crimmins, H. T.; Pace, J.-M.; Nantermetz, P. G., *J. Am. Chem. Soc.*, (2000) **122**, 8453.
- [225] Lange, G. L.; Gottard, C.; Merica, A., *J. Org. Chem.*, (1999) **64**, 6738.
- [226] Sharma, G. V. M.; Vepachedu, S. R., *Tetrahedron*, (1991) **47**, 519.
- [227] Kinoshita, T.; Yoshida, N.; Miwa, T., *Bull. Chem. Soc. Jpn.*, (1990) **63**, 1538.
- [228] Bull, J. R.; Thomson, R. I., *J. Chem. Soc., Perkin Trans. 1*, (1990), 241.
- [229] Gupta, A. K.; Sambasivarao, K.; Opansky, B.; Cook, J. M., *J. Org. Chem.*, (1990) **55**, 4480.
- [230] Wu, J.-C.; Bazin, H.; Chattopadhyaya, J., *Tetrahedron*, (1987) **43**, 2355.
- [231] Gelmi, M. L.; Pocar, D.; Trimarco, P., *Tetrahedron*, (1987) **43**, 3047.
- [232] Kihara, N.; Nakamaki, Y.; Endo, T., *J. Org. Chem.*, (1995) **60**, 473.
- [233] Uenishi, J.; Motoyama, M.; Takahashi, K., *Tetrahedron: Asymmetry*, (1994) **5**, 101.
- [234] Uenishi, J.; Motoyama, M.; Nishiyama, Y.; Wakabayashi, S., *J. Chem. Soc., Chem. Commun.*, (1991), 1421.
- [235] Uenishi, J.; Kubo, Y., *Tetrahedron Lett.*, (1994) **35**, 6697.
- [236] Villemin, D.; Alloum, A. B., *Synth. Commun.*, (1992) **22**, 1351.
- [237] Tomita, K.; Nagano, M., *Chem. Pharm. Bull.*, (1968) **16**, 1324.
- [238] Tomita, K.; Nagano, M.; Oka, H., *Chem. Pharm. Bull.*, (1968) **16**, 914.
- [239] Iyata, T.; Nakano, H., *Bull. Chem. Soc. Jpn.*, (1990) **63**, 3096.
- [240] Chenevert, R.; Paguin, R.; Rodrigue, A., *Synth. Commun.*, (1981) **11**, 817.
- [241] Degani, I.; Fochi, R.; Regondi, V., *Synthesis*, (1979), 178.
- [242] Degani, I.; Fochi, R., *Synthesis*, (1978), 365.
- [243] Haley, N. F.; Fichtner, M. W., *J. Org. Chem.*, (1980) **45**, 2959.
- [244] Brunet, E.; Garcia-Ruano, J. L.; Rodriguez, J. H., *Tetrahedron*, (1984) **40**, 4433.
- [245] Harpp, D. N.; Smith, R. A., *J. Am. Chem. Soc.*, (1984) **104**, 6045.
- [246] Hartung, J.; Schwarz, M.; Svoboda, I.; Fuess, H.; Duarte, M. T., *Eur. J. Org. Chem.*, (1999), 1275.
- [247] Wimalasena, K.; Haines, D. C., *J. Org. Chem.*, (1994) **59**, 6472.
- [248] Barton, D. H. R.; Crich, D.; Potier, P., *Tetrahedron Lett.*, (1985) **26**, 5943.
- [249] Ishida, M.; Ichikawa, K.; Asano, M.; Nakanishi, H.; Kato, S., *Synthesis*, (1987), 349.
- [250] Madding, G. D.; Thompson, M. D., *J. Heterocycl. Chem.*, (1987) **24**, 581.

- [251] Woulfe, S. R.; Miller, M. J., *J. Org. Chem.*, (1986) **51**, 3133.
- [252] Yamazaki, H.; Harada, H.; Matsuzaki, K.; Yoshioka, K.; Takase, M.; Ohki, E., *Chem. Pharm. Bull.*, (1987) **35**, 2243.
- [253] Dhindsa, A. S.; Bryce, M. R.; Lloyd, J. P.; Petty, M. C.; Kobayashi, K.; Tukada, H., *J. Chem. Soc., Chem. Commun.*, (1988), 1391.
- [254] Larsen, J.; Lenoir, C., *Synthesis*, (1989), 134.
- [255] Hartke, K.; Timpe, C., *Heterocycles*, (1993) **35**, 77.
- [256] Lee, L. F.; Schleppnik, F. M.; Howe, R. K., *J. Heterocycl. Chem.*, (1985) **22**, 1621.
- [257] Katritzky, A. R.; Button, M. A. C.; Denisenko, S. E., *Heterocycles*, (2001) **54**, 301.
- [258] Brown, M. D.; Meunier, C. J.; Whitham, G. H., *J. Chem. Soc., Perkin Trans. 1*, (1988), 813.
- [259] Kitamura, T.; Miyake, S.; Kobayashi, S.; Taniguchi, H., *Bull. Chem. Soc. Jpn.*, (1989) **62**, 967.
- [260] Effenberger, F.; Gaupp, S., *Tetrahedron: Asymmetry*, (1999) **10**, 1765.
- [261] Chen, B.-C.; Bednarz, M. S.; Kocy, O. R.; Sundeen, J. E., *Tetrahedron: Asymmetry*, (1998) **9**, 1641.
- [262] Dublanchet, A.-C.; Lusinch, M.; Zard, S. Z., *Tetrahedron*, (2002) **58**, 5715.
- [263] Boiteau, L.; Boivin, J.; Liard, A.; Quiclet-Sire, B.; Zard, S. Z., *Angew. Chem.*, (1998) **110**, 1197; *Angew. Chem. Int. Ed.*, (1998) **37**, 1128.
- [264] Blakskjær, P.; Pedersen, L.; Skrydstrup, T., *J. Chem. Soc., Perkin Trans. 1*, (2001), 910.
- [265] Levi, P.-T. O.; Becker, J. Y.; Ellern, A.; Khodorkovsky, V., *Tetrahedron Lett.*, (2001) **42**, 1571.
- [266] Degani, I.; Fochi, R.; Santi, M., *Synthesis*, (1977), 873.
- [267] Isola, M.; Ciuffarin, E.; Sagramora, L., *Synthesis*, (1976), 326.
- [268] Campagne, E.; Osborn, S. W., *J. Org. Chem.*, (1957) **22**, 561.
- [269] Tedjamulia, M. L.; Tominaga, Y.; Castle, R. N.; Lee, M. L., *J. Heterocycl. Chem.*, (1983) **20**, 1143.
- [270] Hanzlik, R. P.; Weller, P. E.; Desai, J.; Zheng, J.; Hall, L. R.; Slaughter, D. E., *J. Org. Chem.*, (1990) **55**, 2736.
- [271] Meijs, G. F.; Beckwith, A. L. J., *J. Am. Chem. Soc.*, (1986) **108**, 5890.
- [272] Kaszynski, P.; Dougherty, D. A., *J. Org. Chem.*, (1993) **58**, 5209.
- [273] Zhang, B.; Breslow, R., *J. Am. Chem. Soc.*, (1997) **119**, 1676.
- [274] Offer, J.; Boddy, C. N. C.; Dawson, P. E., *J. Am. Chem. Soc.*, (2002) **124**, 4642.
- [275] Dodson, R. M.; Hanson, J. B., *J. Chem. Soc., Chem. Commun.*, (1975), 926.
- [276] Katritzky, A. R.; Grezeskowiak, N.; Jaret, R. S., *J. Chem. Res., Synop.*, (1981), 208.
- [277] Gareau, Y.; Tremblay, M.; Gauvreau, D.; Juteau, H. H., *Tetrahedron*, (2001) **57**, 5739.
- [278] Gala, D.; Chiu, J. S.; Ganguly, A. K.; Girijavallabhan, V. M.; Jaret, R. S.; Jenkins, J. K.; McCombie, S. W.; Nyce, P. L.; Steinman, M., *Tetrahedron*, (1992) **48**, 1175.
- [279] Schonberg, A.; Frese, E.; Knofel, W.; Praefcke, K., *Chem. Ber.*, (1970) **103**, 938.
- [280] Schonberg, A.; Knofel, W.; Frese, E.; Praefcke, K., *Chem. Ber.*, (1970) **103**, 949.
- [281] Breslow, R.; Canary, J. W.; Varney, M.; Wuddell, S. T.; Yang, D., *J. Am. Chem. Soc.*, (1990) **112**, 5212.
- [282] Gareau, Y.; Beauchemin, A., *Heterocycles*, (1998) **48**, 2003.
- [283] Bouhadir, G.; Legrand, N.; Quiclet-Sire, B.; Zard, S. Z., *Tetrahedron Lett.*, (1999) **40**, 277.
- [284] Drake, J. E.; Sarkar, A. B.; Wong, M. L. Y., *Inorg. Chem.*, (1990) **29**, 785.
- [285] Drake, J. E.; Mislankar, A. G.; Yang, J., *Inorg. Chim. Acta*, (1993) **211**, 37.
- [286] Casas, J. S.; Castellano, E. E.; Ellena, J.; Haiduc, H.; Sánchez, A.; Semeniuc, R. F.; Sordo, J., *Inorg. Chim. Acta*, (2002) **329**, 71.
- [287] Drake, J. E.; Mislankar, A. G.; Wong, M. L. Y., *Inorg. Chem.*, (1991) **30**, 2174.
- [288] Boivin, J.; Camara, J.; Zard, S. Z., *J. Am. Chem. Soc.*, (1992) **114**, 7909.
- [289] Karra, R.; Singh, Y. P.; Rai, A. K., *Phosphorus, Sulfur Silicon Relat. Elem.*, (1990) **47**, 357.
- [290] Reddy, N. S.; Ravinder, K.; Krishnainah, P.; Venkateswarlu, Y., *Synlett*, (2001), 625.
- [291] Tiekink, E. R. T., *J. Organomet. Chem.*, (1986) **303**, C53.
- [292] Dakternieks, D.; Di Giacomo, R.; Gable, R. W.; Hoskins, B. F., *J. Organomet. Chem.*, (1988) **353**, 35.
- [293] Dakternieks, D.; Di Giacomo, R.; Gable, R. W.; Hoskins, B. F., *J. Organomet. Chem.*, (1988) **349**, 305.
- [294] Wieber, M.; Schmidt, E.; Burschka, C. H., *Z. Anorg. Allg. Chem.*, (1985) **525**, 127.
- [295] Wieber, M.; Schmidt, E., *Z. Anorg. Allg. Chem.*, (1988) **556**, 189.
- [296] Sakai, S.; Niimi, H.; Kobayashi, Y.; Ishii, Y., *Bull. Chem. Soc. Jpn.*, (1977) **50**, 3271.
- [297] Dakternieks, D.; Giacomo, R. G.; Gable, R. W.; Hoskins, B. F., *J. Am. Chem. Soc.*, (1988) **110**, 6753.
- [298] Cholleton, N.; Gauthier-Gillaizeau, I.; Six, Y.; Zard, S. Z., *Chem. Commun. (Cambridge)*, (2000), 535.
- [299] Galli, R., *J. Org. Chem.*, (1987) **52**, 5349.
- [300] Delduc, P.; Tailhan, C.; Zard, S. Z., *J. Chem. Soc., Chem. Commun.*, (1988), 308.
- [301] Mestre, F.; Tailhan, C.; Zard, S. Z., *Heterocycles*, (1989) **28**, 171.
- [302] Legrand, N.; Quiclet-Sire, B.; Zard, S. Z., *Tetrahedron Lett.*, (2000) **41**, 9815.

- [303] Ferjansčić, Z.; Cekovic, Z.; Saicic, R. N., *Tetrahedron Lett.*, (2000) **41**, 2979.
- [304] Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z., *Tetrahedron Lett.*, (1997) **38**, 1759.
- [305] Biadatti, T.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z., *Tetrahedron Lett.*, (1998) **39**, 19.
- [306] Boivin, J.; Ramos, L.; Zard, S. Z., *Tetrahedron Lett.*, (1998) **39**, 6877.
- [307] Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z., *Tetrahedron Lett.*, (1999) **40**, 2533.
- [308] Boivin, J.; Boutillier, P.; Zard, S. Z., *Tetrahedron Lett.*, (1999) **40**, 2529.
- [309] Boivin, J.; Poithier, J.; Zard, S. Z., *Tetrahedron Lett.*, (1999) **40**, 3701.
- [310] Ollivier, C.; Renaud, P., *J. Am. Chem. Soc.*, (2001) **123**, 4717.
- [311] Tate, E. W.; Zard, S. Z., *Tetrahedron Lett.*, (2002) **43**, 4683.
- [312] Barbier, F.; Pautrat, F.; Quiclet-Sire, B.; Zard, S. Z., *Synlett*, (2002), 811.
- [313] Lusinch, M.; Stanbury, T.; Zard, S. Z., *Chem. Commun. (Cambridge)*, (2002), 1532.
- [314] Gagosz, F.; Zard, S. Z., *Org. Lett.*, (2002) **4**, 4345.
- [315] Boivin, J.; Jailhan, C.; Zard, S. Z., *J. Am. Chem. Soc.*, (1991) **113**, 5874.
- [316] Maslak, V.; Cekovic, Z.; Saicic, R. W., *Synlett*, (1998), 1435.
- [317] Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z., *Tetrahedron Lett.*, (1994) **35**, 1719.
- [318] Udding, J. H.; Giesselink, J. P. M.; Hiemstra, H.; Speckamp, W. N., *J. Org. Chem.*, (1994) **59**, 6671.
- [319] Boivin, J.; Pothier, J.; Ramos, L.; Zard, S. Z., *Tetrahedron Lett.*, (1999) **40**, 9239.
- [320] Miranda, L. D.; Zard, S. Z., *Chem. Commun. (Cambridge)*, (2001), 1068.
- [321] Bacque, E.; Pautrat, F.; Zard, S. Z., *Chem. Commun. (Cambridge)*, (2002), 2312.
- [322] Boutillier, P.; Zard, S. Z., *Chem. Commun. (Cambridge)*, (2001), 1304.
- [323] Lopez-Ruiz, H.; Zard, S. Z., *Chem. Commun. (Cambridge)*, (2001), 2618.
- [324] Zard, S. Z., *Radicals in Organic Synthesis*, Renaud, P.; Sibi, M., Eds.; Wiley-VCH: Weinheim, Germany, (2001); pp 90–108.
- [325] Zard, S. Z., *Angew. Chem.*, (1997) **109**, 724; *Angew. Chem. Int. Ed. Engl.*, (1997) **36**, 672.
- [326] Leaver, D.; Robertson, W. A. H.; McKinnon, D. M., *J. Chem. Soc.*, (1962), 5104.
- [327] Godt, H.; Wann, R. E., *J. Org. Chem.*, (1961) **26**, 4047.
- [328] Overberger, C. G.; Drucker, A., *J. Org. Chem.*, (1964) **29**, 360.
- [329] Leung, M.-K.; Hsieh, D.-T.; Lee, K.-H.; Liou, J.-C., *J. Chem. Res., Synop.*, (1995), 478.
- [330] Degani, I.; Fochi, R.; Gatti, A.; Regondi, V., *Synthesis*, (1986), 894, and references cited therein.
- [331] Lee, A. W. M.; Chang, W. H.; Wong, H. C., *Synth. Commun.*, (1988) **18**, 1531.
- [332] Barbero, M.; Cadamuro, S.; Degani, I.; Fochi, R.; Gatti, A.; Regondi, V., *Synthesis*, (1988), 22.
- [333] Tamami, B.; Kiasat, A. R., *J. Chem. Res., Synop.*, (1998), 454.
- [334] Anisuzzaman, A. K. M.; Owen, L. N., *J. Chem. Soc. C*, (1967) **11**, 1021.
- [335] Taguchi, Y.; Yanagihara, K.; Shibuya, I.; Suhara, Y., *Bull. Chem. Soc. Jpn.*, (1987) **60**, 727.
- [336] Clausen, R. P.; Becher, J., *Tetrahedron*, (1996) **52**, 3171.
- [337] Rovira, C.; Veciance, J.; Santalo, N.; Tarres, J.; Molins, E.; Llorca, J.; Espinosa, E., *J. Org. Chem.*, (1994) **59**, 3307.
- [338] Takiyama, K.; Jigami, T.; Kawashima, M.; Kodani, M.; Aso, Y.; Otsubo, T., *J. Org. Chem.*, (2002) **67**, 4218.
- [339] Apegiani, M.; Bissolino, P.; D'Anello, M.; Perrone, E., *Synlett*, (1998), 319.
- [340] Sarhan, A. A. O.; Murakami, M.; Izumi, T., *J. Heterocycl. Chem.*, (2002) **39**, 691.
- [341] Mayer, R.; Gebhardt, B.; Fabian, J.; Muller, A. K., *Angew. Chem.*, (1964) **76**, 143; *Angew. Chem. Int. Ed. Engl.*, (1964) **3**, 134.
- [342] Dolling, W.; Khoudary, K.; Augustin, M.; Baumeister, U.; Hartung, H., *Tetrahedron*, (1988) **44**, 4399.
- [343] Richter, A. M.; Beye, N.; Fanghänel, E., *Synthesis*, (1990), 1149, and references cited therein.
- [344] Martin, D. J.; Greco, C. C., *J. Org. Chem.*, (1968) **33**, 1275.
- [345] Boger, D. L.; Sakya, S. M., *J. Org. Chem.*, (1988) **53**, 1415.
- [346] Haley, N. F.; Fichtner, M. W., *J. Org. Chem.*, (1980) **45**, 175.
- [347] Sugawara, A.; Sato, T.; Sato, R., *Bull. Chem. Soc. Jpn.*, (1989) **62**, 339.
- [348] Cuthbertson, E.; MacNicol, D. D.; Mallinson, P. R., *Tetrahedron Lett.*, (1975), 1345.
- [349] Armengol, M.; Joule, J. A., *J. Chem. Soc., Perkin Trans. 1*, (2001), 978.
- [350] Herges, R.; Hoock, C., *Synthesis*, (1991), 1151.
- [351] Herges, R.; Hoock, C., *Angew. Chem.*, (1992) **104**, 1652; *Angew. Chem. Int. Ed. Engl.*, (1992) **31**, 1611.
- [352] Fritz, H.; Sutter, P.; Weis, C. D., *J. Org. Chem.*, (1986) **51**, 558.
- [353] Welch, W. M.; Guarino, K. J. C., *J. Org. Chem.*, (1987) **52**, 4401.
- [354] Quallich, G. J.; Bordner, J.; Elliott, M. L.; Morrissey, P.; Volkman, R. A.; Wroblewska-Adams, M. M., *J. Org. Chem.*, (1990) **55**, 367.

- [355] Gamage, S. A.; Smith, R. A. J., *Tetrahedron*, (1990) **46**, 2111.
- [356] Yui, K.; Aso, Y.; Otsubo, T.; Ogura, F., *Bull. Chem. Soc. Jpn.*, (1988) **61**, 953.
- [357] Nakayama, J.; Tanaka, S.; Sugihara, Y.; Ishii, A., *Heterocycles*, (1999) **50**, 103.
- [358] Zong, K.; Chen, W.; Cava, M. P.; Rogers, R. D., *J. Org. Chem.*, (1997) **61**, 8117.
- [359] Chen, W.; Cava, M. P.; Takassi, M. A.; Metzger, R. M., *J. Am. Chem. Soc.*, (1988) **110**, 7903.
- [360] Hurley, M. F.; Chambers, J. Q., *J. Org. Chem.*, (1981) **46**, 775.
- [361] Nilsson, N. H.; Jacobsen, C.; Senning, A., *J. Chem. Soc. D*, (1971), 314.
- [362] Lotz, S.; Gattow, G., *Z. Anorg. Allg. Chem.*, (1990) **589**, 69.
- [363] Knoth, W.; Gattow, G., *Z. Anorg. Allg. Chem.*, (1987) **554**, 172.
- [364] Ueno, Y.; Nakayama, A.; Okawara, M., *Synthesis*, (1975), 277.
- [365] Guziec, F. S., Jr.; Russo, J. M.; Torres, F. F.; Long, G. C.; Tellez, M. R., *J. Chem. Soc., Perkin Trans. 1*, (1989), 1068.
- [366] Mas, A.; Fabre, J.-M.; Torreilles, E.; Giral, L.; Brun, G., *Tetrahedron Lett.*, (1977), 2579.
- [367] Demetriadis, N. G.; Huang, S. J.; Samulski, E. T., *Tetrahedron Lett.*, (1977), 2223.
- [368] Hartke, K.; Lindenblatt, T., *Synthesis*, (1990), 281.
- [369] Hellberg, J.; Moge, M., *Synthesis*, (1996), 198.
- [370] Stansfield, F.; Coomassie, M. D., *J. Chem. Soc., Perkin Trans. 1*, (1979), 2708.
- [371] Larsen, L.; Garner, C. D.; Joule, J. A., *J. Chem. Soc., Perkin Trans. 1*, (1989), 2311.
- [372] Cho, C.-G.; Posner, G. H., *Tetrahedron Lett.*, (1992) **33**, 3599.
- [373] Smith, K.; Lindsay, C. M.; Pritchard, G. J., *J. Am. Chem. Soc.*, (1989) **111**, 665.
- [374] Russell, G. A.; Law, W. C.; Zaleta, M., *J. Am. Chem. Soc.*, (1985) **107**, 4175.
- [375] Ishiguro, T.; Yamaji, K.; Saito, G., *Organic Superconductors*, 2nd ed., Springer: Berlin, (1998).
- [376] Schukat, G.; Fanghanel, E., *Sulfur Rep.*, (1996) **18**, 1.
- [377] Hartke, K.; Kissel, T.; Quante, J.; Matusch, R., *Chem. Ber.*, (1980) **113**, 1898.
- [378] Hansen, T. K.; Becher, J.; Jorgensen, T.; Varma, K. S.; Khedekar, R.; Cava, M. P., *Org. Synth., Coll. Vol. IX*, (1998), 203.
- [379] Wang, C.; Batsanov, A. S.; Bryce, M. R.; Howard, J. A. K., *Synthesis*, (1998), 1615.
- [380] Saygili, N.; Brown, R. J.; Hoelzl, R.; Kathirgamanathan, P.; Mageean, E. R.; Ozturk, T.; Pilkington, M.; Qayyum, M. M. B.; Turner, S. T.; Vorwerg, L.; Wallis, J. D.; Day, P., *Tetrahedron*, (2001) **57**, 5015.
- [381] Becher, J.; Hansen, T. K.; Malhotra, N.; Bojesen, G.; Bowadt, S.; Varma, K. S.; Girmay, B. G.; Kilburn, J. D.; Underhill, A. E., *J. Chem. Soc., Perkin Trans. 1*, (1990), 175.
- [382] Kumar, S. K.; Singh, H. B.; Jasinski, J. P.; Paight, E. S.; Butcher, R. J., *J. Chem. Soc., Perkin Trans. 1*, (1991), 3341.
- [383] Matsumiya, S.; Izuoka, A.; Sugawara, T.; Taruishi, T.; Kawada, Y., *Bull. Chem. Soc. Jpn.*, (1993) **66**, 513.
- [384] Ozturk, T.; Saygili, N.; Ozkara, S.; Pilkington, M.; Rice, C. R.; Tanter, D. A.; Turksoy, E.; Wallis, J. D., *J. Chem. Soc., Perkin Trans. 1*, (2001), 407.
- [385] Ozturk, T., *Tetrahedron Lett.*, (1996) **37**, 2821.
- [386] Ertas, E.; Ozturk, T., *Chem. Commun. (Cambridge)*, (2000), 2039.
- [387] Khodorkovsky, V. Y.; Becker, J. Y.; Bernstein, J., *Synthesis*, (1992), 1071.
- [388] Leriche, P.; Gorgues, A.; Jubault, M.; Becher, J.; Orduna, J.; Garin, J., *Tetrahedron Lett.*, (1995) **36**, 1275.
- [389] Tsiperman, E.; Regev, T.; Becker, J. Y.; Bernstein, J.; Ellern, A.; Khodorkovsky, V.; Shames, A.; Shapiro, L., *Chem. Commun. (Cambridge)*, (1999), 1125.
- [390] Papavassiliou, G. C.; Mousdis, G. A.; Papadima, A., *Z. Naturforsch.*, (2000) **55**, 231.
- [391] Andreu, R.; Garin, J.; Orduna, J.; Royo, J. M., *Tetrahedron Lett.*, (2000) **41**, 5207.
- [392] Yang, X.; Rauchfuss, T. B.; Wilson, S., *J. Chem. Soc., Chem. Commun.*, (1990), 34.
- [393] Steimecke, G.; Sieler, H. J.; Krimse, R.; Hoyer, E., *Phosphorus Sulfur Relat. Elem.*, (1979) **7**, 49.
- [394] Bryce, M. R.; Marshallsay, G. J., *Tetrahedron Lett.*, (1991) **32**, 6033.
- [395] Hansen, T. K.; Lakshmikantham, M. V.; Cava, M. P.; Becher, J., *J. Chem. Soc., Perkin Trans. 1*, (1991), 2873.
- [396] Garin, J.; Orduna, J.; Saviron, M.; Bryce, M. R.; Moore, A. J.; Morisson, V., *Tetrahedron*, (1996) **52**, 11063.
- [397] Papavassiliou, G. C.; Mousdis, G. A.; Yiannopoulos, S. Y.; Zambounis, J. S., *Chem. Scr.*, (1988) **28**, 365.
- [398] Nakamura, T.; Iwazaka, S.-I.; Nakano, H.; Inoue, K.; Nogami, T.; Mikawa, H., *Bull. Chem. Soc. Jpn.*, (1987) **60**, 365.

- [399] Hansen, T. K.; Varma, S. K.; Edge, S.; Charton, A.; Underhill, A. E.; Becher, J., *J. Chem. Soc., Perkin Trans. 1*, (1992), 1807.
- [400] Gemmell, C.; Janairo, G. C.; Kilburn, J. D.; Ueck, H.; Underhill, A. E., *J. Chem. Soc., Perkin Trans. 1*, (1994), 2715.
- [401] Roehrich, J.; Wolf, P.; Enkelmann, V.; Muellen, K., *Angew. Chem.*, (1988) **100**, 1429; *Angew. Chem. Int. Ed. Engl.*, (1988) **27**, 1377.
- [402] Zambounis, J. S.; Mayer, C. W., *Tetrahedron Lett.*, (1991) **32**, 2737.
- [403] Svenstrup, N.; Rasmussen, K. M.; Hansen, T. K.; Becher, J., *Synthesis*, (1994), 809.
- [404] John, D. E.; Batsanov, A. S.; Bryce, M. R.; Howard, J. A. K., *Synthesis*, (2000), 824.
- [405] Moore, A. J.; Bryce, M. R.; Cooke, G.; Marshall, G. J.; Skabara, P. J.; Bastanov, A. S.; Howard, J. A. K.; Daley, S. T. A. K., *J. Chem. Soc., Perkin Trans. 1*, (1993), 1403.
- [406] Fujisawa, M.; Kato, R., *J. Chem. Soc., Dalton Trans.*, (2002), 3763.
- [407] Wagner, M. G.; Madsen, D.; Markussen, J.; Larsen, S.; Schaumburg, K.; Lubert, K.-H.; Becker, J.; Olk, R.-M., *J. Chem. Soc., Perkin Trans. 1*, (1996), 1995.
- [408] Sukumar, K.; Buy, A.; Harris, N. J.; Underhill, A. E., *Synthesis*, (1987), 837.
- [409] Muller, H.; Ueba, Y., *Bull. Chem. Soc. Jpn.*, (1993) **66**, 1773.
- [410] Girmay, B.; Kilburn, J. D.; Underhill, A. E.; Varma, K. S.; Hursthouse, M. B.; Harman, M. E.; Becher, J.; Bojesen, B., *J. Chem. Soc., Chem. Commun.*, (1989), 1406.
- [411] Hansen, T. K.; Jorgensen, T.; Becher, J., *J. Chem. Soc., Chem. Commun.*, (1992), 1550.
- [412] Christiansen, K.; Becher, J.; Hansen, T. K., *Tetrahedron Lett.*, (1992) **33**, 3035.
- [413] Zeltner, S.; Olk, M.-M.; Wagner, M.; Olk, B., *Synthesis*, (1994), 1445.
- [414] Marshall, G. J.; Hansen, T. K.; Moore, A. J.; Bryce, M. R.; Becher, J., *Synthesis*, (1994), 926.
- [415] Ohashi, M.; Mino, N.; Nakayama, N.; Yamada, S., *Chem. Lett.*, (1978), 1189.
- [416] Yamada, S.; Mino, N.; Nakayama, N.; Ohashi, M., *J. Chem. Soc., Perkin Trans. 1*, (1984), 2497.
- [417] Gorgues, A.; Datal, P.; LeCoq, A., *J. Chem. Soc., Chem. Commun.*, (1983), 405.
- [418] Frère, P.; Gallego-Planas, N.; Blanchard, P.; Mabon, G.; Rondeau, D., *Tetrahedron Lett.*, (2002) **43**, 1825.
- [419] Bradshaw, B.; Dinsmore, A.; Collins, D.; Garner, C. D.; Joule, J. A., *J. Chem. Soc., Perkin Trans. 1*, (2001), 3232.
- [420] Kahn, T.; Skabara, P. J.; Coles, S. J.; Hursthouse, M. B., *Chem. Commun. (Cambridge)*, (2001), 369.
- [421] Kahn, T.; Skabara, P. J., *Synth. Met.*, (2001) **120**, 881.
- [422] Jeppesen, J. O.; Takimiya, K.; Thorup, N.; Becher, J., *Synthesis*, (1999), 803.
- [423] Jeppesen, J. O.; Takimoto, K.; Jensen, F.; Brimert, T.; Nielsen, K.; Thorup, N.; Becher, J., *J. Org. Chem.*, (2000) **65**, 5794.
- [424] Gautier, N.; Cariou, M.; Gorgues, A.; Hudhomme, P., *Tetrahedron Lett.*, (2000) **41**, 2091.
- [425] von Voß, J., *Justus Liebigs Ann. Chem.*, (1971) **746**, 92.
- [426] Tzeng, C.-C.; Motola, N. C.; Panzica, R. P., *J. Org. Chem.*, (1983) **48**, 1271.
- [427] Dora, E. K.; Dash, B.; Panda, C. S., *J. Heterocycl. Chem.*, (1983) **20**, 691.
- [428] Herrmann, G.; Süß-Fink, G., *Synthesis*, (1986), 422.
- [429] Staab, H. A.; Walther, G., *Justus Liebigs Ann. Chem.*, (1962) **657**, 98.
- [430] Ried, W.; Beck, B. M., *Justus Liebigs Ann. Chem.*, (1961) **646**, 96.
- [431] Barton, D. H. R.; Elliott, J. D.; Gero, S. D., *J. Chem. Soc., Perkin Trans. 1*, (1982), 2085.
- [432] Yeh, C.-M.; Sun, C.-M., *Synlett*, (1999), 810.
- [433] Gehrhus, B.; Hitchcock, P. B.; Lappert, M. F., *J. Chem. Soc., Dalton Trans.*, (2000), 3094.
- [434] Furstner, A.; Seidel, G.; Kremzow, D.; Lehmann, C. W., *Organometallics*, (2003) **22**, 907.
- [435] Grosso, J. A.; Nichols, D. E.; Nichols, M. B.; Yim, G. K. W., *J. Med. Chem.*, (1980) **23**, 1261.
- [436] Georgiev, V. St.; Bennett, G. A.; Radov, L. A.; Kamp, D. K.; Trusso, L. A., *J. Heterocycl. Chem.*, (1986) **23**, 1359.
- [437] Wieland, G.; Simchen, G., *Liebigs Ann. Chem.*, (1985), 2178.
- [438] Doleschall, G.; Hornyak, G.; Agai, G.; Simig, G.; Fetter, J.; Lempert, K., *Tetrahedron*, (1976) **32**, 57.
- [439] Martin, D.; Tittelbach, F., *Tetrahedron*, (1983) **39**, 2311.
- [440] Vecchia, L. D.; Dellureficio, J.; Kisis, B.; Vlattas, I., *J. Heterocycl. Chem.*, (1983) **20**, 1287.
- [441] Corey, E. J.; Ohtani, M., *Tetrahedron Lett.*, (1989) **30**, 5227.
- [442] Isobe, T.; Fukuda, K.; Ishikawa, T., *J. Org. Chem.*, (2000) **65**, 7770.
- [443] Wenzel, M.; Beckert, R.; Günther, W.; Görls, H., *Eur. J. Org. Chem.*, (1998), 183.
- [444] Schroeder, D. C., *Chem. Rev.*, (1955) **55**, 181.
- [445] Masquelin, T.; Obrecht, D., *Tetrahedron*, (2001) **57**, 153.
- [446] Kaupp, G.; Schmeyer, J.; Boy, J., *Tetrahedron*, (2000) **56**, 6899.

- [447] Benito, J. M.; Gómez-García, M.; Jiménez Blanco, J. L.; Ortiz Mellet, C.; García Fernández, J. M., *J. Org. Chem.*, (2001) **66**, 1366.
- [448] Herges, R.; Dikmans, A.; Jana, U.; Köhler, F.; Jones, P. G.; Dix, I.; Fricke, T.; König, B., *Eur. J. Org. Chem.*, (2002), 3004.
- [449] Benito, J. M.; Jiménez Blanco, J. L.; Ortiz Mellet, C.; García Fernández, J. M., *Angew. Chem.*, (2002) **114**, 3826; *Angew. Chem. Int. Ed.*, (2002) **41**, 3674.
- [450] Skorini, S. J.; Senning, A., *Tetrahedron*, (1980) **36**, 539.
- [451] Hanefeld, W.; Gunes, Z. E., *Liebigs Ann. Chem.*, (1986), 1140.
- [452] Reis, L. V.; Lobo, A. M.; Prabhakar, S., *Tetrahedron Lett.*, (1994) **35**, 2747.
- [453] Ulrich, H.; Richter, R.; Tucker, B., *Chem. Ber.*, (1987) **120**, 849.
- [454] Mikolajczyk, M.; Kielbasinski, P.; Sut, A., *Tetrahedron*, (1986) **42**, 4591.
- [455] Molina, P.; Tarraga, A.; Espinosa, A., *Synthesis*, (1989), 923.
- [456] von Staab, H. A.; Walther, G., *Justus Liebigs Ann. Chem.*, (1962) **657**, 98.
- [457] von Staab, H. A.; Walther, G., *Justus Liebigs Ann. Chem.*, (1962) **657**, 104.
- [458] Campbell, M. M.; Craig, R. C., *J. Chem. Soc., Perkin Trans. 1*, (1980), 766.
- [459] Anthoni, U.; Larsen, C.; Nielsen, P. H., *Acta Chem. Scand.*, (1968) **22**, 1050.
- [460] Perkins, J. J.; Zartman, A. E.; Meissner, R. S., *Tetrahedron Lett.*, (1999) **40**, 1103.
- [461] Moynihan, H. A.; Roberts, S. M.; Weldon, H.; Allcock, G. H.; Anggard, E. E.; Warner, T. D., *J. Chem. Soc., Perkin Trans. 1*, (1994), 769.
- [462] Sugimoto, H.; Makino, I.; Hirai, K., *J. Org. Chem.*, (1988) **53**, 2263.
- [463] Mohanta, P. K.; Dhar, S.; Samal, S. K.; Ila, H.; Junjappa, H., *Tetrahedron*, (2000) **56**, 629.
- [464] Matsumura, N.; Tomura, M.; Mando, R.; Tsuchiya, Y.; Yoneda, S., *Bull. Chem. Soc. Jpn.*, (1986) **59**, 3693.
- [465] Suni, M. M.; Nair, V. A.; Joshua, C. P., *Tetrahedron*, (2001) **57**, 2003.
- [466] Boas, U.; Jacobsen, M. H., *J. Chem. Soc., Chem. Commun.*, (1995), 1995.
- [467] L'abbé, G.; Leurs, S.; Sannen, I.; Dehaen, W., *Tetrahedron*, (1993) **49**, 4439.
- [468] Santagati, A.; Santagati, M.; Modica, M., *Heterocycles*, (1993) **36**, 1315.
- [469] Singh, A. P.; Singh, R.; Verma, V. K., *Heterocycles*, (1988) **27**, 2373.
- [470] Goswami, B. N.; Katakya, J. C. S.; Baruah, J. N., *J. Heterocycl. Chem.*, (1984) **21**, 1225.
- [471] Modica, M.; Santagati, M.; Russo, F.; Selvaggini, C.; Cagnotto, A.; Mennini, T., *Eur. J. Med. Chem.*, (2000) **35**, 677.
- [472] Mekheimer, R. A.; Shaker, R. M., *J. Chem. Res., Synop.*, (1999), 76.
- [473] Kurzer, F.; Secker, J. L., *J. Heterocycl. Chem.*, (1989) **26**, 355.
- [474] Hull, R.; Hollywood, F.; Suschitzky, H., *J. Chem. Soc., Perkin Trans. 1*, (1979), 3037.
- [475] Ernst, S.; Richter, C.; Hobert, A.; Mariam, G. G.; Schulze, K., *J. Heterocycl. Chem.*, (1995) **32**, 275.
- [476] Grashey, R.; Baumann, M.; Hamprecht, R., *Tetrahedron Lett.*, (1972), 2939.
- [477] Schantl, J. G.; Kahlig, H.; Prean, M., *Heterocycles*, (1994) **37**, 1873.
- [478] Schantl, J. G.; Lagoja, I. M., *Heterocycles*, (1997) **45**, 691.
- [479] Bhattacharya, B. K., *J. Heterocycl. Chem.*, (1986) **23**, 113.
- [480] Lee, K.-J.; Kim, S.; Um, H.; Park, H., *Synthesis*, (1989), 638.
- [481] Vicentini, C. B.; Ferretti, V.; Veronese, A. C.; Guarneri, M.; Manfrini, M.; Giori, P., *Heterocycles*, (1995) **41**, 497.
- [482] Barkoczy, J.; Reiter, J., *J. Heterocycl. Chem.*, (1992) **29**, 1677.
- [483] Khalaf, A. A.; El-Shafei, A. K.; El-Sayed, A. M., *J. Heterocycl. Chem.*, (1982) **19**, 609.
- [484] Yamamoto, T.; Muraoka, M.; Kakahashi, M.; Takeshima, T., *J. Chem. Res., Synop.*, (1980), 148.
- [485] Cartwright, D. D. J.; Clark, B. A. J.; McNab, H., *J. Chem. Soc., Perkin Trans. 1*, (2001) 424.
- [486] Kroger, C. F.; Tenor, E.; Beyer, H.; Timpe, H.-J., *Justus Liebigs Ann. Chem.*, (1961) **643**, 121.
- [487] Molina, P.; Alajarin, M., *Synthesis*, (1983), 414.
- [488] Becker, H. G. O.; Heimburger, K.; Timpe, H.-J., *J. Prakt. Chem.*, (1971) **313**, 975.
- [489] Becker, H. G. O.; Nagel, D.; Timpe, H.-J., *J. Prakt. Chem.*, (1973) **315**, 97.
- [490] Tzeng, C.-C.; Rychlewska, U.; Hodgson, D. J.; Panzica, R. P., *J. Heterocycl. Chem.*, (1986) **23**, 33.
- [491] Laus, G.; Klötzer, W., *Synthesis*, (1990), 707.
- [492] Yadav, L. D. S.; Sharma, S., *Synthesis*, (1993), 864.
- [493] Yadav, L. D. S.; Pal, D. R., *J. Chem. Res., Synop.*, (1997), 90.
- [494] Zelenin, K. N.; Alekseyev, V. V.; Gabis, T. Y.; Yakimovitch, S. I.; Pehk, T. J., *Tetrahedron Lett.*, (1990) **31**, 3927.
- [495] Moorman, A. R.; Findak, D. C.; Ku, H. S., *J. Heterocycl. Chem.*, (1985) **22**, 915.
- [496] Kane, J. M.; Staeger, M. A., *Synth. Commun.*, (1992) **22**, 1.

- [497] Shafiee, A.; Naimi, E.; Mansobi, A.; Foroumadi, A.; Shekari, M., *J. Heterocycl. Chem.*, (1995) **32**, 1235.
- [498] Gowda, B. T.; Ramachandra, P., *J. Chem. Soc., Perkin Trans. 2*, (1989), 1067.
- [499] Billman, J. H.; Cleland, E. S., *J. Am. Chem. Soc.*, (1943) **65**, 1300.
- [500] Billman, J. H.; Cleland, E. S., *Org. Synth., Coll. Vol. III*, (1955), 360.
- [501] Mizutani, M.; Sanemitsu, Y., *J. Heterocycl. Chem.*, (1985) **422**, 11.
- [502] Becker, G.; Becker, W.; Uhl, G., *Z. Anorg. Allg. Chem.*, (1984) **518**, 21.
- [503] Kulka, M., *Can. J. Chem.*, (1981) **59**, 1557.
- [504] McCarthy, W. C.; Foss, L. E., *J. Org. Chem.*, (1977) **42**, 1508.
- [505] Khalil, Z. H.; Abdel, A. A.; Yanni, A. S.; Moharam, A. M., *Bull. Chem. Soc. Jpn.*, (1988) **61**, 4143.
- [506] Allcock, H. R.; Rutt, J. S.; Parvez, M., *Inorg. Chem.*, (1991) **30**, 1776.
- [507] Nishiyama, K.; Oba, M.; Oshima, M.; Sugawara, T.; Ueno, R., *Tetrahedron Lett.*, (1993) **34**, 3745.
- [508] Kristian, P.; Bernat, J.; Imrich, J.; Sedlak, E.; Alföldi, J.; Cornanic, M., *Heterocycles*, (2001) **55**, 279.
- [509] Martinez, M. A.; Vega, J. C., *Synthesis*, (1985), 975.
- [510] Millan, D. S.; Prager, R. H., *Tetrahedron Lett.*, (1998) **39**, 4387.
- [511] Millan, D. S.; Prager, R. H., *J. Chem. Soc., Perkin Trans. 1*, (1998), 3245.
- [512] Aslam, M.; Davenport, K. G., *Synth. Commun.*, (1987) **17**, 1761.
- [513] Fabbri, D.; Celogu, G.; De Lucchi, O., *J. Org. Chem.*, (1993) **58**, 1748.
- [514] Gibbs, C.; Gutsche, D., *J. Am. Chem. Soc.*, (1993) **115**, 5338.
- [515] Delaigue, X.; Hosseini, M. W., *Tetrahedron Lett.*, (1993) **34**, 8111.
- [516] Bandarage, U. K.; Simpson, J.; Smith, R. A. J.; Weavers, R. T., *Tetrahedron*, (1994) **50**, 3463.
- [517] Sebök, P.; Tímár, T.; Eszenyi, T.; Patonay, T., *Synthesis*, (1994), 837.
- [518] Sebök, P.; Tímár, T.; Eszenyi, T., *J. Org. Chem.*, (1994) **59**, 6318.
- [519] Meier, H.; Rumpf, N., *Tetrahedron Lett.*, (1998) **39**, 9639.
- [520] Delogu, G.; Fabbri, D.; Dettori, M. A., *Tetrahedron: Asymmetry*, (1998) **9**, 2819.
- [521] Otto, S.; Furlan, R. L. E.; Sanders, J. K. M., *Science*, (2002) **297**, 590.
- [522] Teplý, F.; Stará, I. G.; Starý, I.; Kollárovic, A.; Šaman, D.; Vyskocil, Š.; Fiedler, P., *J. Org. Chem.*, (2003) **68**, 5193.
- [523] Villemin, D.; Hachemi, M.; Lalaoui, M., *Synth. Commun.*, (1996) **26**, 2461.
- [524] Nishide, K.; Miyamoto, T.; Kumar, S. K.; Ohsugi, S.; Node, M., *Tetrahedron Lett.*, (2002) **43**, 8569.
- [525] Barma, D. K.; Bandyopadhyay, A.; Capdevila, J. H.; Falck, J. R., *Org. Lett.*, (2003) **5**, 4755.
- [526] Hakimelahi, G. H.; Zarrinehazad, M.; Jarrahpour, A. A.; Sharghi, H., *Helv. Chim. Acta*, (1987) **70**, 219.
- [527] Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. L., *Can. J. Chem.*, (1987) **65**, 1859.
- [528] Rama Rao, A. V.; Purandare, A. V.; Reddy, E. R.; Gurjar, M. K., *Synth. Commun.*, (1987) **17**, 1095.
- [529] Broka, C.; Gerlits, J. F., *J. Org. Chem.*, (1988) **53**, 2144.
- [530] Shishido, K.; Sukegawa, Y.; Fukumoto, K., *J. Chem. Soc., Perkin Trans. 1*, (1987), 993.
- [531] Beylin, V. G.; Townsend, L. B., *J. Heterocycl. Chem.*, (1988) **25**, 97.
- [532] Kulanthaivel, P.; Pelletier, W., *Tetrahedron*, (1988) **44**, 4313.
- [533] Rabow, L. E.; Stubbe, J.; Kozarich, J. W., *J. Am. Chem. Soc.*, (1990) **112**, 3196.
- [534] Batey, R. A.; Harling, J. D.; Motherwell, W. B., *Tetrahedron*, (1992) **48**, 8031.
- [535] Guidot, J. P.; Gall, T. L., *J. Org. Chem.*, (1993) **58**, 5271.
- [536] Toya, T.; Nagase, H.; Honda, T., *Tetrahedron: Asymmetry*, (1993) **4**, 1537.
- [537] Honda, T.; Hoshi, M.; Kanai, K.; Tsubuki, M., *J. Chem. Soc., Perkin Trans. 1*, (1994), 2091.
- [538] Coleman, R. S.; Grant, E. B., *J. Am. Chem. Soc.*, (1995) **117**, 10889.
- [539] Camps, P.; Contreras, J.; Morral, J.; Muñoz-Torrero, D.; Font-Bardia, M.; Solans, X., *Tetrahedron*, (1999) **55**, 8481.
- [540] Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F., *Tetrahedron: Asymmetry*, (1999) **10**, 4841.
- [541] Kakimoto, Y.-I.; Ogasawara, Y.; Nishida, A.; Kawahara, N.; Nishida, M.; Takayanagi, H., *Tetrahedron*, (2000) **56**, 7173.
- [542] Hughes, R. C.; Dvorak, C. A.; Meyers, A. I., *J. Org. Chem.*, (2001) **66**, 5545.
- [543] Rhee, J. U.; Bliss, B. I.; RajanBabu, T. V., *Tetrahedron: Asymmetry*, (2003) **14**, 2939.
- [544] Geffken, D., *Z. Naturforsch., B*, (1983) **38**, 1008.
- [545] Goering, B. K.; Ganem, B., *Tetrahedron Lett.*, (1994) **35**, 6997.
- [546] Robiette, R.; Cheboub-Benchaba, K.; Peerers, D.; Marchand-Brynaert, J., *J. Org. Chem.*, (2003) **68**, 9809.
- [547] Stájer, G.; Szabo, E. A.; Fulop, F.; Bernath, G.; Kalman, A.; Argay, G., *Tetrahedron*, (1983) **39**, 1829.
- [548] Bernath, G.; Stájer, G.; Szabo, A. E.; Fülöp, F.; Sohar, P., *Tetrahedron*, (1985) **41**, 1353.

- [549] Stájer, G.; Szabo, E. A.; Fulop, F.; Bernath, G.; Sohar, P., *J. Heterocycl. Chem.*, (1983) **20**, 1181.
- [550] Stájer, G.; Szabo, E. A.; Fulop, F.; Bernath, G.; Sohar, P., *J. Heterocycl. Chem.*, (1984) **21**, 1373.
- [551] Smith, G. E. P.; Alliger, G.; Carr, E. L.; Young, K. C., *J. Org. Chem.*, (1949) **14**, 935.
- [552] Kaji, A., *Bull. Chem. Soc. Jpn.*, (1961) **34**, 254.
- [553] Piper, J. R.; Johnston, T. P., *J. Org. Chem.*, (1963) **28**, 981.
- [554] Nakai, T.; Ueno, Y.; Okawara, M., *Tetrahedron Lett.*, (1967), 3831.
- [555] Ueno, Y.; Masuyama, Y.; Okawara, M., *Tetrahedron Lett.*, (1974), 2577.
- [556] Schaumann, E.; Kausch, E.; Rossmannith, E., *Liebigs Ann. Chem.*, (1978) 1543.
- [557] Hiratani, K.; Shiono, H.; Okawara, M., *Chem. Lett.*, (1973) 867.
- [558] Suzuki, T.; Yamochi, H.; Srdanov, G.; Hinkelmann, K.; Wugl, F., *J. Am. Chem. Soc.*, (1989) **111**, 3108.
- [559] O'Connor, C.; Gilbert, J. D.; Wilkinson, G., *J. Chem. Soc. A*, (1969), 84.
- [560] Catheline, D.; Román, E.; Astruc, D., *Inorg. Chem.*, (1984) **23**, 4508.
- [561] Kotali, E.; Varvaglis, A., *J. Chem. Soc., Perkin Trans. 1*, (1987) 2759.
- [562] Albert, A., *J. Chem. Soc., Perkin Trans. 1*, (1980), 2009.
- [563] Brown, D. J.; Cowden, W. B., *Aust. J. Chem.*, (1983) **36**, 1469.
- [564] D'Amico, J. J.; Bollinger, F. G.; Freeman, J. J.; Dahl, W. E., *J. Heterocycl. Chem.*, (1986) **23**, 105.
- [565] Castells, J.; Calahorra, F. L.; Geijo, F., *Heterocycles*, (1986) **24**, 3097.
- [566] Ahlbrecht, H.; Kornetzky, D., *Synthesis*, (1988), 775.
- [567] Pongó, L.; Reiter, J.; Barkóczy, J.; Sohár, P., *J. Heterocycl. Chem.*, (1990) **27**, 1249.
- [568] Cativiela, C.; Diaz de Villegas, M., *Tetrahedron*, (1993) **49**, 497.
- [569] Moore, A. J.; Bryce, M. R., *Synthesis*, (1997), 407.
- [570] Kim, S.; Lim, C. J.; Song, S.-E.; Kang, H.-Y., *Synlett*, (2001), 688.
- [571] Guérin, D.; Carlier, R.; Lorcy, D., *J. Org. Chem.*, (2000) **65**, 6069.
- [572] Guérin, D.; Carlier, R.; Guerro, M.; Lorcy, D., *Tetrahedron*, (2003) **59**, 5273.
- [573] Kanie, K.; Mizuno, K.; Kuroboshi, M.; Hiyama, T., *Bull. Chem. Soc. Jpn.*, (1998) **71**, 1973.
- [574] Pujol, M. D.; Guillaumet, G., *Synth. Commun.*, (1992) **22**, 1231.
- [575] Fitton, A. O.; Rigby, A.; Hurlock, R. J., *J. Chem. Soc. C*, (1969), 230.
- [576] Fitton, A. O.; Rigby, A.; Hurlock, R. J., *J. Chem. Soc. C*, (1968), 996.
- [577] Dunbar, J. E.; Rogers, J. H., *J. Org. Chem.*, (1970) **35**, 279.
- [578] Cameron, B. R.; Darkes, M. C.; Baird, I. R.; Skerlj, R. T.; Santucci, Z. L.; Fricker, S. P., *Inorg. Chem.*, (2003) **42**, 4102.
- [579] Brask, J. K.; Durà-Vilà, V.; Diaconescu, P. L.; Cummins, C. C., *Chem. Commun. (Cambridge)*, (2002), 902.
- [580] Ferris, A. F.; Schutz, B. A., *J. Org. Chem.*, (1963) **28**, 3140.
- [581] Cherbuliez, E.; Buchs, A.; Marszalek, J.; Rabinowitz, J., *Helv. Chim. Acta*, (1965) **48**, 1414.
- [582] Asinger, F.; Saus, A.; Bähr-Wirtz, M., *Liebigs Ann. Chem.*, (1979), 708.
- [583] Grözinger, K. G.; Onan, K. D., *J. Heterocycl. Chem.*, (1986) **23**, 737.
- [584] Vass, A.; Szalontai, G., *Synthesis*, (1986), 817.
- [585] Makomo, H.; Masson, S.; Saquet, M., *Tetrahedron*, (1994) **50**, 10277.
- [586] Hanefeld, W.; Schütz, H., *J. Heterocycl. Chem.*, (1999) **36**, 1167.
- [587] Hanefeld, W.; Bercin, E., *Liebigs Ann. Chem.*, (1985), 58.
- [588] Ram, S.; Wise, D. S.; Townsend, L. B., *J. Heterocycl. Chem.*, (1985) **22**, 1269.
- [589] Nilsson, N. H.; Jacobsen, C.; Sørensen, O. N.; Haunsoe, N. K.; Senning, A., *Chem. Ber.*, (1972) **105**, 2854.
- [590] Gronowitz, S.; Hörnfeldt, A.-B.; Temciuc, M., *Synthesis*, (1993), 483.
- [591] Helgeson, R. C.; Knobler, C. B.; Cram, D. J., *J. Chem. Soc., Chem. Commun.*, (1995), 307.
- [592] Lawrence, R. M.; Biller, S. A.; Dickson, J. K., Jr.; Logan, J. V. H.; Magnin, D. R.; Sulsky, R. B.; DiMarco, J. D.; Gougoutas, J. Z.; Beyer, B. D.; Taylor, S. C.; Lan, S.-J.; Ciosek, C. P., Jr.; Harry, T. W.; Jolibois, K. G.; Kunselman, L. K.; Siusarchyk, D. A., *J. Am. Chem. Soc.*, (1996) **118**, 11668.
- [593] Emrick, T. S., Ph.D. Dissertation, University of Chicago, (1997).
- [594] Abeywickrema, E. W.; Della, E. W., *J. Org. Chem.*, (1980) **45**, 4226.
- [595] Priefer, R.; Lee, Y. J.; Barrios, F.; Wosnick, J. H.; Lebuis, A.-M.; Farrell, P. G.; Harpp, D. N., *J. Am. Chem. Soc.*, (2002) **124**, 5626.
- [596] Tsanaktisid, J.; Raton, P. E., *Tetrahedron Lett.*, (1989) **30**, 6967.
- [597] Eaton, P. E.; Galoppini, E.; Gilardi, R., *J. Am. Chem. Soc.*, (1994) **116**, 7588.
- [598] Fuchigami, T.; Chen, C.-S.; Nonaka, T.; Yen, M.-Y.; Tien, H.-J., *Bull. Chem. Soc. Jpn.*, (1986) **59**, 487.
- [599] Schnell, B.; Kappe, T., *J. Heterocycl. Chem.*, (2000) **37**, 911.

- [600] D'Amico, J. J.; Bollinger, F. G.; Tung, C. C.; Dahl, W. E., *J. Heterocycl. Chem.*, (1987) **24**, 945.
- [601] Perevalova, E. G.; Grandberg, K. I.; Dyadchenko, V. P.; Kalinina, O. N., *J. Organomet. Chem.*, (1988) **352**, C37.
- [602] Heinrich, D. D.; Staples, R. J.; Fackler, J. P., Jr., *Inorg. Chim. Acta*, (1995) **229**, 61.
- [603] Goh, L. Y.; Weng, Z.; Leong, W. K.; Leung, P. H., *Angew. Chem.*, (2001) **113**, 3336; *Angew. Chem. Int. Ed.*, (2001) **40**, 3236.
- [604] Goh, L. Y.; Weng, Z.; Leong, W. K.; Leung, P. H., *Organometallics*, (2002) **21**, 4398.
- [605] Suzuki, T.; Kashiwamura, S.; Kashiwabara, K., *Bull. Chem. Soc. Jpn.*, (2001) **74**, 2349.
- [606] Goshorn, R. H.; Levis, W. W.; Jaul, E., Jr.; Ritter, E. J., *Org. Synth., Coll. Vol. IV*, (1963), 307.
- [607] Jen, K.-Y.; Cava, M. P., *J. Org. Chem.*, (1983) **48**, 1449.
- [608] Newman, M. S.; Hetzel, F. W., *Org. Synth.*, (1971) **51**, 139.
- [609] Hasseroth, U., *Chem. Ber.*, (1968) **101**, 113.
- [610] Kleinpeter, E.; Pihlaja, K., In *Comprehensive Organic Functional Group Transformation*, Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds.; Pergamon: Oxford: UK, (1995); Vol. 6, p 580.
- [611] Kunze, U.; Tittmann, R., *Z. Naturforsch., B*, (1987) **42**, 77.
- [612] Malisch, W.; Spörl, A.; Pfister, H., *J. Organomet. Chem.*, (1998) **568**, 241.
- [613] Weber, L.; Uthmann, S.; Bogge, H.; Muller, A.; Stammmler, H.-G.; Neumann, B., *Organometallics*, (1998) **17**, 3593.
- [614] Kunze, U.; Bruns, A.; Hiller, W.; Mohyla, J., *Chem. Ber.*, (1985) **118**, 227.
- [615] Dahl, O.; Larsen, O., *Acta Chem. Scand.*, (1970) **24**, 1094.
- [616] Takeda, M.; Yoshimura, T.; Fujii, T.; Ono, S.; Shimasaki, C.; Morita, H., *Tetrahedron Lett.*, (1999) **40**, 2327.

Product Class 11: Seleno- and Tellurocarmonic Acids and Derivatives

J. Schmidt and L. A. Silks

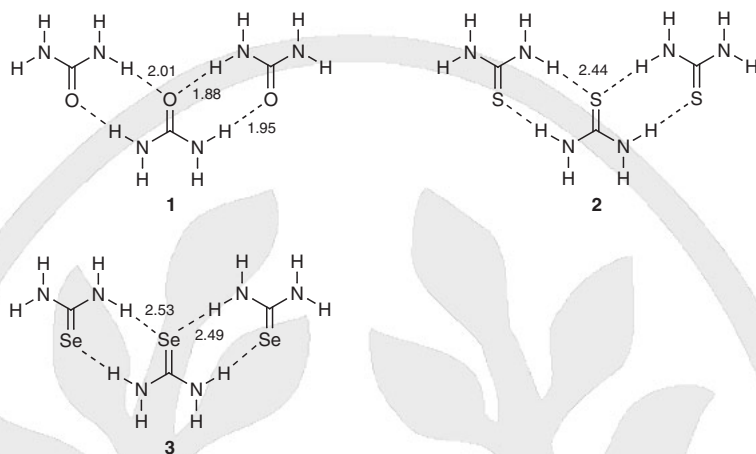
General Introduction

Seleno- and tellurocarmonic acids and their derivatives have been gaining increasing attention because they have unique and interesting chemistries, possess isotopomers which are useful NMR probes, and have application in the areas of organic superconductors and in the syntheses of semiconducting thin films of metal chalcogenides. Studies of the chemistry of this class of compounds or functional groups have been reported with increasing frequency. Early efforts centered on the development of methods for the construction of these compounds, which eventually led to the discovery of a wide range of applications. Although many of the seleno- and tellurocarmonic acids are stable compounds, others may exhibit significant thermal and photolytic instabilities and care should be exercised when handling these compounds. The fundamental reasons for the stability of these compounds can be understood from studies of the structure and physical and chemical properties that have been reported. The discovery of selenium dates back to 1818 and is attributed to two Swedish chemists, Berzelius and Gahn.^[1] The discovery of tellurium is attributed to von Reichenstein in 1783 (although some believe its discovery was in 1782); it was named by Klaproth, who isolated it in 1798. Table 1 illustrates some physical properties of the group 16 family of elements.^[2]

Table 1 Some Physical Properties of the Group 16 Elements^[2]

Element	Atomic Weight	Pauling Electro-negativity	Ionization Potential (eV)	Ionic Radius (Å)	Atomic Radius (Å)	C–X Bond Length (Å)	Ref
O	15.99	3.5	13.61	1.40	0.66	1.42	[2]
S	32.06	2.5	10.36	1.84	1.04	1.82	[2]
Se	78.96	2.4	9.75	1.98	1.17	1.96	[2]
Te	127.6	2.1	9.01	2.21	1.37	2.12	[2]

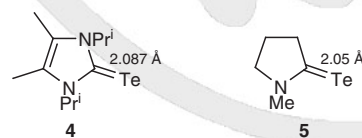
The electronegativity difference between carbon, selenium, and tellurium, as well as the large ionic radii of selenium and tellurium, give rise to a considerable polarization of the C–Se and C–Te bonds. This polarization effect is reflected in the high reactivity of many organoselenium and tellurium compounds.^[2–11] Seleno- and tellurocarmonic acids exhibit some chemical behaviors analogous to oxygen-containing carbonic acids. As is the case with their respective oxygen analogues, telluro- and selenocarbonyls tend to form extended hydrogen-bonded assemblies. These molecular ribbons have been observed in the X-ray analysis of urea (**1**), thiourea (**2**), and selenourea (**3**) and are illustrated in Scheme 1.^[12–14] Table 2 shows some important aspects of these carbonyl compounds.

Scheme 1 Hydrogen Bond Distances for Various Ureas (\AA)^[12–14]**Table 2** Properties of the Ureas

	1	2	3
IR ^a (cm ⁻¹)	2240	1510	1267
C=X (\AA)	1.234	1.689	1.85
H–X (\AA)	1.921	2.457	2.64
N–X (\AA)	2.901	3.415	3.58

^a For carbon dioxide, carbon disulfide, and carbon diselenide.

As can be seen in Scheme 1, the carbonyl heteroatom participates in hydrogen bonding. The strength of this bonding interaction decreases when proceeding from oxygen to selenium. Oxygen is a very strong acceptor whereas sulfur and selenium are considered to be weak acceptors. Tellurium has an electronegativity that is similar to, or even lower than, that of hydrogen, making tellurium hydrogen bonds extremely rare. Relatively few tellurocarbonyl compounds have been constructed if compared to the selenocarbonyl analogues. Scheme 2 shows both a cyclic tellurourea **4** and tellurolactam **5** whose structures have been determined.^[15] The experimentally determined C–Te multiple-bond distances reported are: 1.904 \AA in S=C=Te, 1.923 \AA in $[\text{Cl}_2\text{Os}(\text{CO})(\text{CTe})(\text{PPh}_3)_2]$, 2.043–2.15 \AA in tri- or tetracoordinated tellurium compounds, and 1.987–2.21 \AA in transition-metal complexes of tellurocarbonyls.^[16]

Scheme 2 Representative Tellurocarbonyl Bond Lengths for Ureas and Amides^[15,16]

18.11.1 Product Subclass 1: Selenocarbonyl Dihalides

18.11.1.1 Synthesis of Product Subclass 1

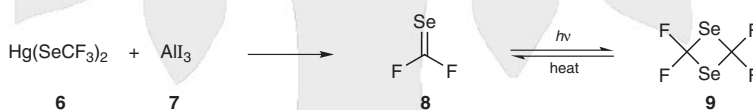
Selenocarbonyl dihalides have been studied by ab initio calculations and molecular spectroscopic techniques. Some aspects of their associated chemistries have been investigated such as the dimerization of the monomers and thermal [2+4] cycloadditions. Generally, the synthesis of this type of compound is challenging and the products are difficult to handle. Selenocarbonyl dihalide monomers, formal equivalents of selenophosgenes (selenocarbonyl dichloride), are not stable at ambient conditions and are usually observed in argon matrix or as low-temperature stabilized intermediates. However, because of their perceived importance to the materials arena they will be discussed here.

18.11.1.1.1 Method 1: Selenocarbonyl Difluoride from Bis(trifluoromethylselanyl)mercury(II)

The most stable of the selenocarbonyl dihalides, selenocarbonyl difluoride (**8**), is obtained in good yields and on preparative scales by reacting bis(trifluoromethylselanyl)mercury(II) (**6**) with aluminum triiodide (**7**) in a solution of octamethylcyclotetrasiloxane (Scheme 3).^[17] The procedure gives rise to polymeric side products, as well as the formation of the dimeric bis(trifluoromethyl)diselane.

Selenocarbonyl difluoride in trichlorofluoromethane dimerizes quantitatively to 2,2,4,4-tetrafluoro-1,3-diselenetane (**9**) upon exposure to light.^[17] This compound is a moderately stable precursor for the monomeric **8** since it undergoes the reverse reaction of its formation on pyrolysis.^[17] The diselenetane **9** also lends itself to halogen exchange with boron trichloride and boron tribromide to yield dimers of chloro- and bromoselenocarbonyl dihalides.^[18]

Scheme 3 Synthesis of Selenocarbonyl Difluoride by Mercury-Promoted Halide Exchange^[18]



Selenocarbonyl Difluoride (**8**):^[18]

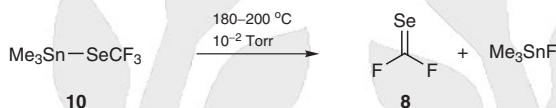
A 250-mL three-necked flask equipped with a thermometer, condenser, and dropping funnel was charged with AlI_3 (20 g, 49 mmol) in octamethylcyclotetrasiloxane (10 mL). The reaction vessel was connected via the condenser to two traps and a high-vacuum line. At 50–55 °C and a vacuum of 5 Torr, a soln of $\text{Hg}(\text{SeCF}_3)_2$ (25 g, 50 mmol) in octamethylcyclotetrasiloxane (120 mL) was added dropwise, while maintaining the reaction temperature below 55 °C. Higher reaction temperatures led to decomposition products, indicated by red octamethylcyclotetrasiloxane-soluble side products in the condenser. Solvents and side products were trapped in the first cooling trap at –100 °C, and the SeCF_2 was collected in the second trap at –196 °C. The SeCF_2 was purified by low-temperature fractional distillation from –100 °C into a trap at –196 °C at 5 Torr to give the yellowish product; yield: 9.12 g [70% based on $\text{Hg}(\text{SeCF}_3)_2$]. Side products consisted mainly of bis(trifluoromethyl)diselane.

18.11.1.1.2

Method 2:**Selenocarbonyl Difluoride from Trimethyl[(trifluoromethyl)selanyl]-stannane**

An alternative route to the difluoride **8** in reportedly “quantitative yields and high purity” from the thermolysis of trimethyl[(trifluoromethyl)selanyl]stannane (**10**) has been published (Scheme 4).^[19] Selenocarbonyl difluoride obtained by this procedure reacts in Diels–Alder additions to dienes to give cycloaddition products in good to excellent yields.

Scheme 4 Synthesis of Selenocarbonyl Difluoride by Pyrolysis of Trimethyl[(trifluoromethyl)selanyl]stannane^[19]

**Selenocarbonyl Difluoride (8):**^[19]

Trimethyl[(trifluoromethyl)selanyl]stannane (**10**; 0.92 g, 3 mmol) was evaporated at 0.01 Torr through a pyrolysis tube (300-mm length, 20-mm diameter) filled with quartz wool at 200 °C. A first cooling trap at −78 °C condensed all unreacted starting material, which was recycled into the pyrolysis. SeCF₂ was obtained as a yellow condensate in a second cooling trap which was chilled to −196 °C. Pyrolysis over a period of 2 h yielded SeCF₂; yield: 0.155 g (40%) (NMR). The SeCF₂ was then used directly without further purification in Diels–Alder cycloaddition reactions by adding an excess of the diene to the SeCF₂ soln at −196 °C, followed by rapid warming to rt.

18.11.1.1.3

Method 3:**Selenocarbonyl Difluoride by Controlled Decomposition of Tris[(trifluoromethyl)selanyl]borane**

This synthesis employs the thermal decomposition of tris[(trifluoromethyl)selanyl]borane (**11**) (Scheme 5).^[18,20,21] The boron compound is volatilized and heated through a glass tube which contains potassium fluoride. The potassium fluoride serves as a boron trifluoride scavenger forming potassium tetrafluoroborate. Although the trapping is somewhat inefficient according to the report, compound **8** can be obtained in 35.5% yield. This procedure also gives rise to polymeric side products, as well as the formation of the dimeric bis(trifluoromethyl)diselane.

Scheme 5 Synthesis of Selenocarbonyl Difluoride by Decomposition of Tris[(trifluoromethyl)selanyl]borane^[18]

**Selenocarbonyl Difluoride (8):**^[18]

B(SeCF₃)₃ (**8**; 10 g, 22 mmol) was heated and the products were distilled at 10^{−2} Torr at 110 °C through a U-shaped glass tube (20-cm length, 1.5-cm diameter) filled with KF on glass wool. The products were fractionated into 2 traps, the first trap at −100 °C condensed starting material and side products, the second trap at −196 °C captured SeCF₂ and BF₃. The decomposition of the unreacted starting material was repeated 3–4 times until no further SeCF₂ was produced. A mixture of SeCF₂ and BF₃ containing traces of (SeCF₂)_n was obtained (6.9 g). The product **8** was difficult to separate from BF₃ and the authors describe an intermediate polymerization step. After removal of part of the BF₃ (0.7 g) by dis-

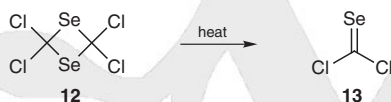
tillation the $\text{SeCF}_2/\text{BF}_3$ mixture was kept at -80°C for 20 h to effect complete polymerization of the selenocarbonyl difluoride. The BF_3 was then removed in vacuo to obtain a white waxlike solid of polymeric $(\text{SeCF}_2)_n$. The polymeric mixture of $(\text{SeCF}_2)_n$ thus obtained (5 g) decomposed on fast heating to $200\text{--}300^\circ\text{C}$ in vacuum within 10–15 min to afford SeCF_2 and its dimer $(\text{SeCF}_2)_2$ quantitatively. The products were fractionated during pyrolysis into a trap at -78°C condensing the $(\text{SeCF}_2)_2$, while a second trap at -196°C captured SeCF_2 . Purification was achieved by trap-to-trap condensation at 0°C , -23°C , and -196°C to give **8**; yield: 1.7 g (35%). The other product was a mixture of 2,2,4,4-tetrafluoro-1,3-diselenetane with 5–10% $(\text{SeCF}_2)_2$.

18.11.1.1.4

Method 4:
Selenocarbonyl Dichloride by Vacuum Pyrolysis of
2,2,4,4-Tetrachloro-1,3-diselenetane

There has been one report of the synthesis of selenocarbonyl dichloride (selenophosgene; **13**).^[21] The reaction involves the pyrolysis of 2,2,4,4-tetrachloro-1,3-diselenetane (**12**) (Scheme 6). The synthesis of the diselenetane has been reported by the same authors^[19] and will not be covered in this section. Pyrolysis of the tetrachloroselenetane **12** has been carried out to obtain and characterize selenophosgene (**13**) at low temperature in an argon matrix by UV, Raman, and IR spectroscopic methods.^[21] The procedure appears to be straightforward, although no yields are reported.

Scheme 6 Synthesis of Selenocarbonyl Dichloride by
 Cycloreversion of 2,2,4,4-Tetrachloro-1,3-diselenetane^[21]



Selenocarbonyl Dichloride (13**):**^[21]

Selenophosgene was prepared by vacuum pyrolysis of 2,2,4,4-tetrachloro-1,3-diselenetane at 350°C . Unreacted dimer was trapped at -15°C . The selenophosgene was then condensed into an argon matrix at -263°C for characterization. No yields were given. The dark blue compound was only stable below -130°C and was characterized by mass spectrometry and low-temperature UV, IR matrix, and Raman matrix spectroscopy.

18.11.2

Product Subclass 2:
Selenocarbonates

This group of compounds has received significant attention because of their ability to undergo interesting and useful reactions, such as deoxygenation. For example, conversion of 1,2-diols into their corresponding cyclic selenocarbonates, followed by treatment with a diazaphospholidine, affords the deoxygenated alkene product.

18.11.2.1

Synthesis of Product Subclass 2

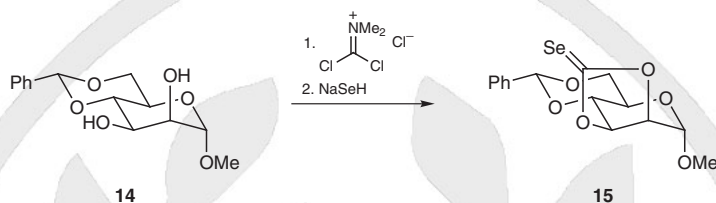
18.11.2.1.1

Method 1:
From Viehe's Salt and Sodium Hydrogen Selenide

The treatment of various thiols, phenols, and amines with Viehe's salt (dichloro-*N,N*-dimethylmethaniminium chloride) followed by the addition of sodium hydrogen selenide, gives rise to compounds bearing the selenocarbonyl group (selenothiocabamates, sele-

nodithiocarbonates, selenothiocarbonates, and selenoureas). Vicinal diols such as **14** also undergo this reaction to give products such as **15** shown in Scheme 7.^[22,23]

Scheme 7 The Methaniminium/Selenocarbonyl Exchange Reaction Using Sodium Hydrogen Selenide^[22,23]



Methyl 4,6-O-Benzylidene-2,3-O-selenocarbonyl-α-D-mannoside (15):^[22,23]

CAUTION: Hydrogen selenide, which may be formed in this synthesis, has a penetrating and disagreeable odor and is extremely toxic.

To dichloro-*N,N*-dimethylmethaniminium chloride (1.0 g, 6 mmol) in dry CH_2Cl_2 (30 mL, 0 °C) under argon were added pyridine (1.9 mL) and methyl 4,6-*O*-benzylidene-α-*D*-mannoside (**14**; 1.7 g, 6.0 mmol). The mixture was stirred for 4 h at 20 °C and then filtered into a NaSeH soln. [The NaSeH soln was prepared from the reaction of elemental Se (800 mg, 8 mmol) with NaBH_4 (1 equiv) in EtOH (20 mL). This reaction was exothermic, accompanied by vigorous H_2 evolution and was complete in a few min to give a colorless soln of NaSeH and $\text{B}(\text{OEt})_3$. Care should be exercised because small amounts of H_2Se have been detected.] Stirring was continued for 5 min and the whole mixture was concentrated under argon. Flash chromatography (silica gel, EtOAc/hexane 2:3) of the residue, with degassed solvents, gave the selenocarbonate **15** as an oil; yield: 1.3 g (58%). This material crystallized as stable white needles on standing; mp 156–158 °C; $[\alpha]_{\text{D}}^{20} +102$.

18.11.2.1.2

Method 2:

Selenocarbonyls from the Reaction of Acetal Derivatives with Bis(dimethylaluminum) Selenide

This method has been developed to aid the study of the syntheses and reactivities of compounds containing multiple selenium bonds. The selenocarbonyl group is the target functionality. One of the goals was to generate and trap selenoaldehydes. Using bis(dimethylaluminum) selenide (**16**) with acetal derivatives provides a new and useful method for the synthesis of a variety of selenocarbonyl compounds such as **17** (Scheme 8).^[24]

Scheme 8 Use of Bis(dimethylaluminum) Selenide to Install the Selenocarbonyl Group^[24]



0,0-Diethyl Selenocarbonate (17):^[24]

CAUTION: Neat trimethylaluminum is highly pyrophoric.

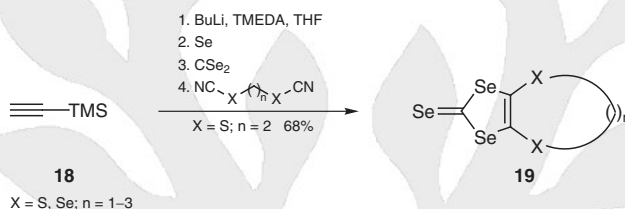
A 1.0 M soln of Me_3Al in hexane (1.1 mL, 1.1 mmol) was added to a soln of hexabutyl-distannaselenane (215 mg, 0.5 mmol) in toluene (10 mL) under argon, and the mixture was stirred for 3 h at 80 °C. After the addition of dioxane (10 mL) as a cosolvent, tetraethyl orthocarbonate (0.6 mmol) was added. The mixture was heated at 80 °C for 2.5 h, then cooled, and the product was purified by flash column chromatography (Florisil). (The

chromatography solvents were not reported, but most likely were mixtures of hexane and CH_2Cl_2 .) The selenocarbonate **17** was obtained as an oil; yield: 74%.

18.11.2.1.3

Method 3:**Selenocarbonates from Carbon Diselenide**

Most methods employing carbon diselenide are for the synthesis of compounds which have the general structures $(\text{R}^1\text{Se})(\text{R}^2\text{S})\text{C}=\text{Se}$ or $(\text{R}^1\text{Se})_2\text{C}=\text{Se}$. A more general use of carbon diselenide is hindered by its propensity to polymerize under a variety of conditions. In addition, the commercial availability is limited. Despite its cost and limited availability, it is operationally easy to use. Frequently, simply adding it to a solution with a co-reactant and reagent will give rise to the product. The example depicted in Scheme 9 is interesting because in this case the construction of the selenocarbonyl group is effected using unusual conditions.^[25]

Scheme 9 Synthesis of 4,5-Fused 1,3-Diselenole-2-selones^[25]**5,6-Dihydro-1,3-diselenolo[4,5-b][1,4]dithiin-2-selone (19, X = S; n = 2):^[25]**

CAUTION: Hydrogen selenide has a penetrating and disagreeable odor and is extremely toxic.

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

To a mixture of trimethylsilylacetylene (**18**; 0.282 mL, 2 mmol) and TMEDA (0.61 mL, 4 mmol) in dry THF (10 mL) cooled to -78°C was added 1.6 M BuLi in hexane (1.25 mL, 2 mmol). The soln was stirred for 30 min at the same temperature. To this lithium acetylide soln, Se (158 mg, 2 mmol) was added in one portion, then the mixture was allowed to warm to 0°C over a period of 2 h and was stirred for an additional 2 h at 0°C . The mixture was cooled to -90°C and CSe_2 (0.14 mL, 2.2 mmol) was added. The mixture was stirred for 3 min, quenched by the addition of ethane-1,2-diylbis(thiocyanate) (288 mg, 2 mmol) and allowed to warm to rt. H_2O (30 mL) was added to the mixture, and the insoluble material was collected by filtration, washed with MeOH (60 mL), and then recrystallized (CS_2) to give red plates of 5,6-dihydro-1,3-diselenolo[4,5-b][1,4]dithiin-2-selone. The filtrate and washings were combined and concentrated in vacuo. The residue was then taken up in CH_2Cl_2 (30 mL), washed with H_2O (90 mL), dried (MgSO_4), and then purified by column chromatography (silica gel, CS_2) to yield further material. Finally, the product was recrystallized (CS_2) to give additional red plates of the product; combined yield: 499 mg (68%); mp $148-149^\circ\text{C}$.

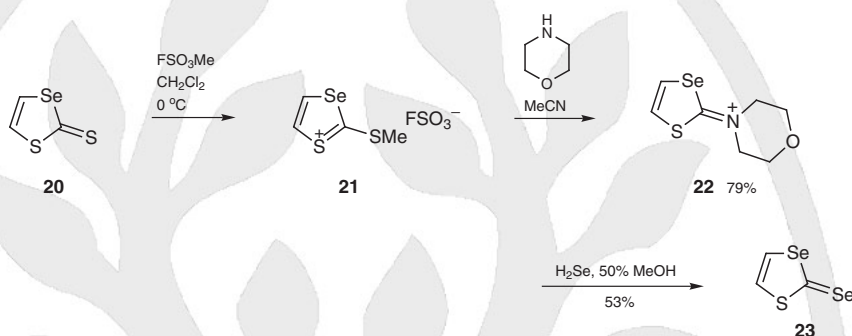
18.11.2.1.4

Method 4:**Selenocarbonates from Substitution Reactions with Sodium Hydrogen Selenide and Hydrogen Selenide**

Conceptually the addition of a highly nucleophilic species, such as neutral selenium or the negatively charged selenium in sodium hydrogen selenide, to an activated carbon atom which has a leaving group attached to it should give rise to the addition product. A

good example of a reagent which possesses these properties is **22** (Scheme 10). The iminium ion serves to withdraw electron density from the carbonyl carbon allowing for a site specific nucleophilic attack by the selenium. The intermediate tetrahedral carbon then expels the protonated morpholine unit giving rise to the selenocarbonyl group in **23**. This procedure enables the thiocarbonyl group in **20** to be replaced by selenocarbonyl via the salt **21**. For a synthesis of a selenodithiocarbonate by substitution with hydrogen selenide see Section 18.11.3.1.4.

Scheme 10 Synthesis of a Mixed S/Se Selenocarbonate^[26]



1,3-Thiaselenole-2-selone (**23**):^[26]

CAUTION: Hydrogen selenide has a penetrating and disagreeable odor and is extremely toxic.

To a soln of the 1,3-thiaselenole-2-thione (**20**; 1.8 g, 10 mmol) in CH_2Cl_2 (10 mL) at 0°C FSO_3Me (2 mL, 25 mmol) was slowly added with stirring. The salt **21** oiled out and solidified to a crystalline mass upon trituration with Et_2O . The crude salt (3 g) was washed by decantation with anhyd Et_2O several times, redissolved in dry MeCN, and treated with dry morpholine (1 mL) at 0°C . The mixture was stirred until all the MeSH was eliminated, then diluted with anhyd Et_2O to complete the precipitation of the morpholinium salt. Filtration, followed by recrystallization (MeCN/ Et_2O), gave white crystals of **22**; yield: 2.7 g (79%); mp 190°C .

The salt **22** (2 g) was suspended in 50% aq MeOH (25 mL) containing sat. NaHCO_3 (5 mL) under argon and then cooled in ice. Dropwise addition of acidified H_2O to Al_2Se_3 (0.6 g, 2.1 mmol) generated H_2Se which was driven by a stream of argon through the morpholine salt soln and subsequently through $\text{Pb}(\text{OAc})_4$ traps to decompose any unreacted excess H_2Se . The mixture, which turned yellow at first, became orange-red. Completion of the reaction was also confirmed by the appearance of black PbSe in the first trap. Argon was blown through the system to drive off any excess unreacted H_2Se before workup. The product was then extracted with CH_2Cl_2 , and the extract was washed with H_2O , dried, and evaporated to a red crystalline residue which was recrystallized (CH_2Cl_2 /hexane) to give **23**; yield: 700 mg (53%); mp 80°C .

18.11.3

Product Subclass 3: Selenocarbamates

Perhaps the simplest way to construct selenocarbamates is by the reaction of carbon diselenide with 1,2- or 1,3-amino alcohols and their derivatives. While formally a condensation reaction, it is procedurally simple and only requires carbon diselenide as the selenocarbonyl transfer agent. Although carbon diselenide is commercially available, the drawbacks of this direct method are that carbon diselenide is toxic and that a byproduct of the reaction is hydrogen selenide. In addition, because of the unpleasant odor of carbon diselenide, high-velocity hoods are required when working with this compound.^[27] With re-

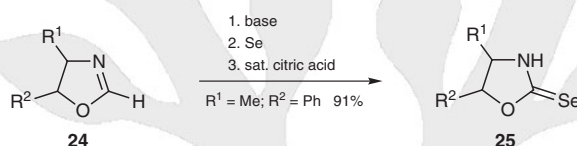
gard to isotope labeling, stable or otherwise, another drawback of this method is the inefficiency associated with using carbon diselenide, as one label is lost in the process. It is much simpler and more cost effective to begin stable isotope labeling with elemental ^{77}Se or ^{75}Se .^[28,29] For these reasons other methods for the installation of the selenocarbonyl unit into molecular frameworks have been developed specifically to avoid the use of carbon diselenide.

18.11.3.1 Synthesis of Product Subclass 3

18.11.3.1.1 Method 1: Synthesis of Cyclic Selenocarbamates from Metalation Reactions

The chiral dihydrooxazoles **24** are constructed in excellent yield and in enantiomerically pure form by the method of Meyers and co-workers.^[30–32] Metalation of dihydrooxazoles **24** can be accomplished using butyllithium, although better yields of the oxazolidine-2-selones **25** are obtained by using lithium diisopropylamide or lithium hexamethyldisilazide (Scheme 11).^[33]

Scheme 11 Synthesis of Cyclic Selenocarbamates^[33]



R ¹	R ²	Configuration	Method ^a	Yield ^b (%)	⁷⁷ Se NMR ^{c,d} (δ)	J _{C–Se} (Hz)	Ref
Me	Ph	4 <i>R</i> ,5 <i>S</i>	A	91	137	240	[33]
Me	Ph	4 <i>S</i> ,5 <i>R</i>	A	98	137	240	[33]
			B	71			[33]
<i>t</i> -Bu	H	4 <i>S</i>	C	90	119	237	[33]
<i>i</i> Pr	H	4 <i>S</i>	B	35–85 ^e			[33]
			C	92	118	233	[33]
Bn	H	4 <i>S</i>	B	36, 37			[33]
			C	98	139	237	[33]
<i>i</i> Bu	H	4 <i>S</i>	C	90	117	237	[33]
Ph	Ph	4 <i>S</i> ,5 <i>R</i>	A	83	156	229	[33]
Ph	H	4 <i>R</i>	A	85	140	237	[33]
			C	29			[33]

^a All reactions are performed using the dihydrooxazole (1–3 g) with base [1.15 equiv; generated using MeLi (1.2 equiv)] and Se (1.2 equiv). Method A: 1. LiHMDS, THF, –78 °C, 1 h; 2. Se, warm slowly; B: 1. BuLi, THF, –78 °C, 1 h; 2. Se, warm slowly; C: 1. LDA, THF, –78 °C, 1 h; 2. Se, warm slowly.

^b Isolated yields after column chromatography (silica gel, step gradient CH₂Cl₂ to Et₂O/CH₂Cl₂ 1:49).

^c Reference against 60% Me₂Se/CDCl₃.

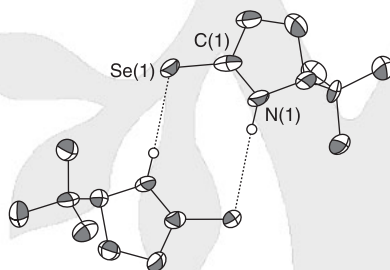
^d The selone ⁷⁷Se chemical shifts are concentration, solvent, and temperature dependent.

^e This reaction was repeated 10 times giving the stated yield range.

After examining a variety of reagents and conditions for deprotonation (Scheme 11), it was found that when there is an aromatic substituent on or near the dihydrooxazole ring, the use of lithium hexamethyldisilazane frequently gives an increased yield. For example, treatment of 1 gram of the dihydrooxazole **24** ($R^1 = \text{Ph}$; $R^2 = \text{H}$) with lithium hexamethyldisilazane gives rise to a pale yellow solution and an isolated yield of 85% of selenated product **25** ($R^1 = \text{Ph}$; $R^2 = \text{H}$). In contrast, treatment with lithium diisopropylamide results in the formation of a deep emerald solution. Addition of selenium, followed by acidification with citric acid and reaction workup, affords only 29% isolated yield of the product. In general, the use of butyllithium gives inconsistent results; the optimized yields for this series of oxazolidine-2-selones ranges from 83–98%. In addition, it has been found that reactions employing lithium hexamethyldisilazane can also be scaled up to give 5–15 grams of the product. Purification by silica gel chromatography using dichloromethane (with small amounts of ethyl acetate for the more polar compounds) affords the chiral selone compounds. In some cases, crystallization using hexanes and ethyl acetate is possible after the chromatography step.

Evidence for the presence of the $\text{C}=\text{Se}$ bond has been confirmed by comparing the ^{13}C – ^{77}Se coupling constants (230–240 Hz) with those previously reported for selenocarboxyls.^[34–37] In addition, crystal structures have been reported (Figure 1).^[38–42] The selones exist as discrete dimers that possess two unique $\text{Se}–\text{H}$ bonds. The nitrogen to selenium distances are on the order of 3.5 Å, and the selenium to hydrogen distance is ~2.35 Å. The $\text{C}=\text{Se}$ bond length is 1.80 Å (Figure 1).

Figure 1 ORTEP Representation of the X-ray Crystal Structure of (*S*)-4-*tert*-Butyloxazolidine-2-selone^[43]



(4*R*,5*S*)-4-Methyl-5-phenyloxazolidine-2-selone (25, $R^1 = \text{Me}$; $R^2 = \text{Ph}$); Typical Procedure:^[44]

CAUTION: This process should be performed in a high velocity fume hood. Bleach can be used to destroy any foul-smelling compounds. Do not combine acids with bleach.

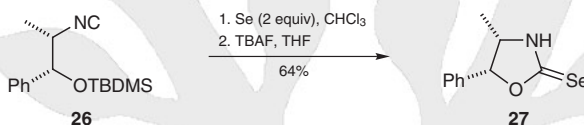
In a three-necked, 500-mL, round-bottomed flask fitted with a septum, ground glass stopper, and N_2 inlet, was placed $(\text{TMS})_2\text{NH}$ (15.01 mL, 71.32 mmol) in THF (250 mL). The soln was chilled to 0 °C, and 1.4 M MeLi in Et_2O (53 mL, 74 mmol) was added. After gas evolution ceased, the mixture was chilled to –78 °C, and (4*R*,5*S*)-4-methyl-5-phenyl-4,5-dihydrooxazole (**24**, $R^1 = \text{Me}$; $R^2 = \text{Ph}$; 10.00 g, 62 mmol) was added dropwise, neat (although a THF soln may be used). The resulting pale yellow soln was stirred for 30 min and then solid Se (5.6 g, 71 mmol, 100 mesh) was added. The mixture was then allowed to warm to rt and stirring was continued for 1 h. The reaction was quenched with degassed sat. citric acid until the pH of the aqueous layer remained acidic (pH ~4–5). The mixture was filtered through a pad of Celite, and the organic layer was isolated and dried (Na_2SO_4). Filtration, followed by removal of the volatiles in vacuo, afforded the crude product. The residue was then taken up in CH_2Cl_2 and filtered through a pad of silica gel. The pad was then washed with 2–5% Et_2O (distilled from benzophenone ketyl)/ CH_2Cl_2 until it was free of selone (by TLC analysis). Alternatively, acid-free EtOAc could be used in place of Et_2O , especially if

there was a concern of peroxides being present. The solvents were removed in vacuo and the residue was purified by flash chromatography (silica gel, CH_2Cl_2) to give selone **25** ($\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Ph}$); yield: 13.56 g (91%); mp 119–120 °C; $[\alpha]_{\text{D}}^{25} +166$ ($c\ 1 \times 10^{-3}$, CHCl_3). Long-term storage (6 months) of selones was best accomplished in CH_2Cl_2 soln at -20°C in the absence of light. A small quantity of a red precipitate (red Se) formed during long-term storage of CHCl_3 –selone solns in capped brown bottles (1–4 months) on the bench top at rt.

18.11.3.1.2

Method 2:**From Addition Reactions to Isoselenocyanates**

The synthesis of selenocarbamates, e.g. **27**, using isoselenocyanates (e.g., from isocyanides **26**) (Scheme 12) has several advantages over those which employ carbon diselenide: (1) the syntheses can be performed to give more than 10 grams of the selone; (2) any commercially available chiral amino alcohol can be used; (3) common and relatively inexpensive reagents are used, most of which do not need any special handling or waste disposal; (4) the use of carbon diselenide as a selenocarbonyl transfer agent is obviated.^[45]

Scheme 12 Synthesis of Cyclic Carbamates from Isocyanides^[45]**(4S,5R)-4-Methyl-5-phenyloxazolidine-2-selone (**27**):**^[45]

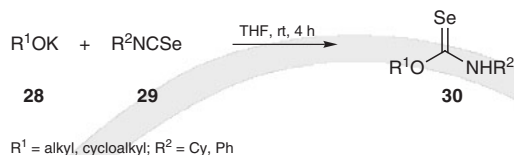
In a one-necked, 250-mL, round-bottomed flask fitted with a reflux condenser and a stirring bar was placed the isocyanide **26** (37.0 g, 0.135 mol) and elemental Se powder (1.99 equiv, 21.2 g, 268 mmol; 100 mesh, >99.5%) in CHCl_3 (50 mL). The mixture was refluxed, with stirring, under a blanket of N_2 for 5 h. The mixture was then filtered to remove any unreacted Se powder, and the filtrate was concentrated in vacuo to give the crude isoselenocyanate, as a red oil (48.4 g, 0.136 mol). This material was used immediately in the next step.

In a one-necked, 250-mL, round-bottomed flask fitted with a septum and a stirring bar was placed the isoselenocyanate (22 g, 62 mmol), prepared as above, in freshly distilled THF (150 mL). The resulting soln was chilled to 0°C . Under an N_2 atmosphere, a 1 M soln of TBAF in THF (50 mL) was added via a syringe. The mixture was stirred for 30 min, followed by filtration through silica gel. The filtrate was concentrated at reduced pressure and the residue purified by flash column chromatography (CH_2Cl_2). Evaporation of the solvent gave the selone **27** as a pale yellow solid; yield: 9.45 g (64% overall from isocyanide **26**).

18.11.3.1.3

Method 3:**By Addition of Alkoxides to Isoselenocyanates**

Barton and co-workers developed a method for the addition of alkoxides **28** to isoselenocyanates **29** to give selenocarbamates **30** (Scheme 13). They found that deprotonation of the alcohols with potassium hydride is superior to the use of sodium hydride or butyllithium in terms of overall yield. The alcohols range from primary to tertiary, and give yields from 60–92%. The authors also mention that all the selenocarbamates prepared show the presence of two rotational isomers in the NMR spectra.^[46]

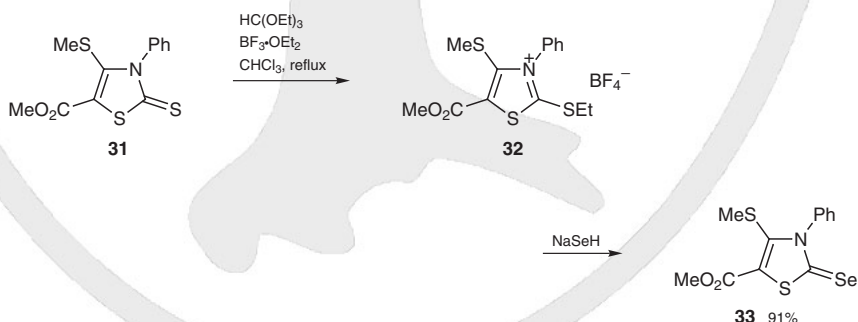
Scheme 13 General Synthesis of Linear Selenocarbamates^[46]**Barton Synthesis of Selenocarbamates 30; General Procedure:**^[46]

An alcohol **28** (1 equiv) was added to KH (3 equiv) in anhyd THF. The mixture was allowed to react under an inert atmosphere for about 2 h. The soln was decanted from the solid residue, slowly transferred to a THF soln of an isoselenocyanate **29** (1.2 equiv), and stirred at rt for 4 h. The reaction was monitored by TLC for the disappearance of the starting material. At the end of the reaction, the soln was diluted with Et₂O, extracted with H₂O and brine, and concentrated to afford an oil. Recrystallization (hexanes/CH₂Cl₂) gave a white crystalline solid. Some of the selenocarbamates were sufficiently stable for further purification by silica gel column chromatography.

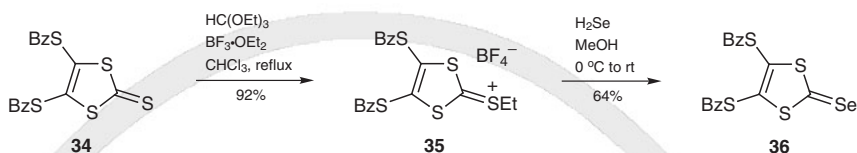
18.11.3.1.4

**Method 4:
Substitution Reactions with Sodium Hydrogen Selenide or
Hydrogen Selenide**

A commonly used method for the installation of the selenocarbonyl group within a heteroatom framework involves the substitution reaction of an activated precursor with hydrogen selenide or sodium hydrogen selenide. As shown in Scheme 14, the thiocarbonyl group in **31** serves as a key functional group capable of reacting with a variety of electrophiles ultimately giving rise to a leaving group by sulfur alkylation.^[47] In this example, the alkylation process using triethyl orthoformate in the presence of boron trifluoride–diethyl ether complex effectively transfers an ethyl group to the thiocarbonyl sulfur of **31**. The resulting iminium group of **32** activates the quaternary carbon for attack by the nucleophilic sodium hydrogen selenide species, giving rise to an intermediate tetrahedral species which can collapse to expel ethanethiolate to afford the selenocarbonyl compound **33** (Scheme 14).^[47–50]

Scheme 14 Thiocarbonyl–Selenocarbonyl Exchange Reactions^[47]

Scheme 15 illustrates that the reaction with hydrogen selenide also successfully gives rise to the selenocarbonyl group. In this case the starting material is a 1,3-dithiolane-2-thione **34**. Alkylation with triethyl orthoformate affords the corresponding sulfonium ion **35**. This ion effectively serves as an activated carbonyl compound allowing for the addition–elimination reaction with hydrogen selenide to form selone **36**.^[51,52]

Scheme 15 Thiocarbonyl–Selenocarbonyl Exchange Reaction Using a 1,3-Dithiolane-2-thione and Hydrogen Selenide^[51,52]**Methyl 4-(Methylsulfanyl)-3-phenyl-2-selenoxo-2,3-dihydrothiazole-5-carboxylate (33):**^[47]

CAUTION: Hydrogen selenide, which may be formed in this synthesis, has a penetrating and disagreeable odor and is extremely toxic.

To a soln of methyl 4-(methylsulfanyl)-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxylate (**31**; 1.00 g, 3 mmol) in CHCl_3 (15 mL) was added $\text{HC}(\text{OEt})_3$ (2 mL, 12 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (2 mL, 22 mmol).^[47–50] The mixture was refluxed overnight. The resulting 2-(ethylsulfanyl)-thiazolium tetrafluoroborate **32** was precipitated with Et_2O , filtered, and dried in vacuo, then redissolved in dry MeCN (15 mL). This soln was added dropwise to a soln of NaSeH prepared from powdered Se (0.53 g, 6 mmol) and NaBH_4 (0.25 g, 6.6 mmol) in abs EtOH (30 mL) under N_2 . After stirring for 20 min, the mixture was diluted with H_2O (100 mL). The precipitate was collected by filtration and washed with H_2O . The resulting yellow solid was dissolved in benzene (**CAUTION: carcinogen**) and the soln was dried (CaCl_2) overnight, then filtered through silica gel and eluted with benzene (6×40 mL). Removal of the solvent gave yellow crystals of the selone **33**; yield: 1.05 g (91%); mp 172 °C.

4,5-Bis(benzoylsulfanyl)-2-(ethylsulfanyl)-1,3-dithiolium Tetrafluoroborate (35):^[51]

$\text{HC}(\text{OEt})_3$ (3.9 g, 25 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (10.5 g, 34 mmol) were added to a CHCl_3 soln (70 mL) of the 1,3-dithiolane-2-thione **34** (6.1 g, 15 mmol). The soln was refluxed for 3.5 h, then cooled using an ice bath. Dry Et_2O (180 mL) was added and the red tarry precipitate was collected by filtration. The red solid became a pale yellow powder after air drying and was used without further purification; yield: 7.4 g (92%).

4,5-Bis(benzoylsulfanyl)-1,3-dithiole-2-selone (36):^[51]

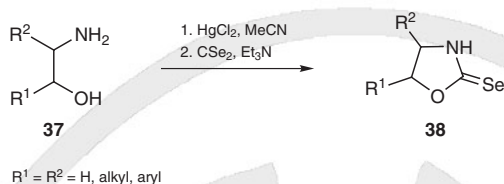
CAUTION: Hydrogen selenide, which may be formed in this synthesis, has a penetrating and disagreeable odor and is extremely toxic.

The tetrafluoroborate **35** prepared above was added in small portions to of a soln of H_2Se in MeOH at 0 °C which was prepared in situ from Se (3.2 g, 41 mmol), NaBH_4 in MeOH (100 mL), and AcOH (4 mL). The resulting soln was stirred for 3.5 h at 0 °C and then for 30 min at rt. Upon addition of BnCl (29 mL, 25 mmol), reddish-orange needle crystals formed from the reaction soln. The product was further purified by chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 1:1) to give the selone **36**; yield: 4.1 g (64%).

18.11.3.1.5

Method 5:**Addition of Carbon Diselenide to 1,2-Amino Alcohols**

The use of carbon diselenide for the construction of cyclic selenocarbamates is a straightforward process. However, a more general use of carbon diselenide is hindered by its propensity to polymerize under a variety of conditions. In addition, the commercial availability is limited. Despite its cost and limited availability, carbon diselenide is operationally easy to use and often simply adding it to a solution with a co-reactant such as 1,2-amino alcohol **37** and reagent will give rise to the product **38** as illustrated in Scheme 16.^[53,54]

Scheme 16 Cyclic Selenocarbamates from 1,2-Amino Alcohols and Carbon Diselenide^[53,54]**Oxazolidine-2-selones **38**; General Procedure:**^[53]

CAUTION: This process should be performed in a high velocity fume hood. Bleach can be used to destroy any foul smelling compounds. Do not combine acids with bleach.

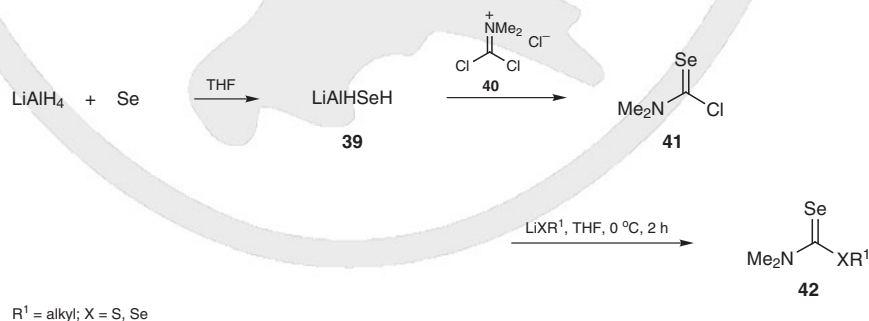
CAUTION: Mercury(II) chloride is a poison by ingestion and is toxic by skin contact. When heated to decomposition it emits toxic fumes of mercury.

A 1,2-amino alcohol **37** (5 mmol) was added to a well stirred soln of HgCl_2 (1.36 g, 5 mmol) in MeCN (20 mL) under argon, resulting in the immediate separation of a colorless solid. CSe_2 (0.32 mL, 5 mmol) was added, followed by Et_3N (1.39 mL, 10 mmol), causing a change in color of the precipitate from colorless to black within seconds. The mixture was stirred for 20 min, then filtered through a pad of Celite into a half-sat. brine soln (200 mL). Three extractions with CH_2Cl_2 (100 mL, then 2×50 mL), drying (MgSO_4), and evaporation to dryness gave the crude oxazolidine-2-selone, which was purified by column chromatography (silica gel 40, EtOAc), followed by recrystallization from appropriate solvents [EtOAc/hexane, benzene (**CAUTION: carcinogen**)/hexane or EtOAc].

18.11.3.1.6

Method 6:**From Lithium Aluminum Hydride Hydroselenide and Viehe's Salt**

This method involves the use of an aluminum–selenium complex **39** and its reaction with Viehe's salt **40**. This formal addition–elimination process, however, allows for more flexibility in trapping the intermediate with a variety of nucleophiles such as amines, lithium alkanethiolates, and lithium alkaneselenolates. The aluminum–selenium complex is reacted with **40** in situ to give presumably the corresponding *N,N*-dimethylselenocarbamoyl chloride (**41**). Addition of the nucleophilic species gives rise to the products **42** (Scheme 17).^[55]

Scheme 17 Construction of the Mixed Carbamates^[55]

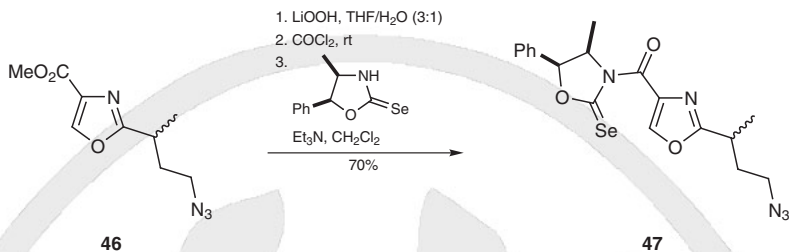
gave the product **45** ($R^1 = 4\text{-Tol}$; $R^2 = \text{Bu}$); yield: 0.86 g (42% assuming the limiting agent was BuTeH); mp 92–93 °C. The product must be stored under argon below –15 °C as soon as possible.

18.11.3.2 Applications of Product Subclass 3 in Organic Synthesis

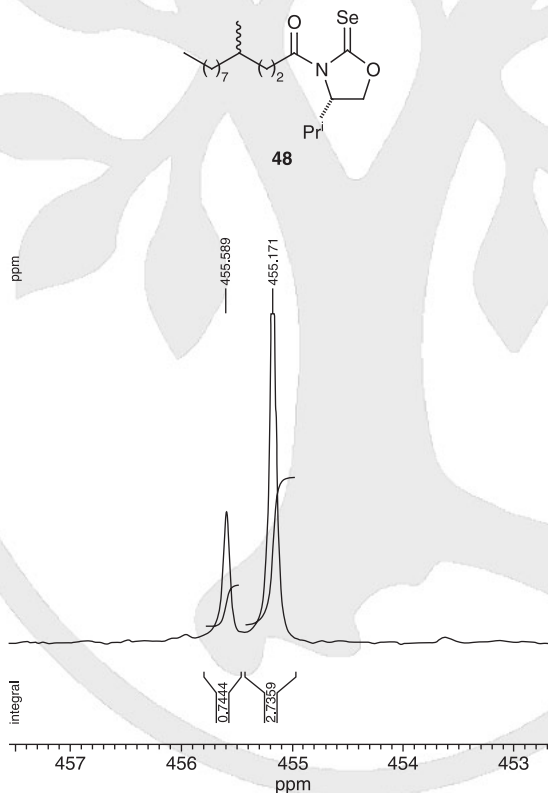
18.11.3.2.1 Method 1: As an Analytical Tool for the Discrimination of Remotely Disposed Chiral Centers

Selenium reagents have enjoyed widespread use in synthetic organic chemistry for selective transformations such as selenoxide eliminations,^[59–63] selenium-promoted chiral oxidations of alkenes,^[64,65] radical-initiated carbocyclizations that employ selenoesters,^[66] and novel stereoselective reactions.^[10,67,68] However, the selenium atom has only recently been exploited as a novel spectroscopic reporter group in the study of various inorganic, organic, and biochemical systems.^[69] The sensitivity of the ^{77}Se nucleus (6.93×10^{-3} with respect to ^1H and 2.98 compared to ^{13}C), its natural abundance (7.5%) and spin ($I = 1/2$) make it an excellent candidate for an NMR reporter nucleus. For NMR spectroscopy applications ^{77}Se has a large chemical shift range (~3400 ppm), and the selenium nucleus is extremely sensitive to its electronic environment. In an effort to gain insight into the electronic and structural features which affect the chemical shift sensitivity of these systems, a variety of chiral cyclic selenocarbamates have been coupled with (\pm)-2-phenylpropanoyl chloride.^[33,43,44,70–75] The results of these ^{77}Se NMR experiments suggest that the greatest chemical shift sensitivity is observed in toluene- d_8 and a remarkably large selenium chemical shift difference of 45.6 ppm is observed for the diastereomers. There has been significant interest in chiral selones and selenides for the detection and quantitation of chirality at remotely disposed centers by ^{77}Se NMR spectroscopy.^[76,77] Numerous reports of their use with carboxylic acids and acid chlorides, amino acids, amines, alcohols, allenic compounds, and alkyl halides exemplify the versatility of chiral selone derivatizing reagents. The optimal conditions for the NMR experiment have been reported and, in addition, it has been demonstrated that these reagents are useful in the determination of the absolute configuration of amino acids using circular dichroism (CD) spectroscopy. In general, these reagents will be most useful for the detection of chiral centers that are remotely disposed. In a few cases where the coupling reaction has proven not to be quantitative, it was observed that this was due to kinetic resolution in the reaction of the enantiomers with the chiral selone when the chiral center was proximal to the coupling sites, particularly for the amine adduct formation reaction. When the chiral center is remote, the differences in the transition states should be minimal and the reaction course, therefore, is not influenced by the distant chiral center.

These chiral selone derivatizing reagents have been used to evaluate the enantiomeric purity of previously uncharacterized synthetic products. An improved preparation of the C26–C32 oxazole subunit **46** of calyculin A has been reported by Smith and co-workers.^[78] The authors demonstrated that commercially available chiral derivatizing agents fail to provide the necessary data to evaluate the enantiomeric purity of the C26–C32 oxazole segment **46**.^[78,79] After forming the selone adduct **47**, the chiral center is seven bonds removed from the selenium nucleus. The ^{77}Se NMR spectrum of the selone adduct displays two unequal resonances separated by more than 1.5 ppm, thereby establishing the enantiomeric purity of the target compound (Scheme 19).

Scheme 19 Oxazole Subunit C26–C32 of Calyculin A^[78]

Selones have been useful in the determination of products obtained in the enzymatic resolution of methyl alkanolic acids.^[80] When the methyl group is three bonds removed from the carbonyl, a level of resolution is achieved using immobilized *Candida rugosa* lipase. Less selectivity is shown when the methyl group is situated on more remote positions. The products of the resolutions are converted into the amide adduct of (*S*)-4-isopropyl-oxazolidine-2-selone, for example **48**, and the enantiomeric ratios determined by ⁷⁷Se NMR (Figure 2). As shown in Figure 2, the exquisite chemical shift sensitivity of the chiral selone shows that the enzymatic process is capable of enriching one enantiomer.^[80]

Figure 2 One-Dimensional ⁷⁷Se NMR Spectrum of the Chiral Selone Derivative of a Partially Resolved Carboxylic Acid^[80]

18.11.3.2.2 **Method 2:**
Stereoselective C–C Bond Formation via
Chiral Selone Promoted Aldol Reactions

Chiral *N*-acylselones have been shown to enolize easily using a Lewis acid, such as titanium(IV) chloride, and a tertiary amine base. The resulting titanium enolate of the acylated selone then reacts with a variety of aldehydes giving the aldol products. The enolate undergoes reactions with, for example, benzaldehyde to afford the aldol product in 87% yield, this being the non-Evans *syn*-product. In special cases, the reaction can be tuned to provide an *anti*-aldol product.^[68]

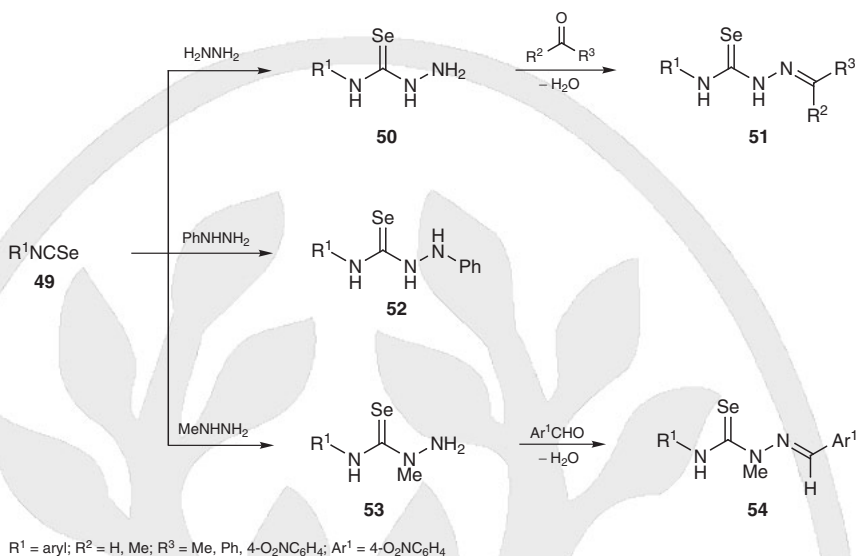
18.11.4 **Product Subclass 4:**
Selenosemicarbazides and Selenosemicarbazones

The synthesis of selenosemicarbazides was first reported by Jensen and co-workers.^[81] The reaction of phenyl isoselenocyanate with hydrazine hydrate produces 4-phenylselenosemicarbazide. The potential for significant biological activity of selenosemicarbazides has been recognized.^[82] Selenosemicarbazides have been shown to have significant antibacterial activity^[83] and to have immunomodulatory effects as they alter neutrophil functions in a mouse model.^[84] Strong antitumor activity against Ehrlich ascites tumor cells have been reported for benzaldehyde/cinnamaldehyde selenosemicarbazones.^[85] Comparative studies of 5-hydroxypyridine-2-carbaldehyde selenosemicarbazone with other compounds showed antineoplastic activity in mice bearing Sarcoma 180 ascites cells which correlates with the inhibition of in vitro DNA formation by ascites cells and the metal-binding capacity. In addition, RNA conversion into DNA is also inhibited by this compound.^[86] Selenosemicarbazides have also been used in the preparation of cadmium–selenium, zinc–selenium, silver–selenium, and mercury–selenium films and deposits.^[87]

18.11.4.1 **Synthesis of Product Subclass 4**

18.11.4.1.1 **Method 1:**
Synthesis from Isoselenocyanates and Hydrazine

Aryl isoselenocyanates **49** react with hydrazine hydrate in organic solvents in good to excellent yields to give the corresponding colorless, odorless, and crystalline arylselenosemicarbazides **50** (Scheme 20).^[88] The exothermic reaction is best run by adding the aryl isoselenocyanate solution to a cooled solution containing a small excess of hydrazine hydrate to avoid the formation of decomposition products. Further reaction to form biselenourea compounds is only observed on heating molar equivalent amounts of the selenoisocyanate in ethanolic solution. Methylhydrazine will give, in up to 90% yield, only 2,4-disubstituted selenocarbazides **53**. The analogous isothiocyanates form both 1,4- and 2,4-disubstituted products with phenylhydrazine, depending on temperature and solvent; selenoisocyanates and phenylhydrazine give 1,4-disubstituted products **52** exclusively and in good yield. These 1,4-disubstituted selenocarbazides will not react with carbonyls, whereas unsubstituted (e.g., **50**) and 2,4-disubstituted selenosemicarbazides (e.g., **53**) can be converted into the corresponding selenosemicarbazones **51** and **54** in near quantitative yield by heating an ethanol solution of the semicarbazide in the presence of acetic acid and an aldehyde or ketone.

Scheme 20 Synthesis of Selenourea Compounds from Isoselenocyanates^[88]**4-Arylselenosemicarbazides 50; Typical Procedure:**^[88]

100% Hydrazine hydrate (5.5 g, 100 mmol; plus small excess) was dissolved in EtOH (50 mL) and cooled in an ice bath. The aryl isoselenocyanate **49** (100 mmol), dissolved in CHCl_3 (50–60 mL), was added dropwise, keeping the temperature below 10 °C. After a short time, a precipitate began to form. The mixture was then kept for 1 h at rt. The precipitate was collected by filtration, washed with ice-cold EtOH, and recrystallized (EtOH) to obtain the crystalline colorless or slightly yellow products **50**; yield: 80–98%.

Benzaldehyde 4-Arylselenosemicarbazones 51 ($\text{R}^2 = \text{H}$; $\text{R}^3 = \text{Ph}$); Typical Procedure:^[88]

4-Arylselenosemicarbazides **50** (10 mmol), prepared as above, and freshly distilled PhCHO (1.1 g, 10 mmol) were refluxed for 10 min in EtOH (50 mL) with a few drops of AcOH. The hot soln was filtered and, on cooling, crystals precipitated, which were recrystallized (EtOH) to give the benzaldehyde 4-arylselenosemicarbazones **51**; yield: 84–96%.

4-Aryl-2-methylselenosemicarbazides 53; Typical Procedure:^[88]

A soln of an aryl isoselenocyanate **49** (20 mmol) in CHCl_3 was slowly added to an ice-cold soln of methylhydrazine (1.0 g, 20 mmol). Precipitation of the product was complete after 30 min. The products were collected by filtration and recrystallized (EtOH) to give 4-aryl-2-methylselenosemicarbazides **53** as colorless to slightly yellow crystals; yield: 8–92%.

In a similar manner, 4-aryl-1-phenylselenosemicarbazides **52** were obtained as slightly colored to colorless crystals from a 4-aryl isoselenocyanate and phenylhydrazine; yield: 75–96%.

18.11.5 **Product Subclass 5:**
Selenoureas

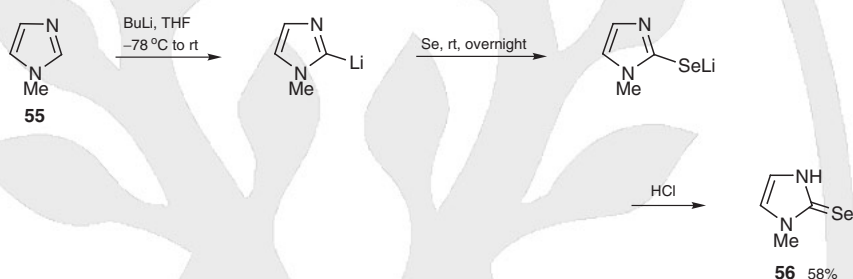
This group of selenocarbonyls was the first to be prepared, probably due to their stability and ease of construction. These selenoureas have been constructed using a variety of methods, perhaps the most easily of them involves the addition of carbon diselenide to amines.

18.11.5.1 Synthesis of Product Subclass 5

18.11.5.1.1 Method 1:
From Metalation Reactions

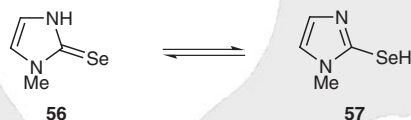
Guziec and co-workers reported a directed metalation route to the selenium analogue of methimazole (1-methyl-1,3-dihydro-2H-imidazole-2-thione).^[89] Methimazole belongs to a class of thiourylene drugs, which are antithyroid agents. It has been speculated that the selenone analogue **56** would offer greater biological activity over the thione derivative. Initial attempts to prepare this analogue with the commonly used alkylation–selenation sequence failed to afford the desired derivatives. An approach involving the metalation of 1-methylimidazole **55** was then developed and optimized (Scheme 21). In addition, this route provides access to unsymmetrical cyclic selenoureas.^[89]

Scheme 21 Metalation of an Imidazole and Subsequent Insertion of Selenium into the C–Li Bond^[89]



One interesting feature of the selenourea unit, is the possibility of tautomers (Scheme 22), as the selenocarbonyl could exist in its enol **57** or keto form **56**. The selenol form would allow the formation of the C=N bond and a cyclic aromatic system. However, it would be expected that the selenol form would be unstable in air, oxidizing to the diselenide. More information about the electronic state of the selenocarbonyl has been obtained by examining the ¹³C and ⁷⁷Se coupling constant for the selenocarbonyl unit. The coupling constant was determined to be ~220 Hz, which is typical of the values obtained for C=Se bonds (230–240 Hz) as opposed to the 110–140 Hz values determined for allylic-like systems which the vinyl selenol form represents.

Scheme 22 Tautomeric Equilibrium of Selenoureas



1-Methyl-1,3-dihydro-2H-imidazole-2-selone (56); Typical Procedure:^[89]

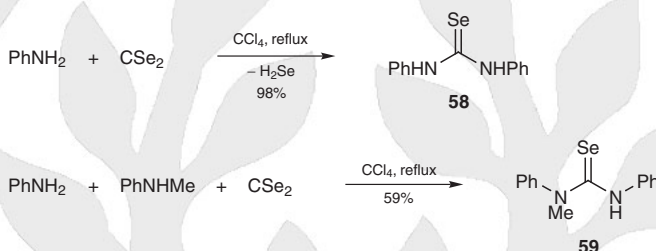
To a soln of 1-methylimidazole (**55**; 0.485 mL, 6.09 mmol) in freshly distilled THF (50 mL) at -78°C was added 1.6 M BuLi in hexanes (3.8 mL, 6.09 mmol) via syringe. The mixture was stirred with cooling for 35 min and then allowed to warm to rt. Then, elemental Se (0.721 g, 9.14 mmol) was added. The resulting mixture was stirred at rt overnight under N_2 . After cooling, the mixture was quenched with H_2O and neutralized with 1 M HCl. The aqueous mixture was extracted with CHCl_3 , and the organic layer was washed with brine and dried (Na_2SO_4). Removal of the solvent afforded an orange solid; yield: 568 mg (58%); mp $130\text{--}133^{\circ}\text{C}$. Recrystallization (EtOAc /hexanes) afforded analytically pure orange crystalline product; mp 142°C .

18.11.5.1.2

**Method 2:
From Carbon Diselenide**

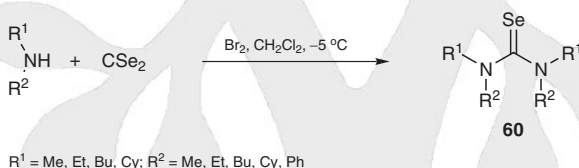
The reaction of carbon diselenide with an excess of primary amines affords symmetrical selenoureas, e.g. **58** (Scheme 23). It has been suggested that this type of reaction goes through an isoselenocyanate intermediate. Methods have been developed to construct symmetrical, unsymmetrical, and a variety of *N*-alkyl-substituted selenoureas, e.g. **59**.^[54,90]

Scheme 23 Double Addition of Anilines to Carbon Diselenide To Give the Selenourea^[54,90]



Tetrasubstituted selenoureas **60** with up to two secondary alkyl or two aryl substituents, the remaining substituents being alkyl, can be prepared in one or two steps from carbon diselenide with overall yields of approximately 60% (Scheme 24).^[91]

Scheme 24 Synthesis of Tetrasubstituted Symmetrical Selenoureas Using an Unusual Bromine-Mediated Reaction^[91]

**1,3-Diphenylselenourea (58); Typical Procedure:**^[54]

CAUTION: Hydrogen selenide has a penetrating and disagreeable odor and is extremely toxic.

A soln of CSe₂ (0.32 mL, 5 mmol) in CCl₄ (100 mL) (**CAUTION:** toxic) was added dropwise over a 1 h period to a stirred refluxing soln of aniline (4.6 mL, 0.05 mol) in CCl₄ (50 mL). A stream of N₂ was passed through the mixture during the entire period. The refluxing was continued for 30 min until evolution of H₂Se was no longer detected using moistened Pb(OAc)₄ paper. The mixture was cooled and filtered to give 1,3-diphenylselenourea; yield: 1.36 g (98%); mp 190–192 °C. The pale gray product was recrystallized (EtOH) under N₂ to give a colorless product with no increase in mp.

1-Methyl-1,3-diphenylselenourea (59); Typical Procedure:^[90]

A soln of CSe₂ (1.7 g, 0.64 mL, 10 mmol) in CCl₄ (100 mL) (**CAUTION:** toxic) was added dropwise over a 2 h period to a stirred refluxing soln of aniline (1.1 g, 12 mmol) and *N*-methylaniline (44 mL, 0.4 mol) in CCl₄ (200 mL). Refluxing was continued for an additional 3 h. A slow stream of nitrogen was passed through the mixture during the entire period. The resulting soln was concentrated at reduced pressure at 50 °C, treated with ice-cold 2 M HCl (250 mL), and extracted with Et₂O. The Et₂O extract was washed with H₂O, dried (MgSO₄), and concentrated to give a syrup. This was dissolved in hot CCl₄ (25 mL) and treated with hexane until slightly cloudy. Cooling to the soln to 0 °C overnight gave the product as pale yellow crystals; yield: 1.7 g (59%); mp 98–99 °C.

Tetraalkylselenoureas 60; General Procedure:^[91]

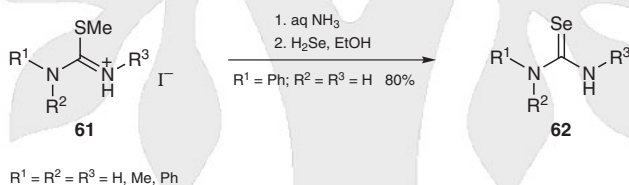
CAUTION: Bromine is a severe irritant of the eyes, mucous membranes, lungs, and skin. Liquid bromine causes severe and painful burns on contact with eyes and skin.

A dialkylamine (20 mL) in CH_2Cl_2 (10 mL) and Br_2 (4 mmol) in CH_2Cl_2 (10 mL) were mixed at -5°C . CSe_2 (4.0 mmol) in CH_2Cl_2 (10 mL) was then added. The mixture was stirred for 1 h at rt. Se (4 mmol) was recovered by filtration. The filtered soln was then washed with H_2O , dried, filtered, and evaporated. The crude selenourea was extracted with hexane at -40°C and the extract was filtered through a short column of silica gel ($1\text{ g}\cdot\text{mmol}^{-1}$). The column was eluted with hexane containing 10–30% Et_2O and the eluate was evaporated in vacuo to give the selenourea.

18.11.5.1.3

Method 3:**From Substitution Reactions with Sodium Hydrogen Selenide or Hydrogen Selenide**

The use of hydrogen selenide or sodium hydrogen selenide as a nucleophilic source of selenium for the installation of the selenocarbonyl group in selenoureas has enjoyed widespread use, because it uses simple precursors. For example, elemental selenium can be reduced with sodium borohydride to give a solution of sodium hydrogen selenide which can be used immediately as an in situ reagent. For the synthesis of mono, *N,N'*-di- and tri-substituted selenoureas **62**, a method has been developed using 2-methylisothiureas **61** which can be prepared by the methylation of the corresponding thioureas with iodo-methane.^[92–96] As illustrated in Scheme 25, the groups on the nitrogen can be selected to provide any combination of substituted selenoureas.

Scheme 25 Selenoureas from Isothiureas^[92–96]**Phenylselenourea (62, $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{R}^3 = \text{H}$); Typical Procedure:**^[96]

CAUTION: Hydrogen selenide has a penetrating and disagreeable odor and is extremely toxic.

CAUTION: Inhalation, ingestion, or absorption of iodo-methane through the skin can be fatal.

MeI (14.3 g, 0.1 mol) was added to a soln of phenylthiourea (15.2 g, 0.1 mol) in a minimum quantity of acetone and the mixture was allowed to stand at rt overnight. The mixture was concentrated and the precipitated product isolated by filtration, washed with Et_2O , and dried to give 2-methyl-1-phenylisothiurea hydroiodide; yield: 26.5 g (90%); mp 144°C .

A soln of the hydroiodide (29.5 g, 0.1 mol) in distilled water (800 mL) was cooled to 0°C and basified with concd aq NH_3 . The precipitated product was collected by filtration, washed thoroughly with H_2O , and dried to give 2-methyl-1-phenylisothiurea (**61**, $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{R}^3 = \text{H}$); yield: 15.7 g (95%); mp 87°C .

Dry H_2Se (32.4 g, 0.4 mmol, generated from Al_2Se_3 by the addition of H_2O , and dried by passing through a CaCl_2 tube) was passed through a soln of 2-methyl-1-phenylisothiurea (**61**, $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{R}^3 = \text{H}$; 16.6 g, 0.1 mmol) in the minimum quantity of refluxing EtOH over a period of 2 h. The mixture was then allowed to stand at rt overnight and concn-

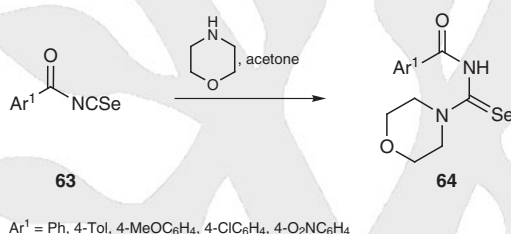
trated on a rotary evaporator. The precipitate was isolated by filtration and recrystallized (EtOH) to give the product; yield: 15.95 g (80%); mp 190 °C.

18.11.5.1.4

Method 4:**From Addition Reactions to Isoselenocyanates**

Isoselenocyanates^[77,96] are valuable starting materials for the construction of selenoureas and selenosemicarbazides, and by extension, important for the synthesis of selenium-containing heterocycles. Several routes are available for the synthesis of isoselenocyanates. These include the reaction of selenium with isocyanides,^[45] alkylation of the selenocyanate ion,^[97] which yields both isoselenocyanates and selenocyanates,^[98] the reaction of selenide ion with *N*-arylcarbimidic dichlorides,^[99] and the reaction of isocyanates with phosphorus(V)–selenium complexes.^[100] Another process developed by Henriksen is a one-step synthesis from primary amines and carbon diselenide.^[101] Primary amines form 1:1 adducts with mercury(II) chloride. This complex reacts with carbon diselenide in the presence of triethylamine to give the isoselenocyanates. Reaction of isoselenocyanates **63** with a variety of amines gives the selenoureas **64** directly (Scheme 26).^[102]

Scheme 26 Synthesis of Selenoureas by the Addition of Amines to Isoselenocyanates^[102]

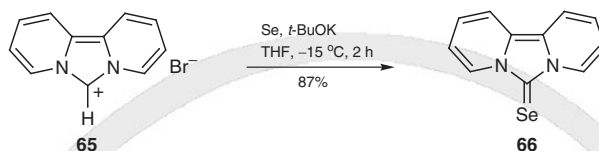
**Selenoureas 64; General Procedure:**^[103]

To a stirred soln of the isoselenocyanate in acetone at rt, NH_3 or a primary or secondary amine (1 equiv) was added. The soln became orange immediately. The disappearance of the isoselenocyanate was determined by TLC analysis. When the isoselenocyanate had reacted, usually after 5–10 min, the soln was poured into H_2O . In most cases a yellow precipitate was formed when the mixture stirred for 1 h. When an emulsion was formed, the mixture was stirred for another few h, and a small amount of MgSO_4 was added to accelerate the precipitation. The suspension was filtered and the resulting solid was air dried. The products were pure enough for further reaction. For analytical purposes, an aliquot was recrystallized to give yellow or yellowish crystals; yield: 60–97%.

18.11.5.1.5

Method 5:**From Carbene Reactions with Selenium**

The reaction of carbenes with molecular oxygen, sulfur, selenium, and tellurium gives rise to the corresponding carbonyl analogues.^[104] This method is limited by the availability of the carbene intermediate. Despite this limitation, this method has allowed the simple construction of a variety of selenoureas and lesser known tellurooureas. As illustrated in Scheme 27, the structurally novel urea derivative **66** is synthesized by treating the nucleophilic dipyridoimidazol-2-ylidene generated from dipyridoimidazolium salt **65** with selenium.^[105] These nucleophilic carbenes are stable in solution at -30°C for several hours and can be trapped by a multitude of electrophiles, both organic and inorganic, to give generally stable derivatives.

Scheme 27 Carbene Generation and Reaction with Selenium^[105]**6H-Dipyrido[1,2-c:2',1'-e]imidazole-6-selone (**66**):**^[105]

To a suspension of dipyrido[1,2-c:2',1'-e]imidazolium bromide (**65**; 0.23 g, 0.93 mmol) in THF (50 mL) was added Se (0.08 g, 1.03 mmol) followed, at -15 °C, by the addition of *t*-BuOK (0.13 g, 1.13 mmol). After 2 h, the mixture was filtered through Celite and the solid was washed with THF (10 mL). The combined filtrate and washings were concentrated to a volume of a few mL and pentane (30 mL) was added. The resulting red suspension was filtered, and the collected solid was washed with pentane (10 mL) and dried in vacuo for 2 h to give the product as an orange-red solid; yield: 0.20 g (87%); mp 225 °C.

18.11.5.1.6

Method 6:**From Addition of Potassium Selenocyanate to Primary Ammonium Salts or Amines**

Selenoureas **69** are prepared from the reaction of potassium selenocyanate **67** with ammonium salts of primary amines, such as **68** (Scheme 28).^[106,107] This method allows the construction of monoalkylselenoureas and does not require the initial generation of an isoselenocyanate or use of hydrogen selenide. The ⁷⁷Se isotope can easily be incorporated into this scheme by fusion of selenium with potassium cyanide.

Scheme 28 Synthesis of a Monoalkyl Selenourea^[106,107]**Potassium Selenocyanate (**67**):**^[107]

CAUTION: Cyanide salts can be absorbed through the skin and are extremely toxic.

A mixture of KCN (10.5 g, 0.161 mol) and Se (12.0 g, 0.152 mol) was heated until the mixture melted. The melt was cooled, taken up in acetone, saturated with CO₂, and then filtered. The filtrate was concentrated giving colorless crystals. The solids were then washed with Et₂O and dried in vacuo to give the product; yield: not reported.

Benzylselenourea (69**):**^[106,107]

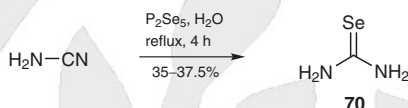
A soln of BnNH₃Cl (**68**; 1.0 g, 6.9 mmol) in abs EtOH was added with stirring to a soln of KSeCN (**67**; 1.0 g, 6.9 mmol) in abs EtOH. The reaction time and conditions were not reported. However, it is possible that the reaction can be monitored for completion by ⁷⁷Se NMR spectroscopy using a long delay time because the T₁ of the KSeCN is relatively long. The solids were removed by filtration and evaporation of the alcohol gave white crystals of **69**; yield: not reported; mp 79–80 °C.

18.11.5.1.7

**Method 7:
From Cyanamide and Phosphorus Pentaselenide**

Selenourea **70** is formed by the reaction of cyanamide and phosphorus pentaselenide (Scheme 29). It was noted that one advantage of this process is the avoidance of the use of hydrogen selenide.^[108]

Scheme 29 Selenourea from Cyanamide and Phosphorus Pentaselenide^[108]


Selenourea (70):^[108]

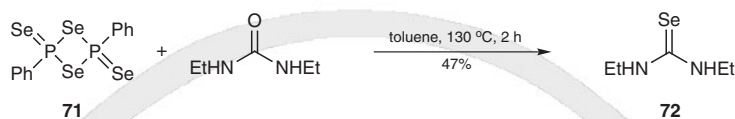
CAUTION: Cyanamide may decompose violently above 50 °C on contact with water, acids, or alkalis, and should be stored below 27 °C. It can cause dermatitis and is an eye, skin, and mucous membrane irritant.

To a refluxing soln of cyanamide (4.2 g, 0.1 mol) in H₂O (20 mL), P₂Se₅ (9.1 g, 0.02 mol) was added portionwise over 3 h. Refluxing was continued for a further 1 h, the hot soln was then filtered, and on standing white needles precipitated. Recrystallization (H₂O) gave the product; yield: 4.3–4.6 g (35–37.5%); mp 205 °C (dec).

18.11.5.1.8

**Method 8:
From the Woollins Reagent**

There have been numerous efforts to develop a selenation reagent that is analogous to Lawesson's reagent, the well-known and frequently used thionation agent. Hill and co-workers reported the use of a Woollins reagent, presumed to be 2,4-diphenyl-1,3,2,4-diselenadiphosphetane 2,4-diselenide (**71**) (Scheme 30), obtained from pentaphenylpentaphospholane and elemental selenium (P/Se ratio 1:2) for converting tungsten(V) and molybdenum(V)–ketenyl complexes into their selenoketenyl counterparts.^[109] The structure of this reagent was subsequently confirmed as **71**.^[110] The use of **71** as an oxygen/selenium carbonyl exchange reagent has been reported.^[111] The range of carbonyl functional groups to which this reagent has been applied is as follows, with the yields of the selenocarbonyl given in parentheses; *N,N*-dimethylbenzamide (72%), *N*-methylbenzamide (70%), *N*-*tert*-butylbenzamide (30%), benzamide (13%), tetramethyloxalamide (38%, monoselenocarbonyl), caprolactam, (44%), and a variety of indolizine-3-carbaldehydes (40–59%). Scheme 30 illustrates the preparation of selenourea **72** from 1,3-diethylurea. The authors noted several advantages of this selenating reagent ranging from its stability in air, long shelf life, and ease of preparation and handling. This is in contrast with other reagents such as sodium hydrogen selenide, hydrogen selenide, bis(diisobutylaluminum) selenide, hexamethyldisilaselanane, and bis(cyclooctane-1,5-diylboryl) selenide, which are either moisture sensitive or require fresh preparation prior to use. Moreover, the authors note that facile purification of the selenocarbonyl compounds and its moderate tolerance towards amine protons makes the Woollins selenating reagent **71** of great promise.^[111]

Scheme 30 Reaction of the Woollins Reagent with a Urea To Give the Selenocarbonyl Derivative^[111]**2,4-Diphenyl-1,3,2,4-diselenadiphosphetane 2,4-Diselenide (71):**^[112]

Na (1.2 g, 52.2 mmol) was dissolved in liq NH₃ (50 mL) at –78 °C and then Se (2.061 g, 26.1 mmol) was added, resulting in a dark red mixture. After 15 min of stirring, the NH₃ was allowed to evaporate and was replaced by toluene (50 mL). An excess of PhPCl₂ (6.60 mL) was added and the soln was refluxed for 24 h. The progress of the reaction was followed by ³¹P NMR. Se (3.435 g, 43 mmol) was added and the mixture was refluxed for an additional 3.5 h. On cooling to rt, the red crystalline product formed and was collected by filtration; yield: 5.68 g (82%).

1,3-Diethylselenourea (72); Typical Procedure:^[111]

To the Woollins reagent **71** (0.2 mmol) with 1,3-diethylurea (0.6 mmol) was added anhyd toluene (2 mL) under N₂. The mixture was then heated to 130 °C for 2 h. The resulting orange soln was cooled to rt. The solvent was then removed in vacuo and the selenourea was purified by column chromatography (silica gel, CH₂Cl₂); yield: 47%.

18.11.6 Product Subclass 6:
Phosphorus-Substituted Selenocarbonyl Derivatives
18.11.6.1 Synthesis of Product Subclass 6
18.11.6.1.1 Method 1:
From Addition Reactions to Carbon Diselenide

There are few reports of the synthesis of phosphorus selenocarbonyl compounds. Triethylphosphine has been added to carbon diselenide to give rise to a zwitterion adduct. This adduct has been useful in the synthesis of a phosphoniodiselenole heterocycle, which is an intermediate in the synthesis of selenium-containing charge-transfer complexes.^[113,114]

18.11.7 Product Subclass 7:
Tellurocarbonyl Dihalides

The preparation of tellurocarbonyl difluoride and a tellurone have allowed the study and characterization of these compounds. For tellurocarbonyl difluoride, which is stable at –196 °C, gas-phase IR and mass spectra were obtained. The isolation of this compound is of great interest because theoretical studies predicted a genuine C=Te bond. The elusiveness of tellurocarbonyls is reflected in their long bond lengths, which leads to a decreased π -overlap, a result of the increasingly diffuse character of the p orbital going from O > S > Se > Te. These compounds may prove to be of interest for both the development of new chemistries and for the deposition of tellurium-containing layers for material chemistry applications.

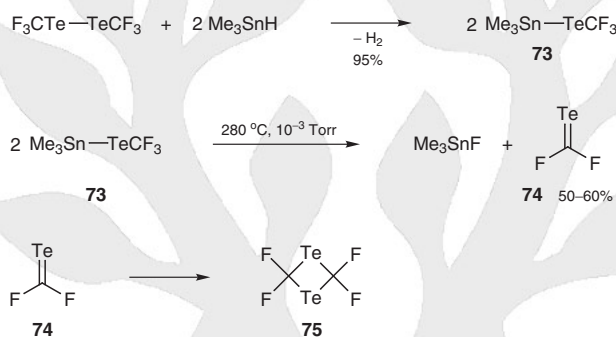
18.11.7.1 Synthesis of Product Subclass 7

18.11.7.1.1 Method 1:

Tellurocarbonyl Dihalides from Trimethyl[(trifluoromethyl)tellanyl]stannane

Two methods for the synthesis of tellurocarbonyl difluoride (**74**) have been investigated. Reaction of bis(trifluoromethyltellanyl)mercury(II) with diethylaluminum iodide gives rise to low yields of tellurocarbonyl difluoride. The other method investigated by these authors involves the pyrolysis of trimethyl[(trifluoromethyl)tellanyl]stannane (**73**) at 280 °C giving 50–60% yields of the tellurocarbonyl compound **74** (Scheme 31).^[115] This material quantitatively dimerizes to 2,2,4,4-tetrafluoro-1,3-ditellurethane (**75**) on warming.^[115–117]

Scheme 31 Synthesis of Trimethyl[(trifluoromethyl)tellanyl]stannane and Tellurocarbonyl Difluoride^[115]

**Tellurocarbonyl Difluoride (74):**^[117]

Trimethyl[(trifluoromethyl)tellanyl]stannane (**73**; 0.81 g, 2.2 mmol), synthesized on a 10 g scale, from $\text{F}_3\text{CTeTeCF}_3$ and Me_3SnH (95% yield, mp $-47\text{ }^\circ\text{C}$), was passed at 10^{-3} Torr and $280\text{ }^\circ\text{C}$ through a pyrolysis tube (30-cm length, 2.5-cm diameter) packed with glass wool. Products of this pyrolysis were trapped in two connected U-tubes, the first cooled to $-45\text{ }^\circ\text{C}$ and the second to $-196\text{ }^\circ\text{C}$. The pyrolysis reaction took 0.5–1.0 h. In the U-tube at $-45\text{ }^\circ\text{C}$ both Me_3SnF and unchanged trimethyl[(trifluoromethyl)tellanyl]stannane (**73**) were retained. In the subsequent trap the tellurocarbonyl difluoride was collected as a violet glass. By continuously raising the liq N_2 level, the entire wall of the trap could be covered with a film of tellurocarbonyl difluoride with a purity of ~95% and suitable for further reaction in the $-196\text{ }^\circ\text{C}$ trap; yield: 0.23 g (59%). The yields varied, depending on the packing density of the glass wool in the pyrolysis tube. If the packing density was too high, the pyrolysis became ineffective as some of the formed tellurocarbonyl difluoride decomposed to Te and C_2F_4 . If the packing density was too low, the pyrolysis was inefficient.

18.11.8 Product Subclass 8:
Telluroureas

18.11.8.1 Synthesis of Product Subclass 8

18.11.8.1.1 Method 1:

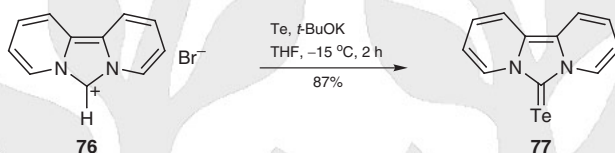
From Carbene Insertion Reactions with Tellurium

Methods for the construction of tellurocarbonyl compounds have significantly lagged behind those for selenocarbonyl compounds.^[118,119] Clearly, one of the major reasons for this lack of progress is the inherent instability of the tellurocarbonyl group, which is reflected

in its bond length of 2.087 Å. For the chromium–tellurium complex it is 2.12 Å and for the telluroamide it is 2.05 Å. Synthetic strategies for the successful generation of tellurocarbonyl compounds have been based on efforts to stabilize the tellurocarbonyl system. Resonance stabilization of the tellurocarbonyl group has been achieved by the placement of aromatic groups in direct π -conjugation or sterically in close proximity. Other approaches involve the trapping of the tellurocarbonyl system as soon as it forms by [4+2] thermal reactions or coordinating a metal to the tellurium atom of the carbonyl system.

As shown in Scheme 32, the reaction of an imidazole carbene, generated from compound **76**, in the presence of tellurium formally gives rise the tellurourea **77**.^[105] This method is restrictive because of the necessity to generate the intermediate carbene.

Scheme 32 Synthesis of a Tellurocarbonyl Compound from an Imidazole Carbene^[105]



Carbenes are neutral compounds featuring a divalent carbon atom with only six electrons in the valence shell. The central carbon atoms can be linear or bent. The use of bulky substituents successfully stabilizes the triplet carbenes. On the other hand, singlet carbenes have enjoyed a renaissance since Arduengo and co-workers prepared a stable crystalline carbene.^[120] Remarkably, the imidazole carbene that they constructed possessed a melting point of 240 °C. Since that report, there have been numerous methods for the construction of stable carbenes. For compound **77** the carbon of the C=Te group has a ¹³C NMR shift of δ 104.2. The researchers concluded that the tellurocarbonyl group could best be characterized as having essentially a single C–Te bond,^[105] although a $J_{\text{Te}-\text{C}}$ coupling constant for the carbonyl was reported, an X-ray crystal structure would have provided additional data to support the existence of a tellurocarbonyl bonding arrangement for these compounds.

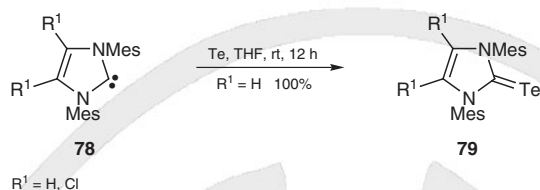
6H-Dipyrido[1,2-*c*:2',1'-*e*]imidazole-6-tellone (**77**); Typical Procedure:^[105]

Te (0.123 g, 0.96 mmol) was added to a suspension of dipyrido[1,2-*c*:2',1'-*e*]imidazolium bromide (**76**; 0.22 g, 0.87 mmol) in THF (30 mL) at -15 °C, followed by *t*-BuOK (0.12 g, 1.00 mmol). After 2 h, the mixture was filtered through Celite and the retained solid was washed with THF (10 mL). The combined filtrate and washings were concentrated to a volume of a few mL and petroleum ether (30 mL) was added. The red suspension was filtered and the collected solid was washed with petroleum ether (10 mL) and dried in vacuo for 2 h to give the product as an orange-red solid; yield: 0.21 g (87%); mp 160 °C (dec).

18.11.8.1.2

Method 2: Starting from Stable Carbenes

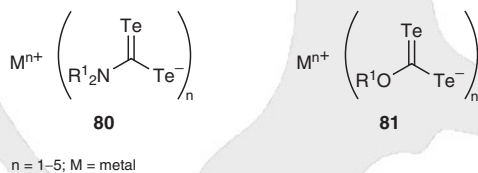
The method of Arduengo and co-workers has improved on the previous method by using stable carbenes. Their work included X-ray studies on **79** ($\text{R}^1 = \text{Cl}$), prepared from **78** ($\text{R}^1 = \text{Cl}$), which indicate that the imidazole ring is planar with no atom deviating more than 0.1 pm from the average plane (Scheme 33). The tellurium atom lies in the average plane of the imidazole ring. The ¹³C NMR chemical shifts for the tellurocarbonyls center around δ 133 and the ¹²⁵Te NMR chemical shift for **79** ($\text{R}^1 = \text{H}$) and **79** ($\text{R}^1 = \text{Cl}$) are δ -149.8 and -4, respectively. These data taken together indicate the potential for some double bond character for the tellurocarbonyl group.^[121]

Scheme 33 Synthesis of a Tellurourea Using a Room Temperature Stable Carbene^[121]**1,3-Dimesylimidazole-2-tellone (79, R¹ = H); Typical Procedure:**^[121]

In a dry box, a 200-mL, round-bottomed flask was charged with 1,3-dimesylimidazol-2-ylidene (**78**, R¹ = H; 1.00 g, 3.28 mmol), Te (0.418 g, 3.29 mmol), and THF (100 mL). The mixture was stirred for 12 h, after which time the soln was slightly cloudy. The soln was warmed to obtain a clear yellow soln, which was filtered through Celite, then concentrated until crystallization began. Hexane was added and the crystallization was allowed to continue at -20 °C. Filtration yielded the yellow crystalline product; yield: 1.4 g (100%); mp 317–318 °C.

18.11.9 Product Subclass 9:
Ditellurocarbonic and Ditellurocarbamic Acids and Their Metal Complexes
18.11.9.1 Synthesis of Product Subclass 9
18.11.9.1.1 Method 1:
By the Uchida Method

This method is described in a patent for making thin films composed of telluride compounds starting with the *N,N*-dialkyl ditellurocarbamates **80** and *O*-alkyl ditellurocarbonates **81** illustrated in Scheme 34.^[122] When these compounds are dissolved in organic solvents and the resulting solution is subjected to pyrolysis under inert gas they give thin films. The patent does not discuss the preparation of these compounds.^[122] However, it was pointed out in a review that there are very few examples of tellurocarbamic acid alkali metal salts, most likely due to the difficulty of their synthesis and purification.^[123]

Scheme 34 Ditellurocarbamates and Ditellurocarbonates^[122]

References

- [1] Berzelius, J. J., *Acad. Handl. Stockholm*, (1818) **39**, 13.
- [2] Luthra, N. P.; Odom, J. D., In *The Chemistry of Organic Selenium and Tellurium Compounds*, Patai, S.; Rappoport, Z., Eds.; Wiley: Chichester, UK, (1986); Vol. 1, p 189.
- [3] Krief, A.; Hevesi, L., *Organoselenium Chemistry I. Functional Group Transformations*, Springer: Berlin, (1988).
- [4] Guziec, F. S., In *The Chemistry of Organic Selenium and Tellurium Compounds*, Patai, S.; Rappoport, Z., Eds.; Wiley: New York, (1987); Vol. 2, p 215.
- [5] Toshimitsu, A.; Uemura, S., In *The Chemistry of Organic Selenium and Tellurium Compounds*, Patai, S.; Rappoport, Z., Eds.; Wiley: New York, (1987); Vol. 2, p 541.
- [6] Jensen, K. A., In *Organic Selenium Compounds: Their Chemistry and Biology*, Klayman, D. L.; Günther, W. H. H., Eds.; Wiley-Interscience: New York, (1973); p 263.
- [7] Shine, R. J., In *Organic Selenium Compounds: Their Chemistry and Biology*, Klayman, D. L.; Günther, W. H. H., Eds.; Wiley-Interscience: New York, (1973); p 273.
- [8] Paetzold, R.; Reichenbacher, M., In *Organic Selenium Compounds: Their Chemistry and Biology*, Klayman, D. L.; Günther, W. H. H., Eds.; Wiley-Interscience: New York, (1973); p 305.
- [9] Fujiwara, S.-I.; Kambe, N.; Sonada, N., In *Organoselenium Chemistry – A Practical Approach*, Back, T. G., Ed.; Oxford University Press: Oxford, (1999); p 223.
- [10] Murai, T.; Kato, S., *Top. Curr. Chem.*, (2000) **208**, 117.
- [11] Guziec, F. S.; In *Organoselenium Chemistry*, Liotta, D., Ed.; Wiley: New York, (1987), p 277.
- [12] Desiraju, G. R.; Steiner, T., In *The Weak Hydrogen Bond In Structural Chemistry and Biology*, Oxford University Press: New York, (1999); p 225.
- [13] Li, Q.; Yip, W. H.; Mak, T. C. W.; *J. Inclusion Phenom. Mol. Recognit. Chem.*, (1995) **23**, 233.
- [14] Wright, W. B.; Meyers, E. A., *Cryst. Struct. Commun.*, (1980) **9**, 1173.
- [15] Kuhn, N.; Henkel, G.; Kratz, T., *Chem. Ber.*, (1993) **126**, 2047.
- [16] Li, G. M.; Zingaro, R. A.; Segi, M.; Reibenspies, J. H.; Nakajima, T., *Organometallics*, (1997) **16**, 756.
- [17] Darmadi, A.; Haas, A.; Koch, B., *Z. Naturforsch., B*, (1980), **35**, 526.
- [18] Haas, A.; Koch, B.; Welcman, N., *Z. Anorg. Allg. Chem.*, (1976) **427**, 114.
- [19] Grobe, J.; Le Van, D.; Welzel, J., *J. Organomet. Chem.*, (1988) **340**, 153.
- [20] Haas, A.; Koch, B.; Welcman, N., *Chem. Ztg.*, (1974) **98**, 511.
- [21] Darmadi, A.; Haas, A.; Willner, H.; Schnöckel, H., *Z. Naturforsch., B*, (1981) **36**, 1261.
- [22] Copeland, C. M.; Ghosh, J.; McAdam, D. P.; Skelton, B. W.; Stick, R. V.; White, A. H., *Aust. J. Chem.*, (1988) **41**, 549.
- [23] Tanaka, K.; Yoshida, K.; Ishida, T.; Kobayashi, A.; Nogami, T., *Adv. Mater. (Weinheim, Ger.)*, (2000) **12**, 661.
- [24] Segi, M.; Takahashi, T.; Ichinose, H.; Li, G. M.; Nakajima, T., *Tetrahedron Lett.* (1992) **33**, 7865.
- [25] Morikami, A.; Takimiya, K.; Aso, Y.; Otsubo, T., *Org. Lett.*, (1999) **1**, 23.
- [26] Lakshmikantham, M. V.; Cava, M. P., *J. Org. Chem.*, (1980) **45**, 2632.
- [27] Paulmier, C., In *Selenium Reagents and Intermediates in Organic Synthesis*, Patai, S., Ed.; Wiley: New York, (1987); Vol. 2, pp 234, 255.
- [28] Oppenheimer, J. E.; Silks, L. A., *J. Labelled Compd. Radiopharm.* (1996) **38**, 281.
- [29] Stocking, E. M.; Schwarz, J. N.; Senn, H.; Salzmann, M.; Silks, L. A., *J. Chem. Soc., Perkin Trans. 1*, (1997), 2443.
- [30] Kamata, K.; Agata, I.; Meyers, A. I., *J. Org. Chem.*, (1998) **63**, 3113.
- [31] Meyers, A. I.; Collington, E. W., *J. Am. Chem. Soc.*, (1970) **92**, 6676.
- [32] Leonard, W. R.; Romine, J. L.; Meyers, A. I., *J. Org. Chem.*, (1991) **56**, 1961.
- [33] Silks, L. A.; Peng, J.; Dunlap, R. B.; Odom, J. D., *J. Org. Chem.*, (1991) **56**, 6733.
- [34] Duddeck, H., *Prog. Nucl. Magn. Reson. Spectrosc.*, (1995) **27**, 1.
- [35] Cullen, E. R.; Guziec, F. S., Jr.; Murphy, C. J.; Wong, T. C.; Andersen, K. K., *J. Am. Chem. Soc.*, (1981) **103**, 7055.
- [36] Wong, T. C.; Guziec, F. S., Jr.; Moustakis, C. A., *J. Chem. Soc., Perkin Trans. 2*, (1983), 1471.
- [37] Wong, T. C.; Ang, T. T.; Guziec, F. S., Jr.; Moustakis, C. A., *J. Magn. Reson.*, (1984) **57**, 463.
- [38] Wu, R.; Barr, M. E.; Hernandez, G.; Orji, C. C.; Silks, L. A., *Recent Res. Dev. Org. Bioorg. Chem.*, (1998) **2**, 29.
- [39] Wu, R.; Odom, J. D.; Dunlap, R. B.; Silks, L. A., *Phosphorus, Sulfur Silicon Relat. Elem.*, (1998) **136**/ **137**, 209.

- [40] Wu, R.; Hernández, G.; Dunlap, R. B.; Odom, J. D.; Martinez, R. A.; Silks, L. A., *Trends Org. Chem.*, (1998) **7**, 105.
- [41] Michalczyk, R.; Schmidt, J.; Moody, E.; Wu, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A., *Angew. Chem.*, (2000) **112**, 3200; *Angew. Chem. Int. Ed.*, (2000) **39**, 3067.
- [42] Demartin, F.; Devillanova, F. A.; Garau, A.; Isaia, F.; Lippolis, V.; Verani, G., *Polyhedron*, (1999) **18**, 3107.
- [43] Peng, J.; Barr, M. E.; Ashburn, D. A.; Odom, J. D.; Dunlap, R. B.; Silks, L. A., *J. Org. Chem.*, (1994) **59**, 4977.
- [44] Wu, R.; Odom, J. D.; Dunlap, R. B.; Silks, L. A., *Tetrahedron: Asymmetry*, (1995) **6**, 833.
- [45] Silks, L. A.; Peng, J.; Dunlap, R. B.; Odom, J. D., *J. Chem. Soc., Perkin Trans. 1*, (1991), 2495.
- [46] Barton, D. H. R.; Parekh, S. I.; Tajbakhsh, M.; Theodorakis, E. A.; Tse, C.-L., *Tetrahedron*, (1994) **50**, 639.
- [47] Tormos, G. V.; Neilands, O. J.; Cava, M. P., *J. Org. Chem.*, (1992) **57**, 1008.
- [48] Bellec, N.; Lorcy, D.; Boubekeur, K.; Carlier, R.; Tallec, A.; Los, Sz.; Pukacki, W.; Trybula, M.; Piekara-Sady, L.; Robert, A., *Chem. Mater.*, (1999) **11**, 3147.
- [49] Bellec, N.; Guérin, D.; Lorcy, D.; Robert, A.; Carlier, R.; Tallec, A., *Acta Chem. Scand.*, (1999) **53**, 861.
- [50] Nagao, Y.; Kumagai, T.; Takao, S.; Abe, T.; Ochiai, M.; Inoue, Y.; Taga, T.; Fujita, E., *J. Org. Chem.*, (1986) **51**, 4739.
- [51] Sato, A.; Kobayashi, H.; Naito, T.; Sakai, F.; Kobayashi, A., *Inorg. Chem.*, (1997) **36**, 5262.
- [52] Cornelissen, J. P.; Pomarede, B.; Spek, A. L.; Reefman, D.; Haasnoot, J. G.; Reedijk, J., *Inorg. Chem.*, (1993) **32**, 3720.
- [53] Kjaer, A.; Skrydstrup, T., *Heterocycles*, (1989) **28**, 269.
- [54] Warner, J. S., *J. Org. Chem.*, (1963) **28**, 1642.
- [55] Ishihara, H.; Koketsu, M.; Fukuta, Y.; Nada, F., *J. Am. Chem. Soc.*, (2001) **123**, 8408.
- [56] Kanda, T.; Aoki, H.; Mizoguchi, K.; Shiraishi, S.; Murai, T.; Kato, S., *Organometallics*, (1996) **15**, 5753.
- [57] Douglass, I. B., *J. Am. Chem. Soc.*, (1937) **59**, 740.
- [58] Zhou, Y.; Heimgartner, H., *Helv. Chim. Acta*, (2000) **83**, 539.
- [59] Huguet, J. L., *Adv. Chem. Ser.*, (1967) **76**, 345.
- [60] Jones, D. N.; Mundy, D.; Whitehouse, R. D., *J. Chem. Soc. D*, (1970), 86.
- [61] Walter, R.; Roy, J., *J. Org. Chem.*, (1971) **36**, 2561.
- [62] Sharpless, K. B.; Gordon, K. M.; Lauer, R. F.; Patrick, D. W.; Singer, S. P.; Young, M. W., *Chem. Scr.*, (1975) **8**, 9.
- [63] Reich, H. J., *Acc. Chem. Res.*, (1979) **12**, 22.
- [64] Krief, A.; Castillo-Colaux, C., *Synlett*, (2001), 501.
- [65] Arigoni, D.; Vasella, A.; Sharpless, K. B.; Jensen, H. P., *J. Am. Chem. Soc.*, (1973) **95**, 7917.
- [66] Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J., *J. Org. Chem.*, (2001) **66**, 7547.
- [67] Wirth, T., *Angew. Chem.*, (2000) **112**, 3890; *Angew. Chem. Int. Ed.*, (2000) **39**, 3740.
- [68] Li, Z.; Wu, R.; Michalczyk, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A., *J. Am. Chem. Soc.*, (2000) **122**, 386.
- [69] Mughesh, G.; du Mont, W. W.; Sies, H., *Chem. Rev.*, (2001) **101**, 2125.
- [70] Silks, L. A.; Dunlap, R. B.; Odom, J. D., *J. Am. Chem. Soc.*, (1990) **112**, 4979.
- [71] Peng, J.; Odom, J. D.; Dunlap, R. B.; Silks, L. A., *Tetrahedron: Asymmetry*, (1994) **5**, 1627.
- [72] Peng, J.; Ashburn, D. A.; Barr, M. E.; Lebioda, L.; Martinez, R. A.; Garber, A. R.; Odom, J. D.; Dunlap, R. B.; Silks, L. A., *J. Org. Chem.*, (1995) **60**, 5540.
- [73] Wu, R.; Silks, L. A.; Odom, J. D.; Dunlap, R. B., *Spectroscopy (Eugene, Oreg.)*, (1996) **11**, 37.
- [74] Wu, R.; Hernández, G.; Odom, J. D.; Dunlap, R. B.; Silks, L. A., *Chem. Commun. (Cambridge)*, (1996), 1125.
- [75] Wu, R.; Odom, J. D.; Dunlap, R. B.; Silks, L. A., *Tetrahedron: Asymmetry*, (1999) **10**, 1465.
- [76] Duddeck, H.; Hotopp, T., *Magn. Reson. Chem.*, (1995) **33**, 490.
- [77] Michelsen, P.; Annby, U.; Gronowitz, S., *Chem. Scr.*, (1984) **24**, 251.
- [78] Smith, A. B.; Friestad, G. K.; Barbosa, J.; Bertounesque, E.; Duan, J. J. W.; Hull, K. G.; Iwashima, M.; Qiu, Y. P.; Spoors, P. G.; Salvatore, B. A., *J. Am. Chem. Soc.*, (1999) **121**, 10478.
- [79] Salvatore, B. A.; Smith, A. B., *Tetrahedron Lett.*, (1994) **35**, 1329.
- [80] Hedenstrom, E.; Nguyen, B.-V.; Silks, L. A., *Tetrahedron: Asymmetry*, (2002) **13**, 835.
- [81] Jensen, K. A.; Frederiksen, E., *Z. Anorg. Allg. Chem.*, (1936) **230**, 31.

- [82] Mautner, H. G.; Kumler, W. D.; Okano, Y.; Pratt, R., *Antibiot. Chemother. (Washington, D. C.)*, (1956) **6**, 51.
- [83] Shafiee, A.; Lalezari, I.; Yazdany, S.; Pournorouz, A., *J. Pharm. Sci.*, (1973) **62**, 839.
- [84] Musik, I.; Koziol-Montewka, M.; Tos-Luty, S.; Pasternak, K.; Latuszynska, J.; Tokarska, M.; Kielczykowska, M., *BioMetals*, (2000) **12**, 369.
- [85] Liu, M.; Xu, P. L.; Wang, Z. J., *Yaoxue Xuebao*, (1992) **27**, 388; *Chem. Abstr.*, (1992) **117**, 171 584.
- [86] Agrawal, K. C.; Booth, B. A.; Michaud, R. L.; Moore, E. C.; Sartorelli, A. C., *Biochem. Pharmacol.*, (1974) **23**, 2421.
- [87] Velikanov, A. A.; Ostrovskaya, I. K.; Garina, N. P.; Turasova, V. A.; Tsurkan, A. A., *Ukr. Khim. Zh. (Russ. Ed.)*, (1983) **49**, 764; *Chem. Abstr.*, (1983) **99**, 81 474.
- [88] Bulka, E.; Ahlers, K.-D.; Tucek, K., *Chem. Ber.*, (1967) **100**, 1373.
- [89] Guziec, L. J.; Guziec, F. S., Jr., *J. Org. Chem.*, (1994) **59**, 4691.
- [90] Warner, J. S.; Page, T. F., *J. Org. Chem.*, (1966) **31**, 606.
- [91] Henriksen, L., *Synthesis*, (1982), 773.
- [92] Klayman, D. L.; Shine, R. J., *J. Org. Chem.*, (1969) **34**, 3549.
- [93] Klayman, D. L.; Shine, R. J., *Chem. Commun.*, (1968), 372.
- [94] Collard-Charon, C.; Renson, M., *Bull. Soc. Chim. Belg.*, (1963) **72**, 149.
- [95] Hartmann, H., *Z. Chem.*, (1971) **11**, 60.
- [96] Cohen, V. I., *Synthesis*, (1980), 60.
- [97] Franklin, W. J.; Werner, R. L., *Tetrahedron Lett.*, (1965), 3003.
- [98] Pedersen, C. T., *Acta Chem. Scand.*, (1963) **17**, 1459.
- [99] Collard-Charon, C.; Renson, M., *Bull. Soc. Chim. Belg.*, (1962) **71**, 531.
- [100] Collard-Charon, C.; Huls, R.; Renson, M., *Bull. Soc. Chim. Belg.*, (1962) **71**, 541.
- [101] Henriksen, L.; Ehrbar, U., *Synthesis*, (1976), 519.
- [102] Zhou, Y.; Heimgartner, H., *Helv. Chim. Acta*, (2000) **83**, 539.
- [103] Zhou, Y.; Linden, A.; Heimgartner, H., *Helv. Chim. Acta*, (2000) **83**, 1576.
- [104] Nakayama, J.; Sugiura, H.; Hoshino, M., *Tetrahedron Lett.*, (1983) **24**, 2585.
- [105] Weiss, R.; Reichel, S., *Eur. J. Inorg. Chem.*, (2000), 1935.
- [106] Spica, P., *Gazz. Chim. Ital.*, (1877) **7**, 90.
- [107] Giua, M.; Bianco, R., *Gazz. Chim. Ital.*, (1959) **89**, 693.
- [108] Geisler, K.; Kuenzler, A.; Bulka, E., DD 291 752, (1991); *Chem. Abstr.*, (1991) **115**, 207 516.
- [109] Baxter, L.; Hill, A. F.; Malget, J. M.; White, A. J. P.; Williams, D. J., *Chem. Commun. (Cambridge)*, (1997), 2049.
- [110] Bhattacharyya, P.; Slawin, A. M. Z.; Woollins, J. D., *J. Chem. Soc., Dalton Trans.*, (2001), 300.
- [111] Bhattacharyya, P.; Woollins, J. D., *Tetrahedron Lett.*, (2001) **42**, 5949.
- [112] Woollins, J. D., personal communication.
- [113] Bianchini, C.; Masi, D.; Mealli, C.; Meli, A.; Sabat, M.; Vizza, F., *Inorg. Chem.*, (1988) **27**, 3716.
- [114] Bianchini, C.; Meli, A.; Dapporto, P.; Tofanari, A.; Zanello, P., *Inorg. Chem.*, (1987) **26**, 3677.
- [115] Boese, R.; Haas, A.; Limberg, C., *J. Chem. Soc., Dalton Trans.*, (1993), 2547.
- [116] Beck, J.; Haas, A.; Herrendorf, W.; Heuduk, H., *J. Chem. Soc., Dalton Trans.*, (1996), 4463.
- [117] Baum, M.; Beck, J.; Haas, A.; Herrendorf, W.; Monsé, C., *J. Chem. Soc., Dalton Trans.*, (2000), 11.
- [118] Lappert, M. F.; Martin, T. R.; McLaughlin, G. M., *J. Chem. Soc., Chem. Commun.*, (1980), 635.
- [119] Geisler, K.; Pfeiffer, W.-D.; Künzler, A.; Below, H.; Bulka, E.; Langer, P., *Synthesis*, (2004), 875.
- [120] Arduengo, A. J.; Harlow, R. L.; Kline, M., *J. Am. Chem. Soc.*, (1991) **113**, 361.
- [121] Arduengo, A. J.; Davidson, F.; Dias, H. V. R.; Goerlich, J. R.; Khasnis, D.; Marshall, W. J.; Prakasha, T. K., *J. Am. Chem. Soc.*, (1997) **119**, 12 742.
- [122] Uchida, H., JP 1989 298 011, (1989); *Chem. Abstr.*, (1991) **114**, 9624.
- [123] Kato, S.; Kanda, T.; Sasaki, H.; Yamada, K.; Mifune, H., *Rev. Heteroat. Chem.*, (2000) **22**, 79.

Product Class 12: Imidic Acids and Derivatives, Isoureas and Derivatives, Sulfur and Selenium Equivalents, and Analogously Substituted Methylene phosphines

T. L. Gilchrist

General Introduction

Previously published information on imidic acid derivatives of this class can be found in *Houben-Weyl*, Vol. E 4, pp 522–608. The chemistry of members of this product class that contain a C=P bond (methylene phosphines) is reviewed in *Houben-Weyl*, Vol. E 1, p 28, although most of the compounds relevant to this section were described after this review was published. There are several other reviews of the preparations and chemical properties of methylenephosphines.^[1–7]

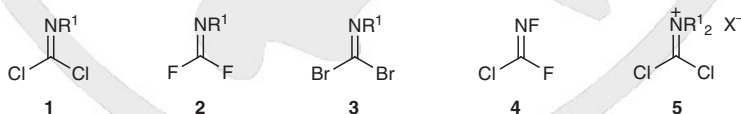
Imidic acid derivatives are well-established organic compounds with many stable examples identified in the literature. In contrast, relatively few methylenephosphines were known before 1980 but knowledge of their chemistry has developed rapidly since then. Many of the compounds of this class are unstable,^[6] but isolable derivatives can be obtained either through electronic stabilization or, more often, by the incorporation of extremely bulky substituents onto phosphorus.

18.12.1

Product Subclass 1: Carbonimidic Dihalides

Previously published information on this product subclass is given in *Houben-Weyl*, Vol. E 4, pp 522–543. The product subclass has also been reviewed in *Comprehensive Organic Functional Group Transformations*^[8] and there are several other earlier reviews of carbonimidic dihalides.^[9–12] The most numerous examples of this subclass are carbonimidic dichlorides **1** and this functional group occurs in marine natural products.^[13–15] Carbonimidic difluorides **2** and carbonimidic dibromides **3** (Scheme 1) are also well represented in the literature, but carbonimidic diiodides decompose readily to isocyanides and iodine.^[16] Both carbonimidic difluorides and carbonimidic dibromides are generally less stable than the corresponding carbonimidic dichlorides; some carbonimidic difluorides rapidly dimerize.^[17] There are also several examples of carbonimidic dihalides bearing two different halogens, as exemplified by *N*-fluorocarbonimidic chloride fluoride (**4**). The subclass also includes iminium salts, dichloroiminium salts **5** being the most important.

Scheme 1 Types of Carbonimidic Dihalides

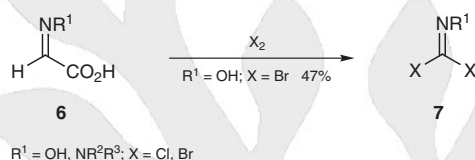


SAFETY: Carbonimidic dihalides should be handled with similar precautions to those that apply to phosgene and thiophosgene because of the presence of easily displaceable halogen atoms.

18.12.1.1 Synthesis of Product Subclass 1

18.12.1.1.1 Method 1:
From Glyoxylic Acid Derivatives and Halogens

(Hydroxyimino)acetic acid (**6**, $R^1 = \text{OH}$) and (dimethylhydrazono)acetic acids **6** ($R^1 = \text{NR}^2\text{R}^3$) react with chlorinating or brominating agents to give carbonimidic dihalides **7** (Scheme 2). Either the appropriate halogens or other halogenating agents such as *N*-halosuccinimides can be used.^[18–20] A convenient large-scale preparative method for *N*-hydroxycarbonimidic dibromide (**7**, $X = \text{Br}$; $R^1 = \text{OH}$) makes use of bromine in water.^[21–24] The oxime can be isolated but it is more often generated and used in situ as a source of bromonitrile oxide. Similarly, the benzylhydrazone **7** ($X = \text{Cl}$; $R^1 = \text{NHBn}$)^[25] and the phenylhydrazone **7** ($X = \text{Br}$; $R^1 = \text{NHPh}$)^[26] are generated from the corresponding hydrazone, but are not isolated. In a related reaction, the hydrazone **7** ($X = \text{Br}$; $R^1 = \text{NMe}_2$) is isolated in 53% yield from the reaction of formaldehyde *N,N*-dimethylhydrazone with bromine.^[27]

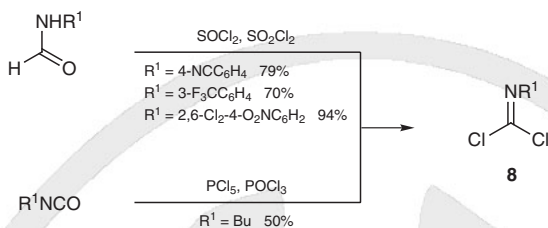
Scheme 2 Halogenation of (Hydroxyimino)- and Hydrazonoacetic Acids^[18–27]***N*-Hydroxycarbonimidic Dibromide (**7**, $R^1 = \text{OH}$; $X = \text{Br}$):^[23]**

CAUTION: Bromine is a severe irritant of the eyes, mucous membranes, lungs, and skin. Liquid bromine causes severe and painful burns on contact with eyes and skin.

Br_2 (5 mL, 67 mmol) was added in 1-mL portions at 10–15 min intervals to a soln of (hydroxyimino)acetic acid (6 g, 67 mmol) in H_2O (200 mL) at 0–5 °C. After the addition of the final portion of Br_2 , the soln had a faint amber color. The soln was extracted with Et_2O ($3 \times 100 \text{ mL}$), and the combined extracts were washed with aq NaHSO_3 , dried, and concentrated to give a colorless solid, which was crystallized (Et_2O /hexanes); yield: 6.5 g (47%); mp 70–71 °C.

18.12.1.1.2 Method 2:
By Halogenation of Formanilides and Isocyanates

A good general method for the preparation of *N*-arylcarbonimidic dichlorides **8** ($R^1 = \text{aryl}$) is the chlorination of formanilides (Scheme 3).^[28–30] Chlorination is usually achieved using a mixture of thionyl chloride and sulfuryl chloride. This method is restricted mainly to the synthesis of *N*-aryl- and *N*-cycloalkylcarbonimidic dichlorides, but it has also been used for the preparation of *N*-(2,6-dichloro-4-methylphenyl)carbonimidic dibromide.^[31] A modification uses simple aliphatic isocyanates (Scheme 3), which can be chlorinated by a mixture of phosphorus pentachloride and phosphoryl chloride to give the corresponding carbonimidic dichlorides **8** in moderate to good yield.^[9] This modification is not generally applicable to aryl isocyanates because they usually give carbodiimides as the major products.

Scheme 3 Chlorination of Formanilides and Isocyanates^[9,28–31]**N-(4-Cyanophenyl)carbonimidic Dichloride (8, $\text{R}^1 = 4\text{-NCC}_6\text{H}_4$); Typical Procedure:**^[28]

CAUTION: Thionyl chloride reacts violently with water producing large volumes of corrosive gases. It is extremely destructive to all tissues.

CAUTION: Sulfuryl chloride can react explosively with alkalis and is an irritant.

4-Cyanoformanilide (25.0 g, 171 mmol) was added with stirring to a mixture of SOCl_2 (500 mL) and SO_2Cl_2 (13.75 mL, 171 mmol) over 1 h. The mixture was refluxed for 24 h and the excess SOCl_2 was then distilled off. The red residue was distilled under reduced pressure to give the title compound as a pale yellow oil that solidified to a crystalline mass; yield: 27.0 g (79%); bp 110 °C/1 Torr.

N-Butylcarbonimidic Dichloride (8, $\text{R}^1 = \text{Bu}$); Typical Procedure:^[9]

BuNCO (49 g, 0.49 mol) was added dropwise to a suspension of PCl_5 (104 g, 0.50 mol) in POCl_3 (80 mL) at 55 °C. The mixture was stirred until a clear soln was obtained. POCl_3 was distilled off under reduced pressure. Further distillation gave the title compound; yield: 38 g (50%); bp 45–45.5 °C/14 Torr.

18.12.1.1.3

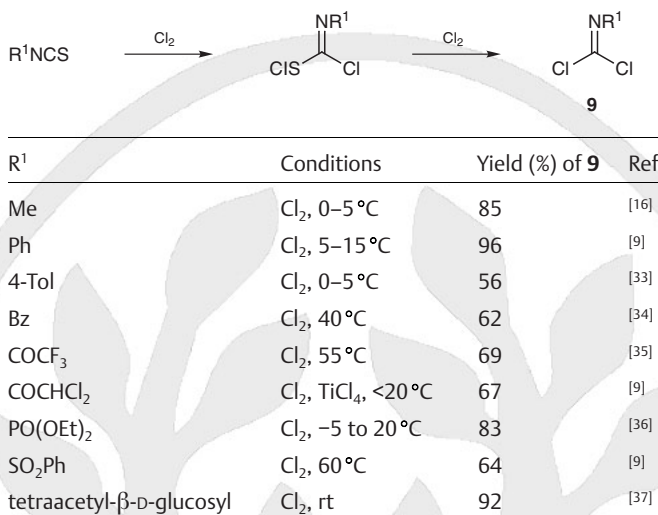
Method 3:**By Halogenation of Isothiocyanates and Related Compounds**

One of the oldest and most general methods for the preparation of carbonimidic dichlorides is the chlorination of the corresponding isothiocyanates. The reaction involves the addition of chlorine to the $\text{C}=\text{S}$ bond, followed by further chlorination and loss of sulfur. The method has not been extensively used for the preparation of carbonimidic difluorides or carbonimidic dibromides. As alternatives to isothiocyanates, sodium salts of dithiocarbamic acids $[\text{NaSC}(\text{S})\text{NHR}^1]$, dithiocarbamic esters $[\text{R}^2\text{SC}(\text{S})\text{NHR}^1]$ and carbonimido-dithioate esters $[(\text{R}_2\text{S})_2\text{C}=\text{NR}^1_2]$ can be used as precursors to carbonimidic dichlorides.

18.12.1.1.3.1

Variation 1:**By Halogenation of Isothiocyanates**

Carbonimidic dichlorides **9** bearing a variety of substituents R^1 on nitrogen are prepared from the corresponding isothiocyanates and chlorine in an inert solvent. Typical examples are given in Scheme 4.^[9,16,32–37]

Scheme 4 Carbonimidic Dichlorides from Isothiocyanates and Chlorine^[9,16,32–37]

Lewis acid catalysts are used to facilitate the chlorination of acyl isothiocyanates.^[9,32] Phenyl isothiocyanate and ethyl isothiocyanate are also converted into the corresponding carbonimidic difluorides in modest yields (17 and 37%, respectively) by reactions with mercury(II) fluoride.^[38]

N-Phenylcarbonimidic Dichloride (**9**, R¹ = Ph); Typical Procedure:^[9]

CAUTION: Sulfur dichloride is toxic, corrosive, a severe irritant, and reacts exothermically with water.

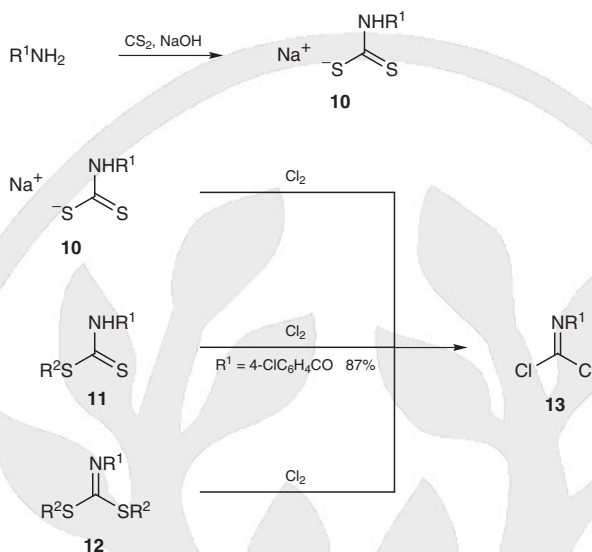
Cl₂ (3075 g, 43.3 mol) was passed into a soln of PhNCS (2905 g, 21.5 mol) in CCl₄ (5 L) (**CAUTION:** toxic) cooled in ice to maintain the temperature at 5–15 °C. The soln was stirred for 1 h, then most of the solvent and the SCl₂ formed in the reaction were distilled off on a water bath at atmospheric pressure. The remaining solvent was then removed under reduced pressure. The residue was distilled on an oil bath (bath temperature 120–130 °C) to give the dichloride; yield: 3622 g (96%); bp 83–85 °C/11 Torr.

18.12.1.1.3.2

Variation 2:

From Dithiocarbamates and Carbonimidodithioates

Sodium salts **10** of N-alkyldithiocarbamic acids react with chlorine to give N-alkylcarbonimidic dichlorides **13** as do dithiocarbamates **11** and carbonimidodithioates **12** (Scheme 5). The sodium dithiocarbamates can be obtained from the reactions of primary amines with carbon disulfide and sodium hydroxide; such transformations can be performed as “one-pot” operations. For example, N-cyclohexylcarbonimidic dichloride (**13**, R¹ = Cy) is obtained from cyclohexylamine in 79% yield by this method.^[9] This variation is also useful for the preparations of both N-acylcarbonimidic dichlorides^[34] and N-sulfonylcarbonimidic dichlorides^[39] since product yields are often higher than from the corresponding isothiocyanates.

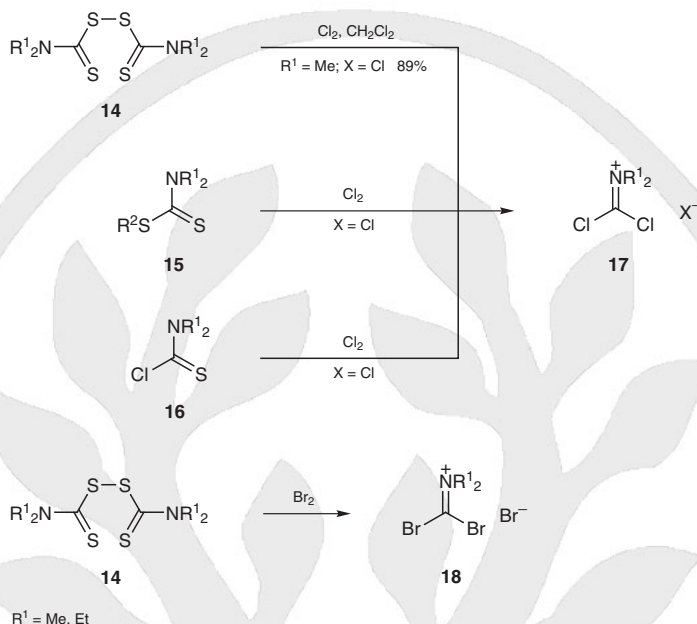
Scheme 5 Chlorination of Dithiocarbamates and Carbonimidodithioates^[9,34,39]

N-(4-Chlorobenzoyl)carbonimidic Dichloride (13, $R^1 = 4\text{-ClC}_6\text{H}_4\text{CO}$); Typical Procedure:^[34] Cl_2 was passed for 3 h into a stirred soln of ethyl N-(4-chlorobenzoyl)dithiocarbamate **11** ($R^1 = 4\text{-ClC}_6\text{H}_4\text{CO}$; $R^2 = \text{Et}$; 5.18 g, 20 mmol) in CH_2Cl_2 (150 mL) at rt. The solvent was removed to leave an oil. Distillation gave the title compound; yield: 4.12 g (87%); bp 90–93 °C/0.02 Torr.

18.12.1.1.3.3

Variation 3:
Dihaloiminium Salts from Dithiocarbamates and Dithiurams

A special application of this method is found in the preparation of dichloroiminium salts **17** ($X = \text{Cl}$), for which dithiurams **14**, tertiary dithiocarbamates **15**, or thiocarbamoyl chlorides **16** are the most commonly used precursors (Scheme 6). The preparation and reactions of dichloroiminium salts **17** have been reviewed.^[40] Thiuram disulfides **14** are stable, readily available compounds and so they are convenient starting materials for the preparation of dichloroiminium chlorides. Chlorination of the disulfide **14** ($R^1 = \text{Me}$) by chlorine in dichloromethane gives the iminium salt **17** ($R^1 = \text{Me}$; $X = \text{Cl}$) in 89% yield;^[41] several other dichloroiminium salts are prepared in the same way.^[40,42] These reactions probably proceed through thiocarbamoyl chlorides **16** as intermediates and a stepwise procedure for the preparation of the salt **17** ($R^1 = \text{Me}$; $X = \text{Cl}$) has been described.^[43] Dithiocarbamates **15** are also readily converted into dichloroiminium salts **17** ($X = \text{Cl}$) by reactions with chlorine.^[40] The corresponding dibromomethyleniminium salts **18** ($R^1 = \text{Me}$, Et ; $X = \text{Br}$) are prepared from thiuram disulfides **14** and bromine (Scheme 6).^[44,45] Difluoroiminium fluorides appear to be less stable than their covalent trifluoromethylamine isomers and have not been isolated.

Scheme 6 Dihalomethyleniminium Halides from Thiuram Sulfides and Related Compounds^[40–45]

(Dichloromethylene)dimethylammonium Chloride (17, R¹ = Me; X = Cl);

Typical Procedure:^[43]

CAUTION: Sulfuryl chloride can react explosively with alkalis and is an irritant.

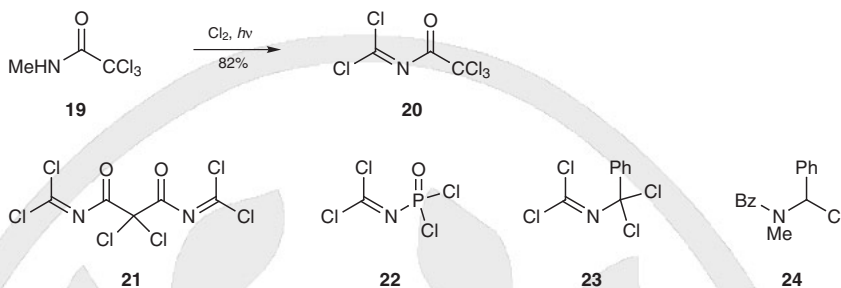
A soln of SO₂Cl₂ (0.81 mL, 0.01 mol) in CH₂Cl₂ (10 mL) was added dropwise to a stirred soln of tetramethylthiuram disulfide (**14**, R¹ = Me; 2.4 g, 0.01 mol) in CH₂Cl₂ (50 mL). The mixture was stirred for 15 min at rt, S₈ was removed by filtration, and the filtrate was concentrated to dryness. The yellow residue was redissolved in CCl₄ (20 mL) (**CAUTION: toxic**) and the soln was refluxed for 5 min. After cooling, the soln was decanted from S₈ deposits that remained upon the walls of the flask. The flask was washed with CCl₄ (2 × 10 mL) and the soln and washings were combined. A soln of PCl₅ (4.16 g, 0.02 mol) in CCl₄ (60 mL) was then added dropwise. A precipitate appeared during the addition. The suspension was refluxed for 1 h, and then it was cooled. The salt was collected by filtration and dried in a vacuum desiccator; yield: 2.9 g (89%); mp 185 °C.

18.12.1.1.4

Method 4:

By Chlorination of *N*-Methylamides

The methylamino group of *N*-methyltrichloroacetamide **19** (Scheme 7) is converted into the (dichloromethylene)amino function of **20** by photochemical chlorination.^[46,47] The same method is also used to prepare the carbonimidic dichlorides **21**^[48] and **22**.^[46] The carbonimidic dichloride **23** is available by the photochemical chlorination and debenzoylation of the amide **24**.^[49] A related method, of limited scope, is the high temperature chlorination and demethylation of *N,N*-dimethylamines.^[50,51] For example, *N*-(2,4,6-trichlorophenyl)carbonimidic dichloride is prepared in high yield by the chlorination of *N,N*-dimethylaniline, followed by heating the mixture to above 200 °C.^[50]

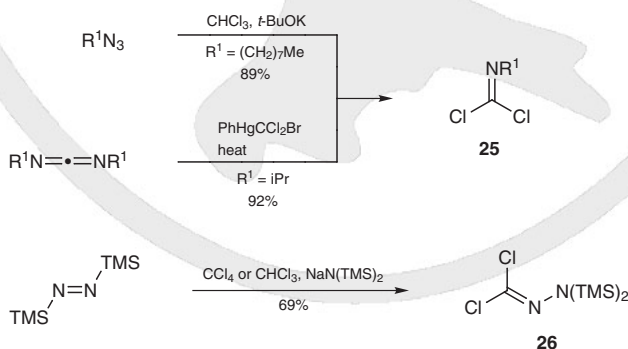
Scheme 7 Chlorination of *N*-Methylamides^[46,47]**(Trichloroacetyl)carbonimidic Dichloride (20); Typical Procedure:**^[47]

Cl_2 was passed for 4 h into a soln of *N*-methyltrichloroacetamide (**19**; 176 g, 1 mol) in CHCl_3 or CCl_4 (80 mL) (**CAUTION: toxic**) at 50–70 °C under UV irradiation. The solvent was removed and chlorination was continued under UV irradiation for 10–12 h at 90–110 °C. The dichloride was obtained by fractional distillation of the product; yield: 200 g (82%); bp 76–77 °C/14 Torr.

18.12.1.1.5

**Method 5:
By Reactions Involving Dichlorocarbene**

Dichlorocarbene is well established as a reactive intermediate in the reactions of chloroform with bases, in the thermal decomposition of sodium trichloroacetate, and in the thermolysis of phenylmercury trihalides. A few useful preparations of carbonimidic dichlorides are achieved by the generation of dichlorocarbene in the presence of a variety of nitrogen compounds (Scheme 8). Thus, *N*-octylcarbonimidic dichloride [**25**, $\text{R}^1 = (\text{CH}_2)_7\text{Me}$] is obtained in high yield from the reaction of octyl azide with dichlorocarbene generated from chloroform in pentane at 0 °C;^[52] the reactions of azides with dichlorocarbene generated under phase-transfer catalysis have also been investigated.^[53] *N*-Isopropylcarbonimidic dichloride (**25**, $\text{R}^1 = \text{iPr}$) is produced from diisopropylcarbodiimide and (bromodichloromethyl)phenylmercury.^[54] Carbon tetrachloride is used as a precursor for dichlorocarbene in a preparation of bis(trimethylsilyl)carbonohydrazonoic dichloride (**26**) from bis(trimethylsilyl)diimide.^[55] Several other individual preparations of carbonimidic dihalides from different nitrogen-containing compounds and dichlorocarbene are recorded; yields are modest.^[8]

Scheme 8 Carbonimidic Dihalides from Dichlorocarbene and Nitrogen Compounds^[52–55]

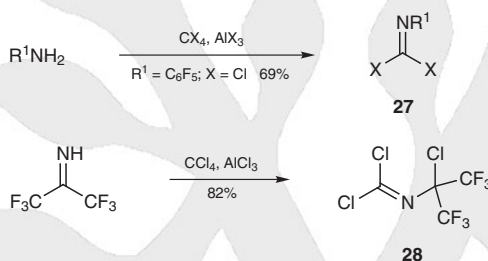
Bis(trimethylsilyl)carbonohydrazonoic Dichloride (26):^[55]

CHCl_3 (0.85 mL, 10.6 mmol) in Et_2O (10 mL) was added dropwise to a soln of bis(trimethylsilyl)diimide (1.81 g, 10.4 mmol) and $\text{NaN}(\text{TMS})_2$ (1.91 g, 10.4 mmol) in Et_2O (20 mL) at -78°C . The dichloride was obtained by fractional distillation of the brown mixture; yield: 1.88 g (69%); bp $50^\circ\text{C}/0.1\text{ Torr}$.

18.12.1.1.6

Method 6:**From Tetrahalomethanes and Aromatic Amines**

There are a few examples of the formation of carbonimidic dichlorides **27** ($\text{X} = \text{Cl}$) by the reactions of halogenated aromatic amines with carbon tetrachloride and aluminum trichloride.^[56,57] (Pentafluorophenyl)carbonimidic dibromide (**27**, $\text{R}^1 = \text{C}_6\text{F}_5$; $\text{X} = \text{Br}$) is prepared from carbon tetrabromide and aluminum tribromide.^[58] A related reaction is the conversion of hexafluoroacetone imine into the carbonimidic dichloride **28** by heating with aluminum trichloride and carbon tetrachloride.^[59] These reactions are summarized in Scheme 9.

Scheme 9 Reaction of Tetrahalomethanes with Aromatic Amines^[56–59]**(Pentafluorophenyl)carbonimidic Dichloride (27, $\text{R}^1 = \text{C}_6\text{F}_5$; $\text{X} = \text{Cl}$); Typical Procedure:**^[57]

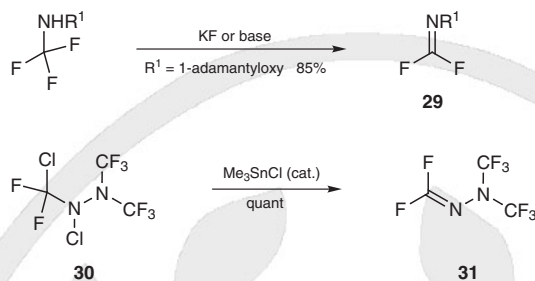
CAUTION: Aluminum trichloride dust is a severe irritant to all tissues and reacts violently with water.

Pentafluoroaniline (4.0 g, 0.022 mol) in CCl_4 (10 mL) (**CAUTION:** toxic) was added with stirring to a suspension of freshly sublimed AlCl_3 (8.8 g, 0.066 mol) in CCl_4 (15 mL) and the mixture was heated for 12 h at $70\text{--}80^\circ\text{C}$. The mixture was then poured onto ice and extracted with Et_2O . The combined extracts were washed with H_2O , dried (MgSO_4), and concentrated. The carbonimidic dichloride was isolated by distillation of the residue, and the product was redistilled; yield: 4.0 g (69%); bp $94^\circ\text{C}/40\text{ Torr}$.

18.12.1.1.7

Method 7:**From Trihalomethylamines by Elimination**

One of the principal methods for the preparation of carbonimidic difluorides **29** is the elimination of hydrogen fluoride from trifluoromethylamines (Scheme 10). The carbonimidic difluorides **29** ($\text{R}^1 = \text{CF}_3$) are prepared by heating the corresponding N-substituted trifluoromethylamines with potassium fluoride.^[60] Reactions of this type that lead to N-alkoxycarbonimidic difluorides are carried out below room temperature.^[61] An alternative is to bring about the elimination of hydrogen fluoride at room temperature, or below, by reaction with an organic base. This method is used for the preparation of compounds **29** ($\text{R}^1 = \text{H}$)^[62] and **29** ($\text{R}^1 = 1\text{-adamantyloxy}$).^[63] Carbonimidic difluorides have also been prepared by the elimination of chlorine: an example is the preparation of the carbonimidic difluoride **31** in quantitative yield from the hydrazine **30** and a catalytic amount of chlorotrimethylstannane.^[64]

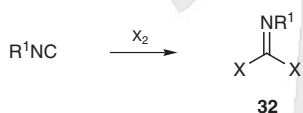
Scheme 10 Carbonimidic Difluorides from Trihalomethylamines^[60–64]***N*-(1-Adamantyloxy)carbonimidic Difluoride (29, R¹ = 1-Adamantyloxy):**^[63]

*i*Pr₂NH (0.36 mL, 2.5 mmol) was added to a soln of *O*-(1-adamantyl)-*N*-(trifluoromethyl)hydroxylamine (0.57 g, 2.4 mmol) in hexane (20 mL). The mixture was left for 0.5 h, the precipitate was removed by filtration, and the filtrate was concentrated to leave an oil. Purification by chromatography (silica gel) gave the title compound as an oil; yield: 0.44 g (85%).

18.12.1.1.8

**Method 8:
By Addition of Halogens to Isocyanides**

One of the most versatile methods for the preparation of carbonimidic dichlorides **32** (X = Cl) is the addition of chlorine to isocyanides (Scheme 11). The addition reactions proceed easily with chlorine or thionyl chloride, and they are usually carried out below room temperature, and in an inert solvent. Many examples of this method for the preparation of carbonimidic dichlorides have been tabulated in a review;^[9] some of these and others are detailed below.^[65–69] The corresponding addition of bromine to isocyanides is the most important method for the preparation of carbonimidic dibromides **32** (X = Br). Fluorine has also been added to isocyanides but the resulting carbonimidic difluorides **32** (X = F) are not fully characterized.^[70]

Scheme 11 Reaction of Isocyanides with Halogens^[9,65–69]

R ¹	X	Conditions	Yield (%) of 32	Ref
Bn	Cl	Cl ₂ , –20 °C	68	[65]
CH ₂ Ts	Cl	Cl ₂ , –5 °C	67	[66]
<i>t</i> -Bu	Cl	Cl ₂ , 0–5 °C	52	[9]
2- <i>t</i> -BuC ₆ H ₄	Cl	Cl ₂ , 2–5 °C	86	[67]
2-PhC ₆ H ₄	Cl	SOCl ₂ , –10 °C	100	[68]
Ph	Br	Br ₂ , 0–5 °C	76	[9]
CH(CN)CO ₂ Me	Br	Br ₂ , 0 °C	96	[69]
2-PhC ₆ H ₄	Br	Br ₂ , 0 °C	100	[68]

***N*-tert-Butylcarbonimidic Dichloride (32, R¹ = *t*-Bu; X = Cl); Typical Procedure:^[9]**

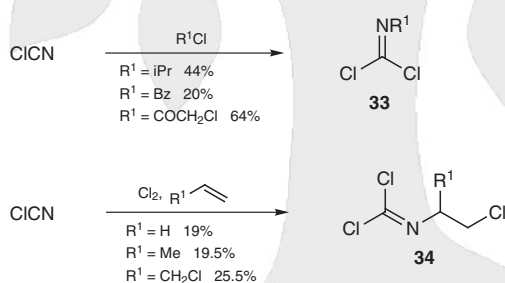
Cl₂ (15 g, 0.21 mmol) was passed into a soln of *tert*-butyl isocyanide (17 g, 0.20 mol) in CHCl₃ (200 mL) at 0–5 °C, with cooling. A strongly exothermic reaction occurred; when this had subsided, the soln was stirred for 10 min at rt. The solvent was distilled off and the title compound was isolated by distillation of the residue; yield: 16 g (52%); bp 129–131 °C.

18.12.1.1.9

Method 9:**By Addition to Cyanogen Chloride**

Carbonimidic dichlorides **33** can be produced by the addition of electrophilic reagents to cyanogen chloride. The addition of acyl chlorides to cyanogen chloride does not require a catalyst; for example, benzoyl chloride and chloroacetyl chloride react with cyanogen chloride at 50 °C under pressure to give the carbonimidic dichlorides **33** (R¹ = Bz) (in 20% yield) and **33** (R¹ = COCH₂Cl) (in 64% yield).^[71] (Scheme 12). The addition reactions of haloalkanes can be catalyzed by Lewis acids such as iron(III) chloride, in which case the carbonimidic dichlorides are isolated as complexes with the Lewis acid.^[72] Inorganic electrophiles such as chlorine and sulfur dichloride also add to cyanogen chloride.^[8] The addition of chlorine is carried out in an autoclave with activated carbon as a catalyst, giving *N*-chlorocarbonimidic dichloride **33** (R¹ = Cl) in 77% yield.^[73] Cyanogen chloride reacts with chlorine in the presence of monosubstituted alkenes to give carbonimidic dichlorides **34** in moderate yield (Scheme 12) (the corresponding 1,2-dichloroalkanes being the major products); analogous addition reactions are also reported with disubstituted alkenes, including cyclohexene.^[74] Similar reactions with vinyl chloride and with 2-chloropropene give the corresponding carbonimidic dichlorides in good yield.^[75] In these reactions the electrophile is probably the carbocation; it is generated by addition of the chlorinium ion to the alkene.

Scheme 12 Addition of Cyanogen Chloride to Alkyl and Acyl Chlorides and to Chlorine^[71–74]

**Complex of *N*-Isopropylcarbonimidic Dichloride **33** (R¹ = *i*Pr) and Iron(III) Chloride:^[72]**

CAUTION: The complex is very hygroscopic and reacts violently with water.

ClCN (12 mL, 0.234 mol) was added to a stirred suspension of FeCl₃ (19 g, 0.117 mol) in *i*PrCl (210 mL) at 5 °C. The soln became red because of the formation of a ClCN•FeCl₃ complex. The mixture was stirred for 20 h at 0 °C. The color changed to greenish yellow and a precipitate of the [Cl₂C=N-*i*Pr]₃•[FeCl₃]₂ complex separated as greenish yellow crystals. These were collected by filtration in the absence of moisture, washed with a little cold *i*PrCl, and dried; yield: 19 g (44%).

Carbonimidic Dichlorides 34; General Procedure:^[74]

CAUTION: Cyanogen chloride evolves corrosive, toxic fumes on contact with water or on heating and trimerization of the crude form may occur violently. It is a severe eye and respiratory tract irritant and a lachrymator.

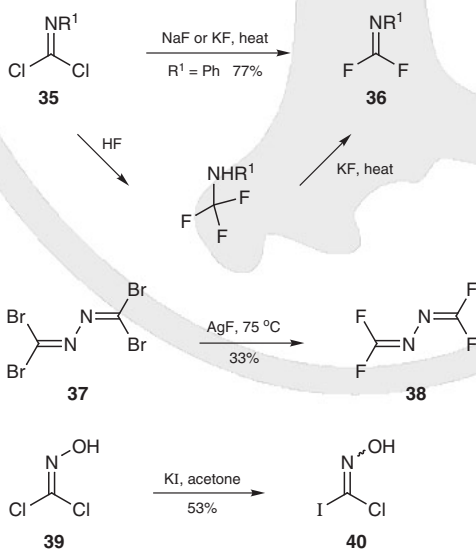
Cl₂ (71 g, 1 mol) was bubbled into a soln of ClCN (123 g, 2 mmol) and an alkene (1.1 mol) in CCl₄ (100 mL) (**CAUTION:** toxic) at 0 °C contained in a three-necked flask fitted with a thermometer, gas inlet tube, stirrer and drying tube. The mixture was then transferred to a distillation apparatus and distilled through a 30-cm Vigreux column. The excess ClCN and CCl₄ were distilled off first under atmospheric pressure. The pressure was reduced and the dichloroalkane was distilled off, followed by the carbonimidic dichloride.

18.12.1.1.10

Method 10:
From Other Carbonimidic Dihalides by Exchange of
a Halogen Atom Bonded to Carbon

This method is useful for the preparation of carbonimidic difluorides **36** from the corresponding carbonimidic dichlorides **35**. However, although it is a fairly general route for these compounds (Scheme 13), for other dihalides it is limited to a few scattered examples. *N*-Arylcarbonimidic dichlorides react with hydrogen fluoride to give trifluoromethylamines, which are then dehydrofluorinated by heating with potassium fluoride;^[17] so, in some cases, this method is an extension of that described in Section 18.12.1.1.7. *N*-Arylcarbonimidic difluorides are also obtained by heating the corresponding carbonimidic dichlorides with sodium fluoride or potassium fluoride in an inert solvent.^[9,76] Other examples include the preparations of carbonimidic difluorides **36** (R¹ = SF₅)^[77] and **36** (R¹ = TeF₅)^[78] from the corresponding carbonimidic dichlorides, and that of the azine **38** from the corresponding tetrabromoazine **37** and silver fluoride (Scheme 13).^[79] Examples of the interconversions of other halogens are rare. Biphenyl-2-ylcarbonimidic dibromide is converted quantitatively into the corresponding carbonimidic dichloride by reaction with thionyl chloride and tin(IV) chloride in excess.^[69] The mixed carbonimidic dihalide **40** is obtained in 53% yield by a reaction of *N*-hydroxycarbonimidic dichloride **39** with potassium iodide in acetone (Scheme 13).^[80]

Scheme 13 Exchange of a Halogen Atom of a Carbonimidic Dihalide Bonded to Carbon^[9,69,76–80]



N-Phenylcarbonimidic Difluoride (36, R¹ = Ph); Typical Procedure:^[76]

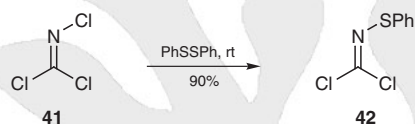
N-Phenylcarbonimidic dichloride (**35**, R¹ = Ph; 400 g, 2.3 mol) and NaF (390 g, 9.3 mol) were heated for 4 h at 200 °C in sulfolane (1 L) in a steel reactor fitted with a stirrer and a short column. The temperature was raised to 240 °C during a further 3 h, and a slight vacuum was applied. A slow distillation started giving N-phenylcarbonimidic difluoride (**36**, R¹ = Ph); yield: 248 g (77%); bp 74–78 °C/50 Torr. The compound was 97.5% pure by GC.

18.12.1.1.11

Method 11:**From Other Carbonimidic Dihalides by Exchange or Modification of the Nitrogen Substituent**

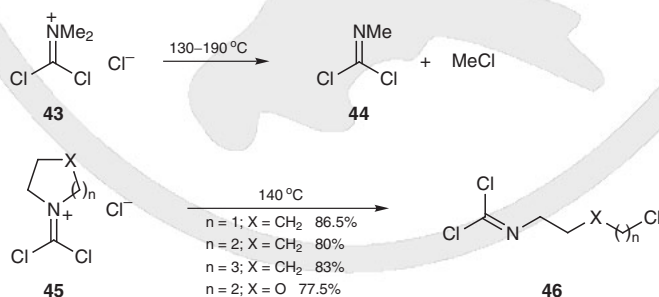
The exchange of one nitrogen substituent for another is not a widely used method of preparation of carbonimidic dihalides. One useful example is the conversion of N-chlorocarbonimidic dichloride (**41**) into the corresponding phenylsulfanyl derivative **42** by reaction with diphenyl disulfide at room temperature (Scheme 14).^[81] The dichloride **41** also adds to alkenes by cleavage of the N–Cl bond.^[73]

Scheme 14 Exchange of the N–Cl Halogen Atom of N-Chlorocarbonimidic Dichloride^[81]



Several examples of standard functional group transformations of the nitrogen substituents are documented. Thus, the hydroxy group of N-hydroxycarbonimidic dichloride (**1**, R¹ = OH) has been methylated,^[82] and phosphorylated,^[83] and acidic hydrolysis of [dichloro(phenyl)methyl]carbonimidic dichloride gives N-benzoylcarbonimidic dichloride in 55% yield.^[49] One type of transformation that has useful applications is the thermal cleavage of dichloroiminium salts, e.g. **43**. Most of these salts are dealkylated on heating to above about 130 °C.^[40] The thermolysis of salt **43** leads to the formation of N-methylcarbonimidic dichloride (**44**) as the principal product (Scheme 15).^[41] This pyrolytic cleavage has been extended to several other dichloroiminium salts including the cyclic dichloroiminium salts **45**. Thermolyses of these salts lead to N-(ω-chloroalkyl)carbonimidic dichlorides **46** (Scheme 15).^[42] The reverse reaction, the N-alkylation of carbonimidic dichlorides to produce iminium salts, is not generally useful because of the weak nucleophilicity of the imine nitrogen atom, but it can be achieved with powerful alkylating agents.^[40]

Scheme 15 Pyrolysis of Dichloroiminium Salts^[41,42]

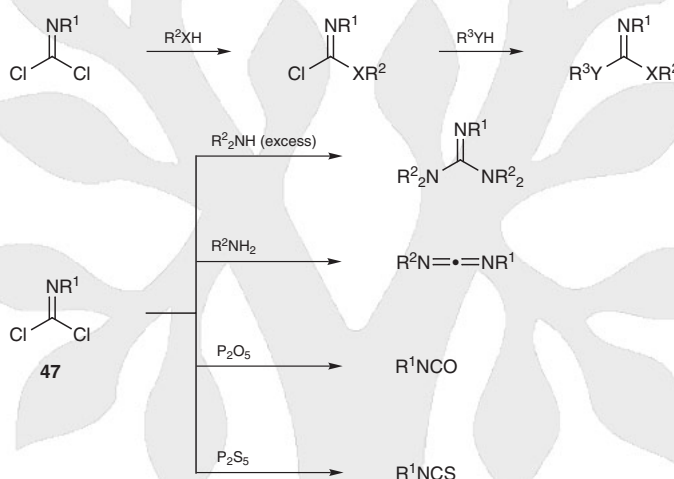


***N*-(ω-Chloroalkyl)carbonimidic Dichlorides 46; General Procedure:^[42]**

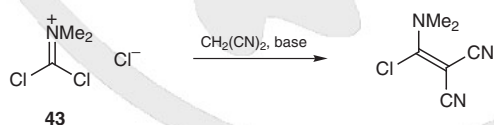
The salts **45** were pyrolyzed by heating in a Kugelrohr apparatus at atmospheric pressure. Decomposition occurred at 140 °C and gave the carbonimidic dichlorides **46**, which were purified by redistillation through a short Vigreux column.

18.12.1.2 Applications of Product Subclass 1 in Organic Synthesis

The reactions of carbonimidic dihalides have been reviewed.^[10,84] Carbonimidic dihalides are highly reactive toward nucleophiles. The ready displacement of one or two halogen atoms by heteroatomic nucleophiles leads to the formation of other carbonimidic acid derivatives, including many members of subclasses described later in this review. Most of these reactions utilize carbonimidic dichlorides **47**. Reactions of carbonimidic dichlorides with secondary amines also lead to the formation of guanidines and, with primary amines, to carbodiimides. The same starting materials are also used to give isocyanates and isothiocyanates. These processes are summarized in Scheme 16.

Scheme 16 Some Applications of Carbonimidic Dichlorides in Synthesis

The extensive applications of dichloroiminium salts in organic synthesis have also been reviewed.^[40] Reactions with carbon nucleophiles are particularly useful; these range from simple condensation reactions (as exemplified by the reaction of the chloride **43** with malononitrile shown in Scheme 17) to more complex transformations requiring 2 or more molecular equivalents of the dichloroiminium salts. Displacement reactions with nitrogen, oxygen, and sulfur nucleophiles also occur easily.

Scheme 17 Reaction of a Dichloroiminium Chloride with Malononitrile^[40]

Carbonimidic dibromides find a particular use as protected forms of isocyanides. The addition of bromine to isocyanides to give carbonimidic dibromides (Section 18.12.1.1.8) is reversible. Debromination may be carried out using activated magnesium^[58,70] or triethyl phosphite.^[85] The latter method is used for the protection and deprotection of a sensitive isocyanide function in the total synthesis of (±)-trichoviridin.

18.12.2

**Product Subclass 2:
Carbonohalidimidic Acid Derivatives**

Members of this subclass are also named as esters of haloformimidic acids. Most of the known compounds contain chlorine as the halogen substituent. These are sufficiently stable to be isolated and distilled but aryl esters are prone to Chapman rearrangement (migration of the aryl group from oxygen to nitrogen) at elevated temperatures. In this subclass, and in other subclasses in which two different substituents are attached to carbon, geometrical isomers are possible. This structural feature has been addressed only rarely in the literature, one example being the isolation and characterization of the geometrical isomers **48A** and **48B** from the reaction of *N*-chlorocarbonimidic dichloride with (chlorooxy)(pentafluoro)- λ^6 -sulfane (F_5SOCl) (Scheme 18).^[86] The two most general methods for the preparation of members of this subclass start from carbonimidic dihalides and from cyanates; others are of limited applicability.

Scheme 18 Geometrical Isomers of a Carbonochloridimidic Ester^[86]

18.12.2.1

Synthesis of Product Subclass 2

18.12.2.1.1

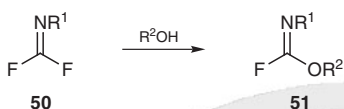
**Method 1:
From Carbonimidic Dihalides and Oxygen Nucleophiles**

The displacement of halide from carbonimidic dihalides by oxygen nucleophiles (Scheme 19) has been used for the preparation of the corresponding monohalo esters; thus, the reaction of *N*-phenylcarbonimidic dichloride with 1 molecular equivalent of sodium ethoxide or sodium phenoxide to give esters **49** ($R^1 = Ph$; $R^2 = Et, Ph$) is a long established reaction and early examples have been reviewed.^[84] Further examples of the preparation of the esters **49** by this method are given in Scheme 19.^[87–91] In an analogous manner, *N*-(trifluoromethyl)carbonimidic difluoride **50** ($R^1 = CF_3$) reacts with prop-2-yn-1-ol and other unsaturated alcohols with displacement of one fluoride to give the monofluorinated esters **51** ($R^1 = CF_3$).^[92,93]

Scheme 19 Displacement of Halide Ion from Carbonimidic Dichlorides^[84,87–91]

R^1	R^2	Conditions	Yield ^a (%) of 49	Ref
Ph	Ph	NaOPh, dioxane	55	[87]
C_6F_5	Ph	K_2CO_3 , PhOH, 80 °C	62	[88]
C_6F_5	Et	K_2CO_3 , EtOH, 80 °C	44	[88]
SF_5	Me	NaOMe, MeOH	16	[89]
4- ClC_6H_4CO	Ph	PhOH, Et_3N	n.r.	[90]
Ph	Et	NaOMe, MeOH	n.r.	[91]
4- ClC_6H_4	Ph	NaOPh, EtOH	n.r.	[91]

^a n.r. = not reported.



Phenyl *N*-Phenylcarbonochloridimidate (49, $\text{R}^1 = \text{R}^2 = \text{Ph}$); Typical Procedure:^[87]

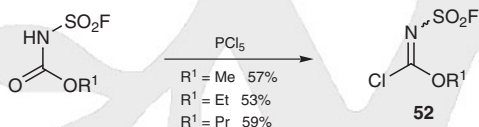
NaOPh (86 g, 0.75 mol) was added in portions to a soln of *N*-phenylcarbonimidic dichloride ($\text{R}^1 = \text{Ph}$; 130 g, 0.75 mol) in 1,4-dioxane (400 mL) during 30 min. The temperature was kept below 35 °C by external cooling. The mixture was refluxed for 1 h, and then cooled, and the precipitate of NaCl was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was distilled to give the title compound; yield: 95 g (55%); bp 170–180 °C/10 Torr.

18.12.2.1.2

**Method 2:
By Chlorination of Carbamates**

The reactions of *N*-(fluorosulfonyl)carbamates with phosphorus pentachloride leads to the formation of the corresponding chlorimidate esters **52** (Scheme 20).^[94] This is not a general method of preparation, and there is only one example where an ester of this type can be isolated. *N*-Phenyl carbamate gives *N*-phenylcarbamoyl chloride or phenyl isocyanate with phosphorus pentachloride. There are also isolated examples of the chlorination of monothiocarbamates to give carbonochloridimidates.^[95]

Scheme 20 Chlorination of *N*-(Fluorosulfonyl)carbamates^[94]



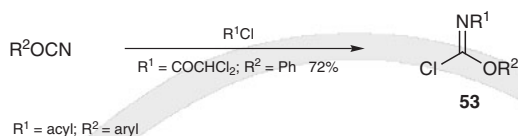
***N*-(Fluorosulfonyl)carbonochloridimidates **52**; General Procedure:**^[94]

An alcohol (MeOH, EtOH, or PrOH, 1 mol) was added dropwise to a soln of fluorosulfonyl isocyanate (125 g, 1 mol) in CCl_4 (300 mL) (**CAUTION: toxic**). PCl_5 (208.5 g, 1 mol) was added, and the temperature of the mixture was slowly raised to boiling. It was refluxed for 6 h, and then CCl_4 and excess POCl_3 were distilled off using a water pump. The residue was distilled through a 30-cm column at low pressure using an oil pump.

18.12.2.1.3

**Method 3:
By Addition to Aryl Cyanates**

Aryl cyanates react with carboxylic acid chlorides to give aryl esters **53** ($\text{R}^2 = \text{aryl}$) of carbonochloridimidic acid (Scheme 21). Other acid halides including phosgene and oxalyl chloride also add to aryl cyanates,^[96] as does phosphorus pentachloride.^[97] The reaction conditions are dependent upon the reactivity of the acid chloride. Aliphatic acid chlorides react between room temperature and 120 °C in an inert solvent, aromatic acid chlorides require higher temperatures, and phosgene and phosphorus pentachloride react below room temperature. These addition reactions have been reviewed.^[98] Chlorine and bromine also add readily to aryl cyanates but the primary addition products are too unstable to allow their isolation.^[99]

Scheme 21 Addition of Acyl Chlorides to Aryl Cyanates^[96]

Phenyl *N*-(Dichloroacetyl)carbonochloridimidate (53, $\text{R}^1 = \text{COCHCl}_2$; $\text{R}^2 = \text{Ph}$);

Typical Procedure:^[96]

PhOCN (23.8 g, 0.2 mol) was added dropwise and slowly to a soln of Cl_2CHCOCl (29.4 g, 0.2 mol) in toluene (100 mL). The soln was refluxed for 1 h to complete the reaction. A small amount of triphenyl cyanurate precipitated out and was removed by filtration. The filtrate was concentrated under water pump pressure to leave a residue (50 g). Distillation gave the title compound; yield: 38 g (72%); bp 99 °C/0.2 Torr.

18.12.3

**Product Subclass 3:
Carbonohalidimidothioates**

Members of this subclass are also called halothioformimidates. Most of the known compounds bear a divalent sulfur atom as indicated in the general formula and nearly all are chloro compounds (there are isolated examples of bromo^[74,100,101] and fluoro compounds^[102,103]). There are also a few sulfones in this category, most of which have been prepared by the addition of chlorine or sulfonyl chlorides to sulfonyl cyanides. These preparations are described in Section 18.12.3.1.4.2.

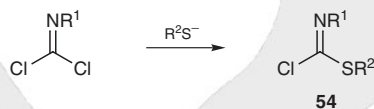
18.12.3.1

Synthesis of Product Subclass 3

18.12.3.1.1

**Method 1:
From Carbonimidic Dichlorides and Sulfur Nucleophiles**

The displacement of chloride ion by thiolate anions (Scheme 22),^[87,90,104–107] and by other sulfur nucleophiles, occurs readily and constitutes a general method for the preparation of members **54** of this subclass bearing a chloro substituent. Unfortunately, the method is often inefficient as mixtures can result from displacement of a second chloride in competition with the first.

Scheme 22 Carbonochloridimidothioates from Carbonimidic Dichlorides and Thiolate Anions^[87,90,104–107]

R^1	R^2	Conditions	Yield ^a (%) of 54	Ref
Ph	Ph	NaSPh	n.r.	[104]
4-ClC ₆ H ₄	C ₆ F ₅	NaSC ₆ F ₅ , acetone	92	[87]
4-ClC ₆ H ₄	Ph	PhSH, Et ₃ N	n.r.	[90]
PO(OEt) ₂	Bu	BuSH, py	n.r.	[105]
Bz	Bn	BnSH, Et ₃ N	60 ^b	[106]
C ₆ F ₅	Ph	PhSH, K ₂ CO ₃	49 ^c	[107]

^a n.r. = not reported.

^b 98.5% pure by HPLC.

^c 85.5% pure by GC.

S-Benzyl N-Benzoylcarbonochloridimidothioate (54, R¹ = Bz; R² = Bn);**Typical Procedure:**^[106]

BnSH (3.70 g, 29.7 mmol) was added to a stirred soln of *N*-benzoylcarbonimidic dichloride (R¹ = Bz; 6.00 g, 29.7 mmol) in dry toluene (350 mL) at 0 °C. A soln of Et₃N (3.00 g, 29.7 mmol) in toluene (20 mL) was added dropwise during 0.5 h. The soln was warmed to rt; analytical HPLC showed that it contained the title compound (65%) and a byproduct (8%) (formed by displacement of both Cl atoms). Additional Et₃N (0.78 g) and BnSH (1.03 g) in toluene (20 mL) were added dropwise at several intervals. After 2 h, the solvent was removed to leave an oil (9.3 g) that contained the title compound (72%) and the byproduct (27%). Preparative layer chromatography (silica gel, hexane/CH₂Cl₂ 2:1) gave the title compound; yield: 5.20 g (60%); 98.5% pure by HPLC.

18.12.3.1.2

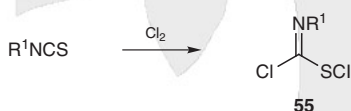
Method 2:**By Chlorination of Isothiocyanates and Related Compounds**

In the preparation of carbonimidic dichloride from isothiocyanates (see Scheme 4), sulfonyl chlorides are intermediates. It is possible to isolate such compounds by careful control of the reaction conditions. Closely related preparative procedures involve the chlorination of carbamates, thiocarbamates, and dithiocarbonimidates under controlled conditions. These variations provide useful preparations of the thioesters **54**, especially those bearing *N*-acyl or *N*-arenesulfonyl substituents.

18.12.3.1.2.1

Variation 1:**By the Addition of Chlorine to Isothiocyanates**

This method (Scheme 23) is successful for the preparation of a range of sulfonyl chlorides **55** including *N*-alkyl and *N*-aryl,^[108,109] fluoromethyl,^[110] and aroyl derivatives,^[111] Diorganophosphoryl derivatives and arenesulfonyl derivatives can also be prepared in this way.^[9]

Scheme 23 Addition of Chlorine to Isothiocyanates^[108–111]

R ¹	Conditions	Yield (%) of 55	Ref
Ph	Cl ₂ , 15–18 °C	95	[109]
Bu	Cl ₂ , 15–18 °C	92	[109]
4-BrC ₆ H ₄ CO	Cl ₂ , rt	69	[111]
CF ₂ Cl	Cl ₂ , 70 °C	85	[110]

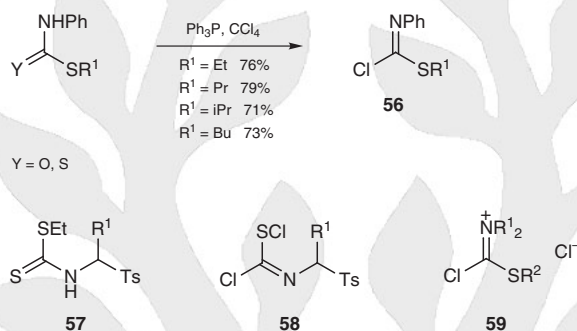
N*-(4-Bromobenzoyl)chloro(imino)methanesulfonyl Chloride (55, R¹ = 4-BrC₆H₄CO);*Typical Procedure:**^[111]

Cl₂ (7.1 g, 0.1 mol) in dry CCl₄ (50 mL) (**CAUTION: toxic**) was added to 4-bromobenzoyl isothiocyanate (24.2 g, 0.1 mol) in CCl₄ (20 mL). The mixture was left to stand for 6 h at rt, and then overnight in the ice compartment of a refrigerator. The precipitate of colorless needles that formed was collected and crystallized; yield: 21.6 g (69%); mp 108–109 °C (dry CCl₄/hexane).

18.12.3.1.2.2

Variation 2:**By Chlorination of Thiocarbamates and Dithiocarbamates**

The chlorination of *S*-alkyl esters of *N*-phenylthiocarbamic acid and *N*-phenyldithiocarbamic acid by triphenylphosphine and carbon tetrachloride provides an efficient synthesis of *S*-alkyl *N*-phenylcarbonochloridimidothioates **56** (Scheme 24).^[112] However, the reactions of chlorine with the *S*-ethyl dithiocarbamates **57** lead instead to sulfenyl chlorides **58**, after elimination of chloroethane.^[95] Chlorination of *N,N*-dialkyldithiocarbamates gives the iminium salts **59** (Scheme 24).^[113]

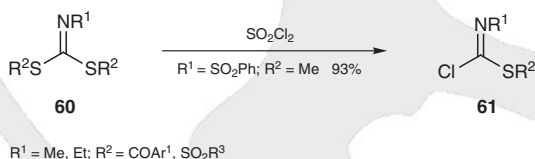
Scheme 24 Chlorination of Thiocarbamates and Dithiocarbamates^[95,112,113]***S*-Alkyl *N*-Phenylcarbonochloridimidothioates **56**; General Procedure:**^[112]

Ph_3P (31.4 g, 0.12 mol) and the appropriate *S*-alkyl *N*-phenylthiocarbamate (0.1 mol) were suspended in MeCN (100 mL). CCl_4 (15.4 g, 0.1 mol) (**CAUTION: toxic**) was added. The mixture was stirred for 8 h between 0 °C and rt. The solvent was then removed and the residue was extracted several times with Et_2O . The combined extracts were concentrated and the residue was distilled under reduced pressure.

18.12.3.1.2.3

Variation 3:**From Carbonimidodithioates**

The reactions of carbonimidodithioates **60** with sulfuryl chloride provide efficient routes to *N*-aroyl- and *N*-(sulfonyl)carbonochloridimidothioates **61** (Scheme 25).^[100,114]

Scheme 25 Chlorination of Carbonimidodithioates^[100,114]***S*-Methyl *N*-(Phenylsulfonyl)carbonochloridimidothioate (**61**, $\text{R}^1 = \text{SO}_2\text{Ph}$; $\text{R}^2 = \text{Me}$);****Typical Procedure:**^[100]

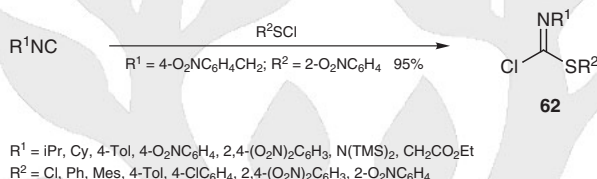
CAUTION: Sulfuryl chloride can react explosively with alkalis and is an irritant.

SO_2Cl_2 (13.4 g, 100 mmol) was added slowly to *S,S*-dimethyl *N*-phenylsulfonylcarbonimidodithioate (**60**; $\text{R}^1 = \text{SO}_2\text{Ph}$; $\text{R}^2 = \text{Me}$) in CCl_4 (100 mL) (**CAUTION: toxic**). The soln was stirred for 1 h at rt, and then warmed to 60 °C for 0.5 h. The solvent was removed and the residue solidified. Crystallization gave the title compound; yield: 11.9 g (93%); mp 65–66 °C (Et_2O).

18.12.3.1.3

Method 3:**By Addition of Sulfenyl Chlorides to Isocyanides**

The addition of a sulfenyl chloride to an isocyanide (Scheme 26) is a good and general method for the preparation of members of this subclass. The reaction takes place under mild conditions to give a carbonochloridimidothioate **62**. The method is used to give a wide range of imidothioates, which are usually in formed in good yields, but in many reports the products are generated in situ and used immediately in a further reaction step without being fully characterized.^[115–124] Examples of compounds **62** that have been isolated from the reaction include those where R¹ = 2,4-dinitrophenyl,^[125] isopropyl,^[126] cyclohexyl and 4-tolyl,^[87] bis(trimethylsilyl)amino,^[127] (ethoxycarbonyl)methyl,^[115] and 4-nitrobenzyl.^[128]

Scheme 26 Addition of Sulfenyl Chlorides to Isocyanides^[89,115–128]

S-(2-Nitrophenyl) N-4-(Nitrobenzyl)carbonochloridiminothioate (62, R¹ = 4-O₂NC₆H₄CH₂; R² = 2-O₂NC₆H₄); Typical Procedure:^[128]

2-Nitrobenzenesulfenyl chloride (2.33 g, 12.3 mmol) in CH₂Cl₂ (15 mL) was added dropwise with stirring to 4-nitrobenzyl isocyanide (2.00 g, 12.3 mmol) in CH₂Cl₂, the temperature being maintained at –40 °C. The mixture was allowed to reach 15 °C, and then the solvent was distilled off. The residue was crystallized to give the title compound; yield: 4.11 g (95%); mp 109–110 °C (CCl₄).

18.12.3.1.4

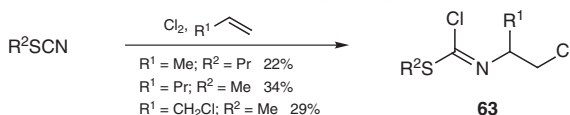
Method 4:**By Electrophilic Additions to Nitriles**

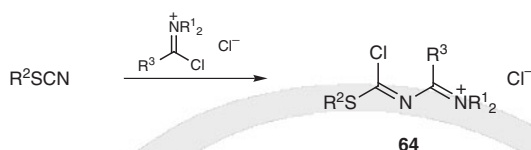
Two variations of this method, both of limited applicability, are described.

18.12.3.1.4.1

Variation 1:**From Thiocyanates and Electrophiles**

The addition of electrophilic chlorides to thiocyanates is, in principle, a method for the preparation of members of this subclass. This approach is analogous to addition reactions with cyanogen chloride and with aryl cyanates (Sections 18.12.1.1.9 and 18.12.2.1.3). However, in practice the method is not widely used. The addition of chlorine in the presence of alkenes leads to the formation of the *N*-β-chloroalkyl derivatives **63** in moderate yields (Scheme 27).^[74] *N,N*-Dialkylcarbonimidium chlorides also add to the triple bond to give salts **64**.^[129]

Scheme 27 Electrophilic Addition of Chlorine to Thiocyanates in the Presence of an Alkene^[74,129]



S-Alkyl N-(β-Chloroalkyl)carbonochloridiminothioates 63; General Procedure:^[74]

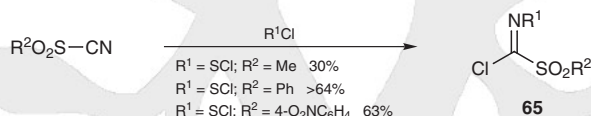
An alkene (1.1 mol) and a thiocyanate (1 mol) were added to a three-necked flask fitted with a thermometer, stirrer, a gas inlet tube, and a CaCl₂ tube. The flask was placed in a cooling bath at -25 °C. Cl₂ (1 mol) was then introduced, the temperature of the mixture being kept to 0 °C. The mixture was distilled under reduced pressure.

18.12.3.1.4.2

**Variation 2:
From Sulfonyl Cyanides and Electrophiles**

There are a few S,S-dioxides present in this subclass that are prepared by the additions of electrophiles, mostly chlorine or sulfur chlorides, to sulfonyl cyanides (Scheme 28).^[130,131] This is the only method for the preparation of these S,S-dioxides that has general use, but liquid products are difficult to purify as decomposition, or partial decomposition, may occur on attempted distillation. The chloride **65** (R¹ = SCl; R² = 4-O₂NC₆H₄) is a solid, which is stable at 0 °C.

Scheme 28 Electrophilic Addition to Sulfonyl Cyanides^[130,131]



N-(Chlorosulfenyl)-C-sulfonylcarbonimidic Chlorides 65 (R¹ = SCl); General Procedure:^[131]

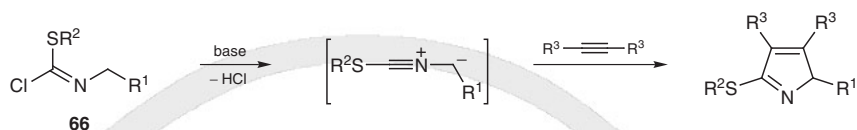
CAUTION: Sulfur dichloride is toxic, corrosive, a severe irritant, and reacts exothermically with water.

A soln containing equimolar amounts of SCl₂ and a sulfonyl cyanide, together with a catalytic amount of TBACl in CH₂Cl₂ was prepared at 0 °C. Evaporation of the solvent gave the appropriate title compound.

18.12.3.2

Applications of Product Subclass 3 in Organic Synthesis

Members of this product subclass are useful intermediates for the synthesis of a variety of five-membered heterocycles. The high reactivity of the chlorine atom as a leaving group allows nucleophiles to be introduced and subsequent cyclization reactions produce heterocycles. Thiazoles,^[124] thiazolium salts,^[132] imidazoles,^[119,123,124] and oxazoles^[115,119] have all been produced by such reactions. The salts **59** (see Scheme 24) are also used to construct heterocycles from bifunctional nucleophiles.^[133] Compounds having the general structure **66**, in which the substituent R¹ is a conjugative electron-withdrawing group [e.g., CO₂Et, P(O)(OEt)₂, Ts], are sources of sulfur-substituted nitrile ylides that participate in 1,3-dipolar cycloaddition reactions with electrophilic alkenes and alkynes (Scheme 29). These reactions provide routes to pyrroles and dihydropyrroles.^[128,134]

Scheme 29 Carbonochloridiminothioates as Sources of Nitrile Ylides^[128,134]

18.12.4

**Product Subclass 4:
Carbamimidic Halides**

The compounds in this product subclass are also called haloformamidines. Most of the known compounds contain chlorine as the halogen substituent; these compounds are quite common in the literature and there are several established methods for their preparation. There are also a few compounds that contain functional groups other than amino (e.g., nitro, azido) as the nitrogen substituent and examples of these are included in this review, where appropriate.

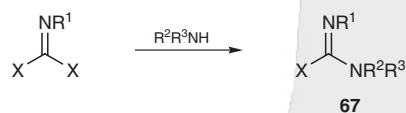
18.12.4.1

Synthesis of Product Subclass 4

18.12.4.1.1

**Method 1:
From Carbonimidic Dihalides and Amines**

The reactions of carbonimidic dihalides with amines (Scheme 30) offer, in principle, a general route to carbamimidic halides **67**.^[92,135–138] However, like other reactions of this type where only one of the two halogen atoms present in the substrate is displaced, it is not always possible in practice to carry out the conversions cleanly. Primary and secondary aliphatic amines that are both good nucleophiles and bases react quite cleanly with carbonimidic dihalides at below room temperature in a 2:1 ratio. Activating substituents on the nitrogen atom of the carbonimidic dihalides facilitate nucleophilic attack. Reactions of *N*-aroylcarbonimidic dichlorides^[135] and of *N*-(arenesulfonyl)carbonimidic dichlorides^[139] may be carried out in a very selective manner by using trimethylsilyldialkylamines instead of the free dialkylamines as nucleophiles.

Scheme 30 Reaction of Carbonimidic Dihalides and Amines^[89,91,135–138]

R ¹	R ²	R ³	X	Conditions	Yield (%) of 67	Ref
4-ClC ₆ H ₄	Me	Me	Cl	Me ₂ NH, 10–20 °C	98	[136]
C ₆ F ₅	Ph	Me	Cl	PhNHMe, rt	91	[137]
4-ClC ₆ H ₄ CO	Ph	Me	Cl	PhNHMe, Et ₃ N, rt	— ^a	[91]
Bz	Me	Me	Cl	Me ₂ NTMS, –45 °C	89	[135]
SF ₅	Et	Et	Cl	Et ₂ NH, rt	88	[89]
CF ₃	Cy	H	F	CyNH ₂ , Et ₃ N, KF, rt	73	[138]

^a Yield not reported.

N-(4-Chlorophenyl)-N',N'-dimethylcarbamimidic Chloride (67, $R^1 = 4\text{-ClC}_6\text{H}_4$; $R^2 = R^3 = \text{Me}$; $X = \text{Cl}$); **Typical Procedure:**^[136]

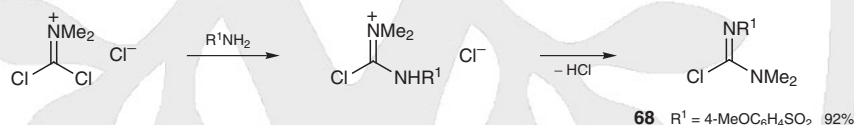
A soln of the dichloride ($R^1 = 4\text{-ClC}_6\text{H}_4$; 31.3 g, 0.15 mol) in benzene (**CAUTION: carcinogen**) was cooled in ice to 10–20 °C and gaseous Me_2NH (13.8 g, 0.3 mol) was introduced. The mixture was filtered to remove $\text{Me}_2\text{NH}\cdot\text{HCl}$ and the filtrate was concentrated to leave the title compound; yield: 32 g (98%); bp 157–160 °C/10 Torr.

18.12.4.1.2

Method 2:**From Dichloroiminium Salts and Nitrogen Nucleophiles**

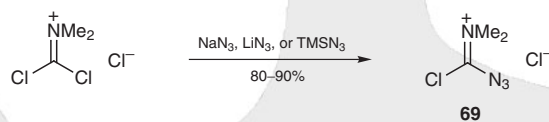
This method, although clearly related to that in Section 18.12.4.1.1, differs from it in two respects. Firstly, because of the much greater reactivity of the salts, a wider range of nitrogen nucleophiles can be used in displacement reactions. Secondly, the *N,N*-dialkyliminium unit is often retained in the product as a dialkylamino substituent on a new $\text{C}=\text{N}$ bond. These features are illustrated in Scheme 31 for the reaction of (dichloromethylene)dimethylammonium chloride with nucleophiles containing the primary amino group, which lead to the formation of *N,N*-dimethylcarbamidic chlorides **68**. This type of reaction takes place with aromatic primary amines, including those that are weakly nucleophilic,^[41] hydrazines ($R^1 = \text{NR}_2$),^[140] *O*-alkylhydroxylamines ($R^1 = \text{OR}^2$),^[40] carbamates ($R^1 = \text{CO}_2\text{R}^2$),^[40] and arenesulfonamides ($R^1 = \text{SO}_2\text{Ar}^1$).^[141] Isocyanates also react to give compounds of the same type by loss of phosgene; for example, trichlorovinyl isocyanate gives the chloride **68** [$R^1 = \text{C}(\text{Cl})=\text{CCl}_2$] (86%).^[142]

Scheme 31 Reaction of (Dichloromethylene)dimethylammonium Chloride with Compounds Containing the Primary Amino Group^[40,41,140–142]



Monosubstitution of (dichloromethylene)dimethylammonium chloride by azide anion can be achieved by reaction with sodium or lithium azide, or with trimethylsilyl azide, to give the azidoiminium chloride **69** (Scheme 32).^[143]

Scheme 32 Substitution by Azide Anions^[143]



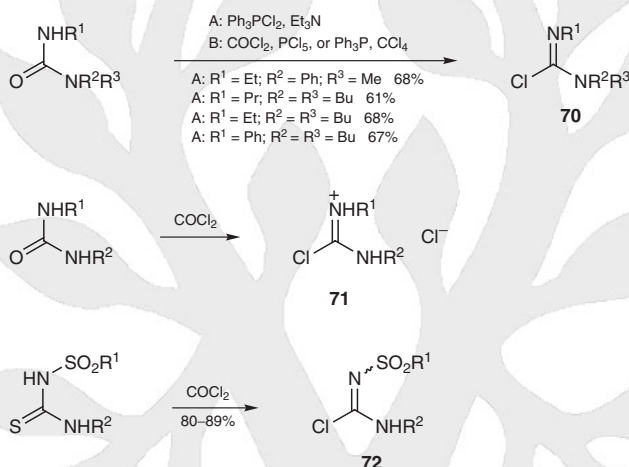
N-(4-Methoxybenzenesulfonyl)-N',N'-dimethylcarbamimidic Chloride (68, $R^1 = 4\text{-MeOC}_6\text{H}_4\text{SO}_2$); **Typical Procedure:**^[141]

4-Methoxybenzenesulfonamide (0.935 g, 5.0 mmol) and $\text{Cl}_2\text{C}=\text{NMe}_2^+\text{Cl}^-$ (0.89 g, 5.5 mmol) were suspended in benzene (20 mL) (**CAUTION: carcinogen**) and the suspension was refluxed for 1–2 h until the evolution of HCl was complete. The solvent was distilled off and the solid residue was crystallized to give the title compound; yield: 1.27 g (92%); mp 121–122 °C (EtOH).

18.12.4.1.3

Method 3:
By Chlorination of Ureas and Thioureas

Carbamimidic chlorides **70** are produced by the chlorination of trisubstituted ureas by phosgene,^[144–146] by phosphorus pentachloride,^[147] and by triphenylphosphine/carbon tetrachloride or dichlorotriphenylphosphine.^[148,149] The last procedure appears to be the most versatile and applies to both ureas and thioureas with three aryl substituents.^[149] *N,N'*-Disubstituted ureas give the iminium salts **71** with phosgene.^[150] *N*-(Fluorosulfonyl)-*N',N'*-dialkylureas are chlorinated by phosphorus pentachloride,^[151] and *N*-(arenesulfonyl)-*N'*-alkylthioureas are chlorinated by phosgene at low temperature to give *N*-(arenesulfonyl)carbamimidic chlorides **72**.^[152] These reactions are illustrated in Scheme 33.

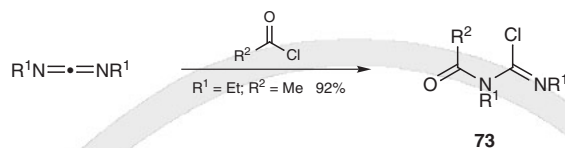
Scheme 33 Carbamimidic Chlorides by Chlorination of Ureas and Thioureas^[144–152]

Carbamimidic Chlorides 70; General Procedure:^[149]

With strict exclusion of air, Ph_3PCl_2 (3.3 g, 0.1 mol), a trisubstituted urea (0.1 mol), and Et_3N (10.1 g, 0.1 mol) were dissolved in MeCN (150 mL) at -20°C . The mixture became yellow, and then $\text{Et}_3\text{N}\cdot\text{HCl}$ crystallized out. The mixture was allowed to warm to rt during 4 h, the solvent was removed, and the residue was extracted with Et_2O (3×100 mL). The Et_2O was distilled off from the combined extracts in the absence of air and the residue was distilled under reduced pressure.

18.12.4.1.4

Method 4:
By Addition of Acid Chlorides to Carbodiimides

The additions of carboxylic acid chlorides to carbodiimides form a limited method for the preparation of *N*-acylcarbamimidic chlorides **73** (Scheme 34). Successful preparations require a combination of a nucleophilic carbodiimide and a reactive acid chloride.^[153] Thus, primary aliphatic carbodiimides react with acetyl chloride to give isolable adducts, but secondary aliphatic and aromatic carbodiimides do not; secondary aliphatic carbodiimides require more electrophilic acyl chlorides such as chloroacetyl chloride^[154] or phosgene.

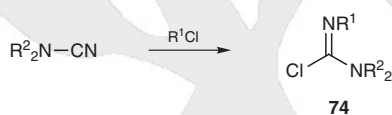
Scheme 34 Addition of Acid Chlorides to Carbodiimides^[153,154]***N*-Acetyl-*N,N'*-diethylcarbamimidic Chloride (73, R¹ = Et; R² = Me); Typical Procedure:**^[153]

Diethylcarbodiimide (4.9 g, 50 mmol) and AcCl (3.93 g, 50 mmol) were dissolved in dry CH₂Cl₂ (100 mL) at 0 °C. After the soln had been allowed to stand for 1 h at rt, the solvent was distilled off and the residue was distilled under oil pump vacuum to give the title compound; yield: 8.1 g (92%); bp 33–34 °C/0.01 Torr.

18.12.4.1.5

**Method 5:
By Electrophilic Addition to Cyanamides**

An efficient method for the preparation of carbamimidic chlorides **74** involves the addition of an electrophilic chloride to a dialkylcyanamide. The method is simple and a wide range of electrophilic chlorides are used (Scheme 35).

Scheme 35 Addition of Electrophilic Chlorides to Cyanamides^[155–160]

R¹	R²	Conditions	Yield (%) of 74	Ref
4-O ₂ NC ₆ H ₄ CO	Me	4-O ₂ NC ₆ H ₄ COCl, 70 °C	52	[155]
4-O ₂ NC ₆ H ₄ CO	^a	4-O ₂ NC ₆ H ₄ COCl, 70 °C	82	[156]
4-ClC ₆ H ₄ CO	^a	4-ClC ₆ H ₄ COCl, 70 °C	67	[156]
4-ClC ₆ H ₄ CO	^b	4-ClC ₆ H ₄ COCl, 70 °C	96	[156]
COBz	iPr	BzCOCl, 80 °C	75	[157]
SO ₂ Cl	Et	SO ₂ Cl ₂ , rt to 50 °C	80–95	[158]
POCl ₂	Et	POCl ₃ , 80 °C	87	[158]
PSCl ₂	Et	PSCl ₃ , rt	75	[159]
PCl ₂	Me	PCl ₃ , 20 °C	90	[160]
2-O ₂ NC ₆ H ₄ S	^b	2-O ₂ NC ₆ H ₄ SOCl, 45 °C	89	[156]
4-O ₂ NC ₆ H ₄ SO	^b	4-O ₂ NC ₆ H ₄ SOCl, 25 °C	73	[156]

^a NR₂₂ = morpholino.^b NR₂₂ = pyrrolidin-1-yl.**Carbamimidic Chlorides 74; General Procedure:**^[156]

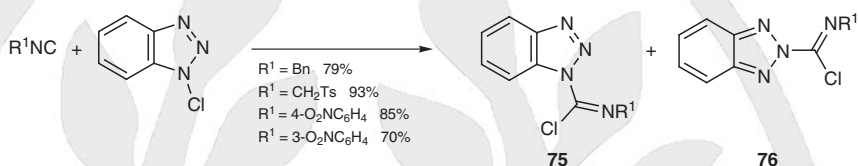
The appropriate acid chloride (10 mmol) and cyanamide (12 mmol) were carefully mixed together, and then warmed to produce a homogeneous soln. Normally, the mixture was heated at 60–75 °C for between 1 and 48 h (depending upon the acid chloride), whereupon the product separated as a crystalline solid. This was purified either by two crystallizations (MeCN) or by taking it up in CHCl₃, filtering, and precipitating it from the filtrate by the addition of Et₂O.

18.12.4.1.6

Method 6:
From Isocyanides and 1-Chlorobenzotriazole

Although not a general method, the addition of certain isocyanides to 1-chlorobenzotriazole (Scheme 36) provides a route to a mixture of the corresponding isomeric carbamimidic chlorides **75** and **76**. These compounds are not separated, but are used directly as the synthetic equivalents of carbonimidic dichlorides in subsequent reactions.^[161]

Scheme 36 Carbamimidic Chlorides from Isocyanides and 1-Chlorobenzotriazole^[161]


1-(Chloroformimidoyl)benzotriazoles **75 and 2-(Chloroformimidoyl)benzotriazoles **76**;**
General Procedure:^[161]

1-Chlorobenzotriazole (788 mg, 5 mmol) in $CHCl_3$ (30 mL) was slowly added to a soln of an isocyanide (5 mmol) with stirring at rt. Removal of the solvent gave mixtures of the title compounds, which were used without purification in further transformations. However, pure samples of **75** ($R^1 = 4-O_2NC_6H_4$), mp 218–220 °C, and **76** ($R^1 = 4-O_2NC_6H_4$), mp 213–214 °C, can be obtained after column chromatography (Et_2O /pentane).

18.12.5

Product Subclass 5:
Carbonimidic Halides Bearing a Phosphorus Substituent

This is a small subclass and one in which there is a limited range of compounds. The known members are λ^5 -phosphorus compounds, most of them conforming to the general formula $X[R^3R^2P(O)]C=NR^1$ ($X = \text{halo}$). Many of these are arylhydrazones or oximes that are made by a Japp–Klingemann type reaction on an α -halodialkoxyphosphorylacetaldehyde. There are individual examples of the displacement of chloride^[162] or fluoride ion^[163] from imines by phosphorus nucleophiles to give compounds of this subclass, but none has been developed into a general method.

18.12.5.1

Synthesis of Product Subclass 5

18.12.5.1.1

Method 1:
From (Dialkoxyphosphoryl)- α -haloacetaldehydes or from
[Bis(dialkylamino)phosphoryl]- α -haloacetaldehydes by
Diazo Coupling or Nitrosation

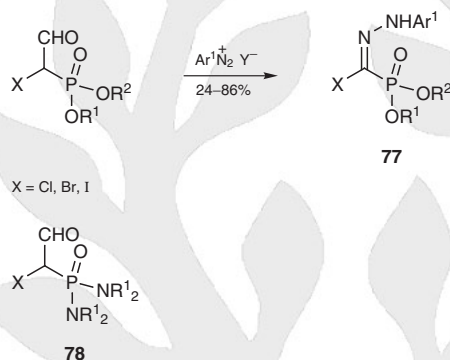
(Dialkoxyphosphoryl)- α -haloacetaldehydes provide substrates for efficient routes to halogenated (dialkoxyphosphoryl)formyl hydrazones and related oximes. The formyl group of the starting material is lost in either type of reaction.

18.12.5.1.1.1

**Variation 1:
Arylhydrazones by Diazo Coupling**

Preparations of arylhydrazones **77** from the corresponding aldehydes require that the latter are treated with arenediazonium chlorides in aqueous ethanol at 15–20 °C.^[164–166] The halogen substituent can be chlorine, bromine, or iodine and the aryl substituent is phenyl or a 4-substituted phenyl group (Scheme 37). Analogous reactions have been described starting from the phosphonamides **78**.^[167]

Scheme 37 From (Dialkoxyphosphoryl)- α -haloacetaldehydes and Related Compounds by Diazo Coupling^[164–167]



It is also possible to exchange the halogen atom (chlorine or bromine) in the arylhydrazones **77** for fluorine or iodine by reaction with the appropriate sodium or potassium halide.^[168]

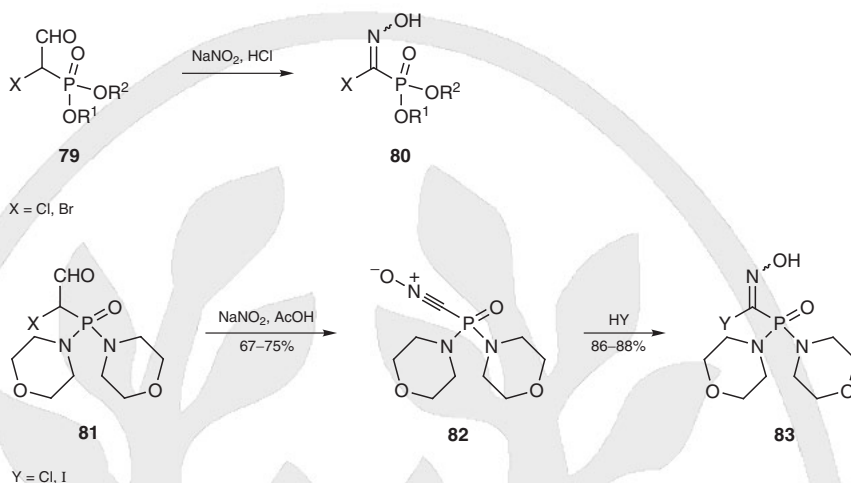
Bromo(dimethoxyphosphoryl)methanone 4-Nitrophenylhydrazone (77, R¹ = R² = Me; Ar¹ = 4-O₂NC₆H₄; X = Br); Typical Procedure:^[166]

Bromo(dimethoxyphosphoryl)acetaldehyde (16.1 g, 0.07 mol) in EtOH (15 mL) was added at 15–20 °C to an aqueous soln of 4-nitrobenzenediazonium chloride, prepared from 4-nitroaniline (9.6 g, 0.07 mol), NaNO₂ (4.9 g, 0.07 mol), and 36% HCl (14 mL). The crystals that separated were washed with H₂O, and Et₂O, and then recrystallized (MeCN); yield: 14.1 g (57%); mp 163–165 °C.

18.12.5.1.1.2

**Variation 2:
Oximes by Nitrosation**

In reactions analogous to those described in Section 18.12.5.1.1.1, the aldehydes **79** give oximes **80** when treated with sodium nitrite and hydrochloric acid in aqueous ethanol.^[169–171] The halogen atom in the starting aldehyde can be chlorine or bromine. When the same procedure is carried out on the phosphonamides **81** an isolable nitrile oxide **82** is produced, but this compound can then be converted into the halogenated oximes **83** (Y = Cl, I) by the addition of hydrogen chloride or hydrogen iodide, as appropriate (Scheme 38).^[172]

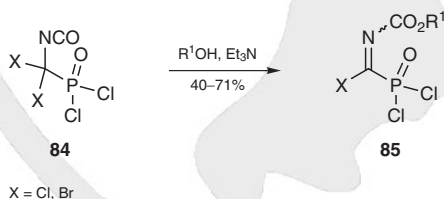
Scheme 38 Nitrosation and the Addition of Hydrogen Halide to α -Halo(phosphoryl)acetaldehydes^[169–172]**(Dimorpholinophosphinyl)iodomethanone Oxime (83, Y = I):**^[172]

A soln of KNO_2 (2.1 g, 0.025 mol) in H_2O (5 mL) was added to a suspension of chloro(dimorpholinophosphinyl)acetaldehyde (**81**; 7.2 g, 0.026 mol) in 98% AcOH (20 mL) and ice (50 g). The mixture was stirred for 0.5 h then extracted with CHCl_3 (3×50 mL). The CHCl_3 was removed from the combined extracts and the oily residue was triturated with Et_2O to produce a solid. Crystallization gave the nitrile oxide **82**; yield: 4.3 g (67%); mp $104\text{--}106^\circ\text{C}$ ($\text{MeCN}/\text{Et}_2\text{O}$). 56% HI (2 mL) was added to a soln of the nitrile oxide **82** (2.0 g, 7.66 mmol) in MeCN (10 mL). The pale yellow crystals of the oxime **83** (Y = I) that separated were washed with MeCN ; yield: 2.6 g (86%); mp $139\text{--}140^\circ\text{C}$ (dec).

18.12.5.1.2

Method 2:**From Dihalo(dichlorophosphoryl)methyl Isocyanates and Alcohols**

This method is illustrated in Scheme 39. It is used to convert the isocyanates **84** (X = Cl or Br) into the esters **85** by the addition of an alcohol and the elimination of a hydrogen halide.^[173,174]

Scheme 39 From Dihalo(dichlorophosphoryl)methyl Isocyanates and Alcohols^[173,174]**Ethyl N-(Dichlorophosphorylbromomethylene)carbamate (85, R¹ = Et; X = Br):****Typical Procedure:**^[174]

EtOH (1.15 g, 0.025 mol) and Et_3N (2.53 g, 0.025 mol) in Et_2O (20 mL) were added slowly with stirring and cooling at $0\text{--}5^\circ\text{C}$ to dibromo(dichlorophosphoryl)methyl isocyanate (**84**, X = Br; 8.29 g, 0.025 mol) in Et_2O (50 mL). The mixture was stirred for 3 h at rt, then left overnight. $\text{Et}_3\text{N}\cdot\text{HBr}$ was removed by filtration (yield: 94.5%) and the filtrate was concentrated under reduced pressure. The residue was distilled to give the title compound; yield: 4.16 g (59%); bp $98\text{--}102^\circ\text{C}/0.2$ Torr.

18.12.6 Product Subclass 6: Carbonimidic Diesters

Members of this subclass are also called iminocarbonate diesters. They are well represented in the literature, both as N-unsubstituted esters and with a variety of functional groups bonded to the nitrogen atom.

18.12.6.1 Synthesis of Product Subclass 6

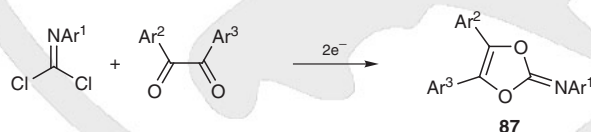
18.12.6.1.1 Method 1: From Carbonimidic Dihalides and Oxygen Nucleophiles

A commonly used general method for the preparation of members of this subclass is the displacement of chloride ion from carbonimidic dichlorides by reactions with either alcohols or phenols under basic conditions (Scheme 40). These reactions usually lead to symmetrically substituted carbonimidic diesters **86**. There are also a few examples of the displacement of fluoride ion from carbonimidic difluorides.^[41,67,91,175–183] In addition, the iminodioxolenes **87** are produced in high yields by the cathodic reduction of diaryl substituted 1,2-diones in the presence of *N*-arylc carbonimidic dichlorides (Scheme 40).^[184,185]

Scheme 40 Displacement of Chloride from Carbonimidic Dichlorides^[41,67,89,175–185]

R ¹	R ²	Conditions	Yield (%) of 86	Ref
Bn	Me	NaOMe, 65 °C	85	[184]
Me	Me	NaOMe	48	[185]
CH ₂ Ts	Me	NaOMe, rt	67	[67]
Bz	Ph	PhOH, py, rt	72	[180,181]
Bz	4-BrC ₆ H ₄	4-BrC ₆ H ₄ OH, Et ₃ N, 0–20 °C	80	[181]
PO(OEt) ₂	Me	MeOH, Et ₃ N	80	[182]
SF ₅	Me	NaOMe, rt	88	[89]
SO ₂ Ph	Et	EtOH, NaOH	79	[183]
– ^a	Ph	PhOH, 40 °C	90	[41]

^a Starting material is Cl₂C=NMe₂⁺ Cl[–].



Diphenyl *N*-Benzoylcarbonimidate (**86**, R¹ = Bz; R² = Ph); Typical Procedure:^[181]

PhOH (4.71 g, 50 mmol) and Et₃N (5.05 g, 50 mmol) in toluene (40 mL) were added dropwise to a stirred soln of *N*-benzoylcarbonimidic dichloride (R¹ = Bz; 5.05 g, 25 mmol) in toluene (20 mL) at 0 °C. After the addition was complete, the mixture was allowed to warm to 20 °C, and then it was stirred for a further 24 h. The precipitate of Et₃N•HCl was removed by filtration and washed with toluene (2 × 10 mL). The combined toluene solns were warmed and hexane was added until crystallization started. Stepwise cooling to 25 °C,

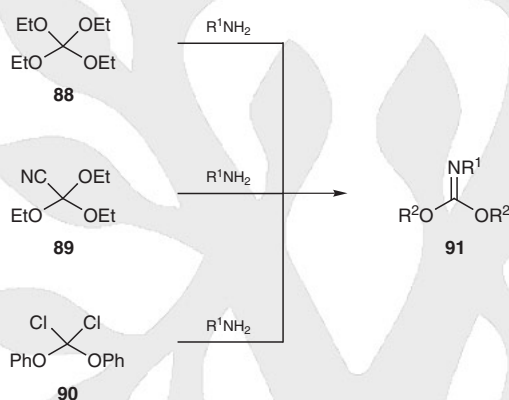
5°C, and –20°C produced fine colorless needles, which were collected by filtration, combined, washed with hexane (2 × 20 mL), and dried under high vacuum. This gave the title compound; yield: 5.71 g (72%); mp 103–105°C.

18.12.6.1.2

Method 2:**From Tetraethyl Orthocarbonate and Related Compounds with Amino Compounds**

This method is a simple and high-yielding procedure for the preparation of a limited number of carbonimidic diesters **91** in which either tetraethyl orthocarbonate **88**, triethoxyacetonitrile **89**, or dichlorodiphenoxymethane **90** is reacted with a primary amino compound. The imine bond is introduced into the product by the loss of two leaving groups (Scheme 41).^[186–188]

Scheme 41 Reaction of Tetraethyl Orthocarbonate and Related Compounds with Amino Compounds^[186–188]



Precursor	R ¹	R ²	Conditions	Yield (%) of 91	Ref
88	4-Tol	Et	4-TolNH ₂ , 138°C	45	[186]
88	NHTs	Et	TsNHNH ₂ , EtOH, 78°C	62	[186]
89	Ph	Et	PhNH ₂ , 80–140°C	67	[186]
89	Bn	Et	BnNH ₂ , 90°C	45	[186]
90	CN	Ph	H ₂ NCN, rt	91	[187]
90	SO ₂ NH ₂	Ph	H ₂ NSO ₂ NH ₂ , 0–20°C	63	[188]

Diphenyl N-Sulfamoylcarbonimidate (91, R¹ = SO₂NH₂; R² = Ph).^[188]

Freshly distilled (PhO)₂CCl₂ (**90**; 54 g, 0.2 mol) in MeCN (150 mL) was dripped into a stirred, ice-cold soln of H₂NSO₂NH₂ (20 g, 0.21 mol) in MeCN (500 mL) over a period of 6–8 h. The ice bath was removed and the mixture was stirred for a further 48 h at rt. It was filtered to remove a small amount of precipitate, and the solvent was removed from the filtrate. The oily residue crystallized after Et₂O was added, and the mixture was cooled in an ice bath. The title compound was recrystallized (EtOH); yield: 37 g (63%); mp 106–107°C.

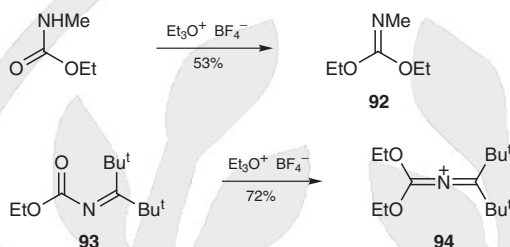
18.12.6.1.3

Method 3:**By the O-Alkylation of Carbamates**

Carbamate esters can be O-alkylated by powerful alkylating agents such as triethyloxonium tetrafluoroborate. Two examples are shown in Scheme 42. Diethyl N-methylcarbon-

imideate **92** is produced by the ethylation of ethyl *N*-methylcarbamate.^[185] Iminocarbamates give azaallenium salts on alkylation;^[189,190] this is illustrated by the formation of 1,1-di-*tert*-butyl-3,3-diethoxy-2-azaallenium tetrafluoroborate **94** from the iminocarbamate **93**.^[189]

Scheme 42 Diethyl *N*-Methylcarbonimide and an Azaallenium Salt by the O-Alkylation of Carbamates^[185,189]



1,1-Di-*tert*-butyl-3,3-diethoxy-2-azaallenium Tetrafluoroborate (94); Typical Procedure:^[189]

Ethyl (di-*tert*-butylmethylene)carbamate (**93**; 4.69 g, 22 mmol) and triethyloxonium tetrafluoroborate (3.80 g, 20 mmol) in dry CH_2Cl_2 (30 mL) were refluxed for 4 h, and then cooled to rt. The soln was filtered, and dry Et_2O was added to the filtrate at its boiling point until it became turbid. Colorless crystals were obtained when the filtrate was cooled in a stepwise manner to rt, 5 °C, and -20 °C. The crystals were washed with dry Et_2O (2 × 20 mL), and dried under reduced pressure; yield: 4.76 g (72%); mp 85–88 °C (with darkening above 80 °C).

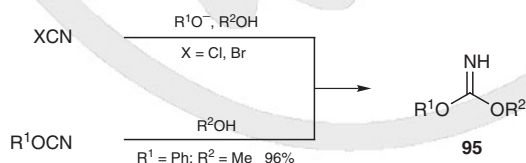
18.12.6.1.4

Method 4:

By the Addition of Alcohols to Cyanogen Halides and Cyanates

The formation of a *N*-unsubstituted carbonimide ester by the addition of an alcohol or a phenol to a cyanogen halide (Scheme 43) is a long established reaction.^[87] Mixed esters **95** ($\text{R}^1 \neq \text{R}^2$) can be obtained by addition of the sodium salt of one alcohol, followed by the addition of a second alcohol.^[191] Symmetrical or mixed esters can also be obtained by the catalyzed addition of alcohols to cyanate esters. For example, diethyl carbonimide **95** ($\text{R}^1 = \text{R}^2 = \text{Et}$) is isolated in 36% yield from the addition of ethanol to ethyl cyanate under hydrogen chloride catalysis.^[192] Diphenyl carbonimide **95** ($\text{R}^1 = \text{R}^2 = \text{Ph}$) is prepared in 97% yield from phenyl cyanate and potassium cyanide in a 2:1 ratio; the role of the cyanide ion being to displace phenoxide anion from 1 equivalent of phenyl cyanate.^[193] The addition of ethanol and chlorine to potassium cyanide provides a route to diethyl *N*-chlorocarbonimide.^[194] The addition of alkanols to phenyl cyanate under catalysis by potassium iodide leads to mixed esters **95** ($\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{alkyl}$).^[195]

Scheme 43 Carbonimide Esters from Cyanogen Halides or Cyanate Esters and Alcohols^[87,191–195]



Methyl Phenyl Carbonimide (95, $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{Me}$); Typical Procedure:^[195]

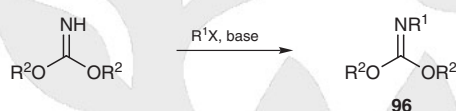
KI (4.15 g, 25 mmol) in MeOH (50 mL) was mixed at rt with PhOCN (2.98 g, 25 mmol). The temperature of the mixture was raised by 10–15 °C and, after 10 min, the excess MeOH

was distilled off under water-pump pressure, and the remaining crystalline residue was extracted with Et₂O; the catalyst being removed by filtration. The Et₂O soln was washed with 0.5 M NaOH to remove any PhOH, and then the solvent was removed. The residue was distilled under reduced pressure to give the title compound; yield: 3.62 g (96%); bp 98–100 °C/10 Torr.

18.12.6.1.5

Method 5:**From Other Carbonimide Esters by Substitution on Nitrogen**

Because carbonimides unsubstituted on nitrogen are readily available, a range of N-substituted compounds **96** can be conveniently prepared by electrophilic substitution. This method is used particularly for the preparation of N-sulfenyl, N-sulfonyl, and N-phosphenyl derivatives (Scheme 44).^[181,196–201]

Scheme 44 Carbonimides by Substitution on Nitrogen^[181,196–201]

R ¹	R ²	Conditions	Yield (%) of 96	Ref
CO ₂ Et	Et	ClCO ₂ Et, collidine, 0 °C to rt	68	[196]
CO ₂ Ph	Ph	ClCO ₂ Ph, collidine, 0 °C to rt	68	[196]
Ac	Et	AcCl, Et ₃ N, 0 °C to rt	71	[181]
COiPr	Et	iPrCOCl, Et ₃ N, 0 °C to rt	83	[181]
Bz	Et	BzCl, Et ₃ N, 0 °C to rt	81	[181]
2-O ₂ NC ₆ H ₄ S	Et	2-O ₂ NC ₆ H ₄ SCl, py, –40 °C to rt	66	[197]
Ts	Et	TsCl, Et ₃ N, rt	71	[198]
SO ₂ NH ₂	4-O ₂ NC ₆ H ₄	H ₂ NSO ₂ Cl, Et ₃ N, 20 °C	37	[199]
S(O) ^a	4-Tol	SOCl ₂ , Et ₃ N, –40 °C	76	[200]
PPh ₂	Et	Ph ₂ PCl, Et ₃ N, 0 °C	>80	[201]

^a This product is (4-TolO)₂C=NS(O)N=C(O-4-Tol)₂.

Diethyl N-Acylcarbonimides 96 (R¹ = Acyl); General Procedure:^[181]

The appropriate carboxylic acid chloride (0.1 mol) was added slowly to a stirred soln of diethyl carbonimide (11.7 g, 0.1 mol) and Et₃N (10.1 g, 0.1 mol) in dry CCl₄ (100 mL) at 0 °C. After the mixture had been stirred for 24 h at rt, the precipitate was removed by filtration and washed with CCl₄ (**CAUTION: toxic**). The combined washings were concentrated on a rotary evaporator and the oily residue was fractionally distilled.

18.12.7

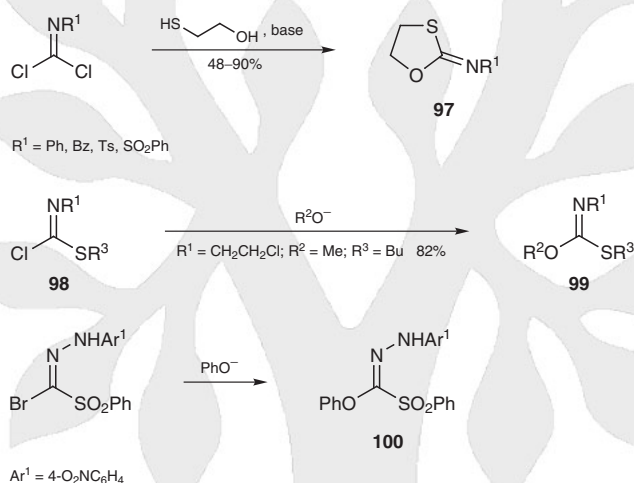
Product Subclass 7:**Carbonimidothioate Diesters**

Members of this subclass have been prepared by methods that are analogous to those used in Section 18.12.6. Alkylation methods are relatively of greater importance for carbonimidothioates because S-alkylation is easier than O-alkylation.

18.12.7.1 Synthesis of Product Subclass 7

18.12.7.1.1 Method 1:
From Carbonimidic Halides by Displacement of Halide Ion

Successive displacement of a chloride ion from a carbonimidic dichloride by sulfur or oxygen nucleophiles is not an important method for the preparation of carbonimidodithioate esters because of the difficulty in controlling the two steps. The method succeeds when the second displacement is intramolecular, as in reactions with 2-sulfanylethanol, which give 1,3-oxathiolan-2-imines **97** (Scheme 45),^[183,202,203] or with 2-sulfanylphenol.^[204] A more general method for the formation of carbonimidodithioates **99** is the displacement of chloride ion from carbonochloridimidodithioates **98** by alkoxides or phenoxides.^[205,206] Analogous displacement reactions of bromide are also recorded;^[207] a similar displacement in the sulfone series gives the phenyl ester **100**.^[208] Sodium benzenesulfinate is used as a nucleophile to displace bromide by benzenesulfonyl groups.^[209]

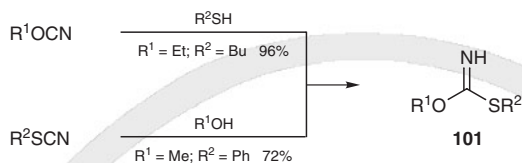
Scheme 45 Displacement of Halide from Carbonimidic Halides^[183,202–209]

S-Butyl O-Methyl N-(2-Chloroethyl)carbonimidodithioate (99, $\text{R}^1 = \text{CH}_2\text{CH}_2\text{Cl}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{Bu}$); Typical Procedure:^[205]

Butyl N-(2-chloroethyl)carbonochloridimidodithioate (**98**, $\text{R}^1 = \text{CH}_2\text{CH}_2\text{Cl}$; $\text{R}^3 = \text{Bu}$; 107 g, 0.5 mol) was added dropwise to a stirred and cooled soln of NaOMe (29.7 g, 0.55 mol) in MeOH (275 mL) at such a rate that the temperature remained below 5 °C. A precipitate of NaCl appeared. After 15 min, the mixture was filtered and the solvent was removed from the filtrate. The residue was taken up in H₂O and the oil that separated was extracted with 3 portions of Et₂O. The combined extracts were dried, the Et₂O was removed, and the residue was distilled to give the title compound; yield: 86 g (82%); bp 84–87 °C/0.004 Torr.

18.12.7.1.2 Method 2:
By Nucleophilic Additions to Cyanates or Thiocyanates

N-Unsubstituted carbonimidodithioates **101** are prepared by the additions of thiols to cyanates,^[210,211] or by the additions of alcohols to thiocyanates (Scheme 46).^[212]

Scheme 46 Nucleophilic Additions to Cyanates or Thiocyanates^[210–212]**S-Butyl O-Ethyl Carbonimidothioate (101, R¹ = Et; R² = Bu); Typical Procedure:**^[211]

BuSH (1.80 g, 0.02 mol) was added to ethyl cyanate (0.71 g, 0.01 mol) in dry Et₂O (5 mL). The soln was kept at 30 °C for 20 h, then the Et₂O, and excess BuSH were distilled off using an oil pump at a bath temperature of 45 °C. The title compound remained as an oil that could not be distilled without decomposition; yield: 1.55 g (96%).

O-Methyl S-Phenyl Carbonimidothioate (101, R¹ = Me; R² = Ph); Typical Procedure:^[212]

CAUTION: Cyanide salts can be absorbed through the skin and are extremely toxic.

PhSCN (13.5 g, 0.1 mol) and NaCN (0.7 g, 0.014 mol) were added to MeOH (200 mL) at 0 °C. After 6 h, excess MeOH was concentrated and petroleum ether (200 mL) was added. The soln was washed twice with H₂O, dried, and concentrated. The residue was distilled to give the title compound as an oil that solidified at rt; yield: 12 g (72%); bp 82–89 °C/3 Torr; mp 35–36 °C.

18.12.7.1.3

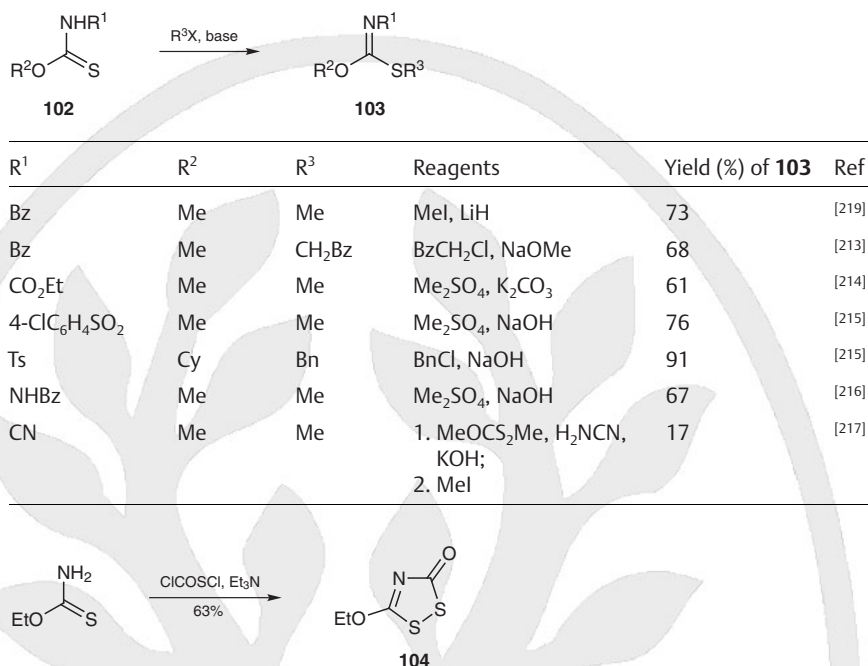
Method 3:**By the S-Alkylation of O-Alkyl Thiocarbamates and Related Compounds**

A general route to compounds of this subclass is the S-alkylation of O-alkylthiocarbamate esters. These esters can be isolated and S-alkylated, but a common alternative procedure starts from isothiocyanates. Sodium salts of the esters are generated from the isothiocyanates by the addition of a sodium alkoxide, and the product salts are then alkylated directly to give carbonimidothioates.

18.12.7.1.3.1

Variation 1:**By the S-Alkylation of O-Alkyl Thiocarbamates**

The S-alkylation of thiocarbamate esters **102** to afford O,S-dialkyl carbonimidothioates **103** (R² = R³ = alkyl) may be carried out using a variety of alkylating agents and bases (Scheme 47).^[213–219] A possible alternative approach, the O-alkylation of S-alkylthiocarbamates, has rarely been used, although a procedure of this type has been described for N-cyanocarbonimides **103** (R¹ = CN; R² = Me; R³ = Me,^[220] Ac^[221]). An example of a combined N-alkylation and electrophilic substitution on sulfur is provided by the preparation of the dihydrodithiazolone **104** from O-ethyl thiocarbamate and chlorocarbonylsulfonyl chloride.^[218] In the absence of a base salts can be isolated; for example, O-phenyl thiocarbamate gives the hydriodide of S-methyl O-phenyl carbonimidothioate (91%) when heated with excess iodomethane.^[210]

Scheme 47 S-Alkylation of O-Alkyl Thiocarbamates^[213–219]

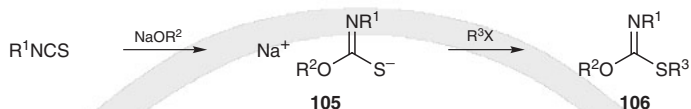
O,S-Dimethyl N-(4-Chlorophenylsulfonyl)carbonimidodithioate (103, R¹ = 4-ClC₆H₄SO₂; R² = R³ = Me); Typical Procedure:^[215]

CAUTION: Dimethyl sulfate is corrosive and irritating to the skin, eyes, and respiratory system and is a probable human carcinogen.

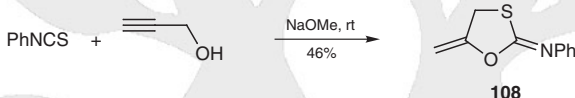
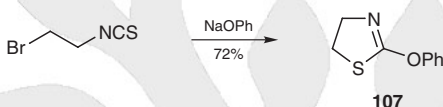
NaOH (1 g) in H₂O (2 mL) was added to a stirred soln of **102** (R¹ = 4-ClC₆H₄SO₂; R² = Me; 6.65 g, 0.025 mol) in DMF (25 mL). Then Me₂SO₄ (3.15 g, 0.025 mol) in DMF (10 mL) was dripped in slowly. After 1 h, the soln was poured into H₂O (200 mL), and a precipitate was collected by filtration, and dried. From this material the title compound was isolated by crystallization (MeOH); yield: 5.3 g (76%); mp 96–97 °C.

18.12.7.1.3.2 Variation 2: From Isothiocyanates, Alcohols, and Alkylating Agents

Isothiocyanates are the starting materials in other procedures that employ alkoxides and an alkylating agent to form O,S-dialkyl carbonimidodithioates **106** via the sodium salt **105**. This variation is a convenient “one-pot” procedure; it is quite versatile as shown by the range of examples in Scheme 48.^[184,185,222,223] The alkylation step can be intramolecular, as in the synthesis of the dihydrothiazole **107** from bromoethyl isothiocyanate and sodium phenoxide,^[224] and the oxathiolidine **108** from phenyl isothiocyanate and prop-2-yn-1-ol.^[225] Reactions of 2,2-dibutyl-1,3,2-oxathiaastannolidine with a series of alkyl isothiocyanates and also with phenyl isothiocyanate give the corresponding oxathiolidines **109** in moderate to good yields.^[226]

Scheme 48 O,S-Dialkyl Carbonimidodithioates from Isothiocyanates, Alcohols, and Alkylating Agents^[184,185,222–226]

R ¹	R ²	R ³	Reagents	Yield (%) of 106	Ref
Me	Me	Me	1. NaOMe; 2. MeI	56	[185]
Bn	Me	Me	1. NaOMe, 10 °C; 2. MeI, rt	72	[184]
CH ₂ TMS	Et	Et	1. EtOH, (Bu ₃ Sn) ₂ O, 60 °C; 2. EtOTf, K ₂ CO ₃ , rt	60	[222]
Ph	Me	CH ₂ CO ₂ Me	1. NaOMe, rt; 2. MeO ₂ CCH ₂ Br, rt	72	[223]



O,S-Dimethyl N-Benzylcarbonimidodithioate (106, R¹ = Bn; R² = R³ = Me); Typical Procedure:^[184]

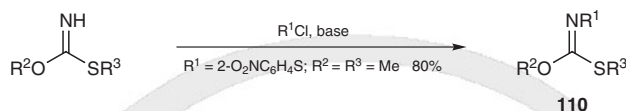
CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

BnNCS (14.9 g, 0.10 mol) was added dropwise at 10 °C to an ice-cooled soln of Na (2.42 g, 0.105 mol) in dry MeOH (30 mL) under N₂. The mixture was stirred for 0.5 h at 20 °C then MeI (14.9 g, 0.105 mol) was added dropwise, the temperature being kept below 25 °C. The mixture was stirred for 5 h at 20 °C, after which time a sample no longer showed an absorption at $\tilde{\nu}_{\text{max}}$ 2200 cm⁻¹ due to isothiocyanate in the IR spectrum. The solvent was distilled off and Et₂O (100 mL) and ice-cold H₂O (100 mL) were added to the residue. The aqueous phase was separated off and was extracted with Et₂O (3 × 30 mL). The combined extracts were dried (Na₂SO₄), the solvent was removed, and the residue was distilled through a short Vigreux column. This gave the title compound as an oil; yield: 14.0 g (72%); bp 74–78 °C/0.15 Torr.

18.12.7.1.4

Method 4:
From Other Carbonimidodithioates by Substitution on Nitrogen

N-Substitutions by electrophilic reagents of N-unsubstituted carbonimidodithioates are used to prepare a few compounds of the type **110** (Scheme 49). Sulfonation reactions are carried out using the appropriate sulfonyl halides,^[227] and sulfenations with arenesulfenyl chlorides.^[197]

Scheme 49 Carbonimidothioates by Substitution on Nitrogen^[197,227]

***O,S*-Dimethyl *N*-(2-Nitrophenylsulfanyl)carbonimidothioate (110, $\text{R}^1 = 2\text{-O}_2\text{NC}_6\text{H}_4\text{S}$; $\text{R}^2 = \text{R}^3 = \text{Me}$); Typical Procedure:**^[197]

2-Nitrobenzenesulfenyl chloride (1.90 g, 10 mmol) in THF (20 mL) was added at -40°C to a soln of *O,S*-dimethyl carbonimidothioate (1.05 g, 10 mmol) and pyridine (0.79 g, 10 mmol) in THF (20 mL). The mixture was stirred for 0.5 h at rt, then filtered, and the solvent was removed from the filtrate. The residue was extracted with CHCl_3 , the combined extracts were filtered through Kieselgel, then concentrated. The residue was crystallized twice [benzene (**CAUTION: carcinogen**)/petroleum ether] to give the title compound; yield: 2.07 g (80%); mp $109\text{--}110^\circ\text{C}$.

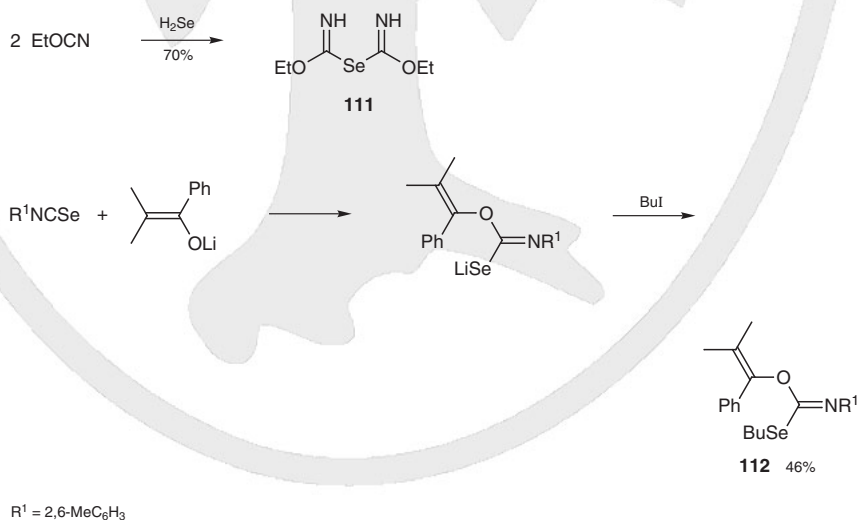
18.12.8

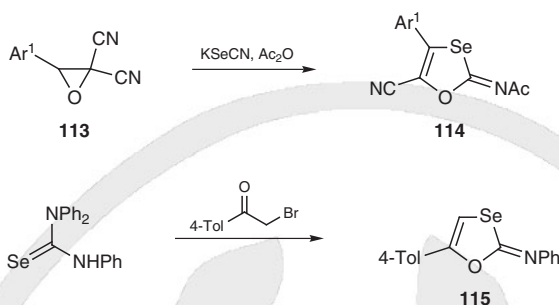
**Product Subclass 8:
Carbonimidoseleoic Diesters**

18.12.8.1

Synthesis of Product Subclass 8

This subclass is small and there are no general methods of preparation. Individual compounds are prepared by methods that are analogous to those used in Section 18.12.7. The individual methods are summarized in Scheme 50. The addition of hydrogen selenide to ethyl cyanate yields the carbonimidoseleoate **111** as an unstable solid.^[211] 2,6-Dimethylphenyl isoselenocyanate is converted into the carbonimidoseleoate **112** by the addition of a lithium enolate, followed by Se-alkylation with 1-iodobutane.^[228] A series of 1,3-oxaselenol-2-imines **114** are prepared by the reaction of the epoxides **113** with potassium selenocyanate and acetic anhydride.^[229] A 1,3-oxaselenol-2-imine **115** is also isolated from the reaction of 2-bromo-1-(4-tolyl)ethanone with triphenylselenourea.^[230]

Scheme 50 Carbonimidoseleoate Diesters^[211,228–230]



18.12.9

**Product Subclass 9:
Carbamimidic Esters (Isoureas)**

This subclass is a large one. Compounds of this type are commonly referred to as isoureas or as pseudoureas. Methods for the synthesis of isoureas and their properties and applications have been reviewed.^[231]

18.12.9.1

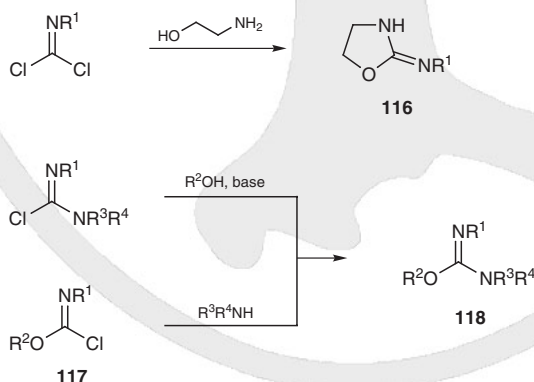
Synthesis of Product Subclass 9

18.12.9.1.1

**Method 1:
From Carbamimidic Chlorides and Oxygen Nucleophiles**

The displacement of chloride ion from carbonimidic dichlorides is a useful method only for reactions with bidentate nucleophiles that lead to the formation of cyclic isoureas; for example, reactions with 2-aminoethanol that give the oxazolidin-2-imines **116** (Scheme 51).^[232,233] Reactions of carbamimidic chlorides with oxygen nucleophiles are of wider scope, and reactions with sodium alkoxides or sodium phenoxides take place readily to give isoureas **118**.^[41,89,91,152,234–236] An alternative displacement reaction, that between carbonochloridimide esters **117** and amines,^[87,105] has been used less frequently. The isoureas **118** ($\text{NR}^3\text{R}^4 = \text{NCS}$) are prepared by the addition of isothiocyanate ions to carbonochloridimide esters (Scheme 51).^[126]

Scheme 51 Displacement of Chloride Ion To Give Isoureas^[41,87,89,91,105,126,145,152,232–236]



R ¹	R ²	R ³	R ⁴	Reagents and Conditions	Yield (%) of 118	Ref
4-ClC ₆ H ₄	Me	Me	Me	NaOMe, 20–40 °C	40	[89]
4-O ₂ NC ₆ H ₄	Ph	Me	Me	NaOPh, 40 °C	36	[41]
Ph	2-MeO ₂ CC ₆ H ₄	Et	Et	2-MeO ₂ CC ₆ H ₄ OH, NaOMe, 50 °C	~100	[145]
Ts	Et	Bu	H	NaOEt, rt	60	[152]
SF ₅	Me	Et	Et	NaOMe, rt	— ^a	[91]
POCl ₂	Me	Ph	H	MeOH, Et ₃ N, 0–20 °C	95	[234]
POCl ₂	Et	Et	Et	NaOEt, 20–25 °C	76	[235]
H ^b	Me	H	H	Cl(H ₂ N)C=NH•HCl, MeOH, 65 °C	91	[236]

^a Not isolable in a pure form.

^b As the hydrochloride salt.

***N,N*-Dimethyl-*N'*-4-(nitrophenyl)-*O*-phenylisourea (**118**, R¹ = 4-O₂NC₆H₄; R² = Ph; R³ = R⁴ = Me); Typical Procedure:**^[41]

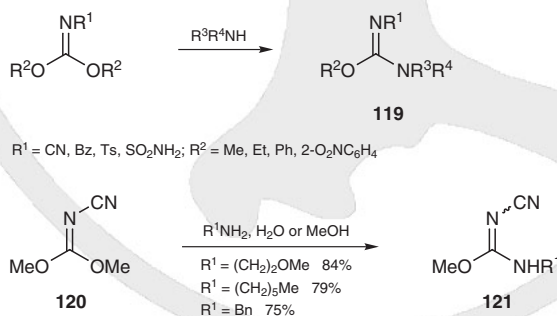
NaOPh (3.48 g, 30 mmol) in dioxane (80 mL) was added to a soln of *N,N*-dimethyl-*N'*-4-nitrophenylcarbamidoyl chloride (6.83 g, 30 mmol) in dioxane (200 mL). The mixture was stirred for 3 h at 40 °C, and then the precipitate of NaCl was removed by filtration. The solvent was removed from the filtrate and the oily residue was purified by chromatography (silica gel) to give the title compound; yield: 3.1 g (36%); mp 98–99 °C (Et₂O).

18.12.9.1.2

**Method 2:
From Carbonimidic Diesters and Amines**

Carbonimidic diesters that bear a strongly electron-withdrawing substituent on nitrogen (e.g., R¹ = CN, SO₂R³) react readily with ammonia and with primary or secondary aliphatic amines to give isoureas **119** (Scheme 52).^[188,199,237–241] Ammonia and several primary amines can be used in displacement reactions with dimethyl *N*-cyanocarbonimidate (**120**). The appropriate isourea **121** is then obtained in good yield after a reaction in water or methanol at room temperature.^[237]

Scheme 52 Reaction of Carbonimidic Diesters with Amines^[188,199,237–241]



***N*-Cyano-*O*-methylisoureas **121**; General Procedure:**^[237]

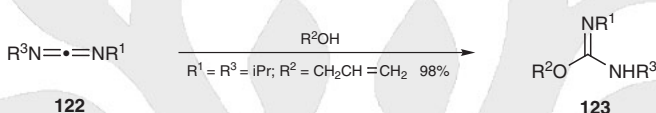
A primary amine (0.1 mol) was added to a soln of methyl *N*-cyanocarbonimidate (**120**; 11.4 g, 0.1 mol) in H₂O (50–100 mL) or MeOH (30–80 mL). The mixture was stirred, normally at rt, for a period between 5 min and 10 h. If a solid precipitate separated it was collected by filtration, washed with H₂O, and dried. Alternatively, the soln was concentrated to

dryness and the residue was suspended in H₂O, EtOH, or iPrOH, collected by filtration, and dried. The product was purified by crystallization from an appropriate solvent.

18.12.9.1.3

Method 3:**By Addition of Alcohols to Carbodiimides**

The additions of alcohols to carbodiimides **122** (Scheme 53), particularly to diisopropylcarbodiimide, have been reviewed.^[242] The additions of alcohols require a catalyst; copper(I) chloride or copper(II) chloride can be employed successfully.^[243,244] This type of reaction is applied to the additions of chiral alcohols to dicyclohexylcarbodiimide as a means of inverting their configuration.^[245] The addition of methanol to dicyclohexylcarbodiimide is achieved by first adding imidazole to give an isolable intermediate guanidine; this is then converted into the isourea **123** (R¹ = R³ = Cy; R² = Me) by heating in methanol.^[246] Ethanol can be added to the activated carbodiimide **122** (R¹ = CONCy₂; R³ = Cy) without the need for a catalyst.^[247]

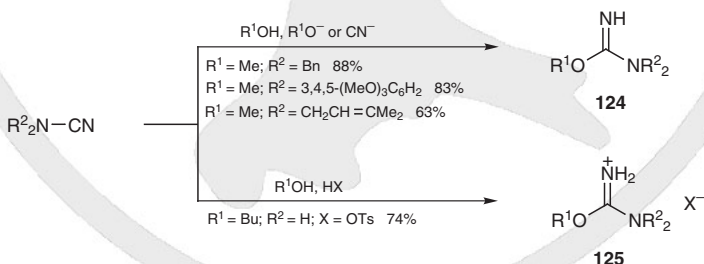
Scheme 53 Addition of Alcohols to Carbodiimides^[242–247]

O-Allyl-N,N'-diisopropylisourea (123, R¹ = R³ = iPr; R² = CH₂CH=CH₂); Typical Procedure:^[244] CuCl₂ (0.01 g) was added to mixture of allyl alcohol (5.81 g, 0.1 mol) and diisopropylcarbodiimide (12.6 g, 0.1 mol) cooled in an ice bath. After 0.5 h, the mixture was allowed to warm to rt, and it was then allowed to stand at this temperature for 48 h. The title compound was isolated by distillation; yield: 18 g (98%); bp 75–76 °C/10 Torr.

18.12.9.1.4

Method 4:**By Addition of Alcohols to Cyanamides**

The addition of alcohols to cyanamides leads to N-unsubstituted isoureas **124** (Scheme 54). The reactions are catalyzed by sodium alkoxides,^[248] potassium cyanide,^[249] sodium hydride,^[250] dry hydrogen chloride^[248] or 4-toluenesulfonic acid.^[251–253] Under acidic conditions isouronium salts **125** are isolated.

Scheme 54 Addition of Alcohols to Cyanamides^[248–253]

N,N-Dialkyl-O-methylisoureas 124 (R¹ = Me); General Procedure:^[249]

CAUTION: Cyanide salts can be absorbed through the skin and are extremely toxic.

A soln of a dialkylcyanamide (0.1 mol) and KCN (6.5 g, 0.1 mol) in MeOH (200 mL) was refluxed for 24 h. The solvent was distilled off, and H₂O was added to the residue, which was extracted with Et₂O. The combined extracts were washed with H₂O, dried, and concentrated.

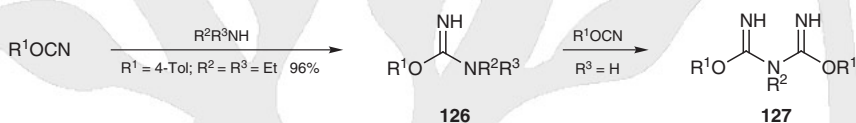
O-Butoxyisouronium 4-Toluenesulfonate (125, R¹ = Bu; R² = H; X = OTs);**Typical Procedure:**^[253]

Anhyd TsOH was obtained by heating the commercial monohydrate under high vacuum at 80–90 °C for 10 h. A mixture of anhyd TsOH (21 g, 0.12 mol), cyanamide (5 g, 0.12 mol), and BuOH (18 mL, 0.20 mol) in dry CHCl₃ (100 mL) was stirred under N₂ at rt for 5 d. A precipitate was removed by filtration, the filtrate was reduced in volume (to ca. 15 mL) on the rotary evaporator, and Et₂O (200 mL) was added. The precipitate was collected, and the combined solids were washed with Et₂O, and dried in air; yield: 24.2 g (74%); mp 89–91 °C.

18.12.9.1.5

Method 5:**By Addition of Amines to Cyanates**

Aryl cyanates react readily with primary and secondary amines to give N-unsubstituted isoureas **126** (Scheme 55).^[254] The reactions do not require a catalyst and, with ammonia or simple primary amines, a second addition can take place if the aryl cyanate is present in excess, giving the isoureas **127**. Aromatic heterocycles with a ring secondary amino group, such as imidazole and benzotriazole, also react easily with aryl cyanates to give 1:1 adducts.^[254] Hydroxylamine^[255] and glycine^[254] also add to aryl cyanates.

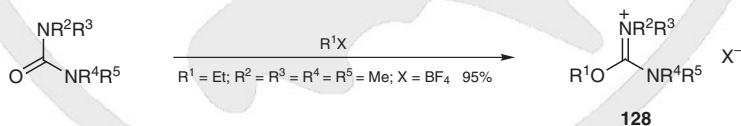
Scheme 55 Addition of Amines to Cyanates^[254,255]**N,N-Diethyl-O-(4-tolyl)isourea (126, R¹ = 4-Tol; R² = R³ = Et); Typical Procedure:**^[254]

Et₂NH (21.9 g, 300 mmol) was dripped at rt into a soln of 4-tolyl cyanate (39.9 g, 300 mmol) in acetone (200 mL). The temperature of the mixture rose and was kept below 50 °C by external cooling. At the end of the addition the acetone was distilled off, and the residue was purified by distillation; yield: 59.2 g (96%); bp 82–84 °C/0.06–0.08 Torr.

18.12.9.1.6

Method 6:**By the O-Alkylation of Ureas**

Urea and alkylureas react on oxygen with powerful alkylating agents such as dimethyl sulfate,^[256] methyl 4-toluenesulfonate,^[256] and triethyloxonium tetrafluoroborate.^[257] The products isolated are usually the isouronium salts **128** (Scheme 56).

Scheme 56 O-Alkylation of Ureas^[256,257]**O-Ethyl-N,N,N',N'-tetramethylisouronium Tetrafluoroborate (128, R¹ = Et;****R² = R³ = R⁴ = R⁵ = Me; X = BF₄); Typical Procedure:**^[257]

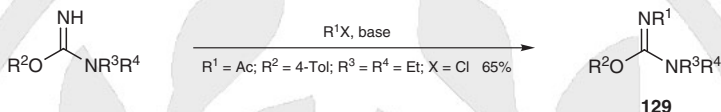
Tetramethylurea (5.8 g, 0.05 mol) and Et₃OBF₄ (9.5 g, 0.05 mol) were mixed. After a short time the mixture boiled, and then separated into two layers. The solid that had formed was collected by filtration, washed with Et₂O, and dried; yield: 11 g (95%); mp 82–83 °C (EtOH).

18.12.9.1.7

**Method 7:
From Other Isoureas by Substitution on Nitrogen**

A few N-unsubstituted isoureas are substituted on nitrogen by typical electrophiles, such as acetyl chloride (and other acyl chlorides), phenyl isocyanate, and trialkyloxonium tetrafluoroborates, to afford isoureas **129** (Scheme 57).^[87,254]

Scheme 57 Synthesis from Other Isoureas by Substitution on Nitrogen^[87,254]



***N*'-Acetyl-*N,N*-diethyl-*O*-(4-tolyl)isourea** (**129**, $\text{R}^1 = \text{Ac}$; $\text{R}^2 = 4\text{-Tol}$; $\text{R}^3 = \text{R}^4 = \text{Et}$).^[254]

AcCl (4.0 g, 0.05 mol) was added to a soln of *N,N*-diethyl-*O*-(4-tolyl)isourea (10.3 g, 0.05 mmol) in acetone (50 mL) at rt; this was followed by the addition of Et₃N (5.1 g, 0.05 mol). The precipitate of Et₃N•HCl was removed by filtration. The solvent was removed from the filtrate and the oily residue was distilled to give the title compound; yield: 8.0 g (65%); bp 120–124 °C/0.3 Torr.

18.12.9.2

Applications of Product Subclass 9 in Organic Synthesis

The main application of isoureas is as alkylating agents for oxygen, nitrogen, and sulfur nucleophiles, especially under acidic conditions in which the corresponding urea is the leaving group.^[231,258] Even hydrogen halides can be alkylated by isoureas. Isoureas find applications as precursors to guanidines, by nucleophilic displacement of the alkoxy or aryl-oxy function.

18.12.10

**Product Subclass 10:
Imides with an Oxygen and a Phosphorus Substituent**

Members of this subclass are, with a few exceptions,^[259,260] λ⁵-phosphorus compounds bearing oxygen on a λ⁵-phosphorus atom as indicated in the general formula {(R²O)[R³R⁴P(O)]C=NR¹}. There are two methods of preparation that have some general application.

18.12.10.1

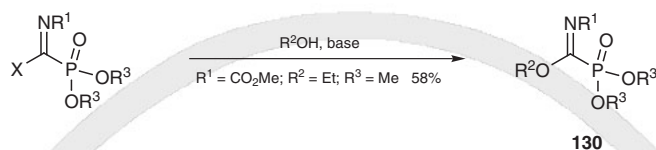
Synthesis of Product Subclass 10

18.12.10.1.1

**Method 1:
By the Displacement of Halides from Imidoyl Halides by
Oxygen Nucleophiles**

Dialkylphosphoryl compounds **130** can be synthesized by a general procedure illustrated in Scheme 58, in which the starting materials are iminocarbamates ($\text{R}^1 = \text{alkoxycarbonyl}$)^[173,174] or arylhydrazones ($\text{R}^1 = \text{arylamino}$).^[168,261] The halogen substituent (X) is either chlorine or bromine. Most reactions are performed with either methanol or ethanol as the nucleophile under basic conditions, but sodium sulfite can also be used in the presence of hydrochloric acid.^[261]

Scheme 58 Displacement of Halide Ion from Imidoyl Halides by Oxygen Nucleophiles^[168,173,174,261]



Methyl [Ethoxy(dimethoxyphosphoryl)methylene]carbamate (130, R¹ = CO₂Me; R² = Et; R³ = Me); Typical Procedure:^[173]

Methyl [chloro(dimethoxyphosphoryl)methylene]carbamate (11.5 g, 0.05 mol) in Et₂O (20 mL) was added with stirring and cooling (5–10 °C) to NaOEt (3.4 g, 0.05 mol) in EtOH (100 mL). The mixture was stirred for 3 h at 20 °C, and then left to stand overnight. NaCl was removed by filtration and the solvent was removed from the filtrate. Distillation of the residue gave the title compound; yield: 6.9 g (58%); bp 70–71 °C/0.04 Torr.

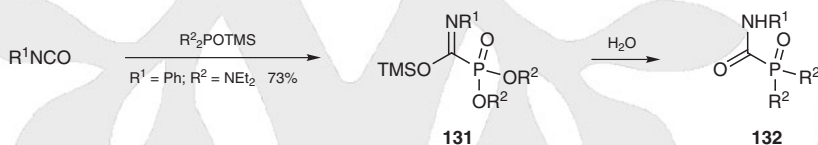
18.12.10.1.2

Method 2:

From (Trimethylsiloxy)phosphorus(III) Compounds and Isocyanates

This method (Scheme 59) is used to produce a few members of this subclass.^[262,263] In these compounds **131** the phosphorus substituent (R²) can be diethylamino, butoxy, or methyl, and the isocyanate substituent (R¹) is methyl or phenyl. The products are sensitive to moisture and are readily hydrolyzed to phosphonates **132**.

Scheme 59 From (Trimethylsiloxy)phosphorus(III) Compounds and Isocyanates^[262,263]



Trimethylsilyl Bis(diethylaminophosphoryl)-N-phenylcarboximidate (131, R¹ = Ph; R² = NEt₂):^[262]

PhNCO (3.3 g, 0.028 mol) was added dropwise under argon to (trimethylsiloxy)bis(diethylamino)phosphine (7.3 g, 0.028 mol) to give the title compound as an unstable oil. It was hydrolyzed by atmospheric moisture to afford the phosphonate **132** (R¹ = Ph; R² = NEt₂); yield: 7.8 g (73%).

18.12.11

Product Subclass 11:

Carbonimidodithioic Diesters

This subclass includes a large number of stable compounds. They are commonly referred to as iminodithiocarbonates.

18.12.11.1

Synthesis of Product Subclass 11

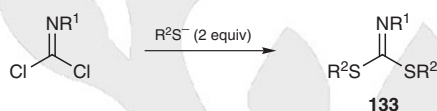
Methods of preparation are broadly similar to those described for earlier subclasses although S-alkylation reactions predominate because of the relatively easy attack on sulfur by electrophiles.

18.12.11.1.1

Method 1:
From Carbonimidic Halides and Sulfur Nucleophiles

A method of preparation of carbonohalidimidothioic esters **54** (Scheme 22, Section 18.12.3.1.1) is the displacement of chloride from carbonimidic dichlorides by a sulfur nucleophile. In the presence of an excess of the nucleophile the reaction goes further and both chlorine atoms are displaced to give carbonimidodithioic diesters **133** (Scheme 60).^[32,39,107,183,203,264] Examples of this method are confined almost entirely to carbonimidic dichlorides, although the successive displacement of bromide ion from the azines **134** by two different sulfur nucleophiles is described.^[207] Compounds of this subclass containing a sulfur(VI) function are obtained by displacement of bromide from the sulfones **135** ($R^1 = \text{OTHP}$,^[101,265] $4\text{-O}_2\text{NC}_6\text{H}_4\text{NH}$ ^[208]) by thiolate anions. Typical examples of displacement from carbonimidic dichlorides are given in Scheme 60.

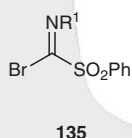
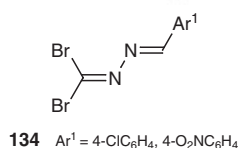
Scheme 60 Displacement of Chlorine from Carbonimidic Halides with Sulfur Nucleophiles^[32,37,39,101,107,183,203,207,208,264,265]



R^1	R^2	Reagents	Yield (%) of 133	Ref
Ph	<i>t</i> -Bu	<i>t</i> -BuSNa	65	[264]
C_6F_5	Ph	PhSH, K_2CO_3	55	[107]
Ts	Ph	PhSH, <i>t</i> -BuONa	82	[39]
Bz	^a	$\text{HSCH}_2\text{CH}_2\text{SH}$, pyridine	76	[203]
COSPh^b	Ph	PhSH, Et_3N	46	[32]
SO_2Ph	Et	EtSH, NaOH	84	[183]
$\text{PO}(\text{OEt})_2$	Ph	NaSPh	81	[37]

^a $R^2, R^2 = (\text{CH}_2)_2$.

^b $R^1 = \text{CONCS}$ in the starting material.

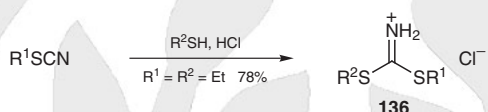

Diphenyl *N*-Pentafluorophenylcarbonimidodithioate (133, $R^1 = \text{C}_6\text{F}_5$; $R^2 = \text{Ph}$);
Typical Procedure:^[107]

PhSH (0.27 g, 2.4 mmol) in MeCN (3.5 mL) and *N*-(pentafluorophenyl)carbonimidic dichloride (0.32 g, 1.2 mmol) in MeCN (3.5 mL) were each added to a vigorously stirred suspension of K_2CO_3 (0.17 g, 1.2 mmol) in MeCN (3.5 mL). The mixture was stirred for 125 h at 20°C, before the precipitate that had formed was removed by filtration and washed with H_2O . The solvent was removed under reduced pressure, and the residue was crystallized to give the title compound; yield: 0.27 g (55%); mp 133–134°C (petroleum ether, bp 70–100°C).

18.12.11.1.2

Method 2:**By Addition of Thiols to Thiocyanates**

Although this method (Scheme 61) has not been used extensively, it does provide a route to N-unsubstituted compounds in which the substituents R^1 and R^2 can be either identical or different. The reactions are catalyzed by hydrogen chloride so that the products are isolated in the form of their hydrochloride salts **136**.^[266]

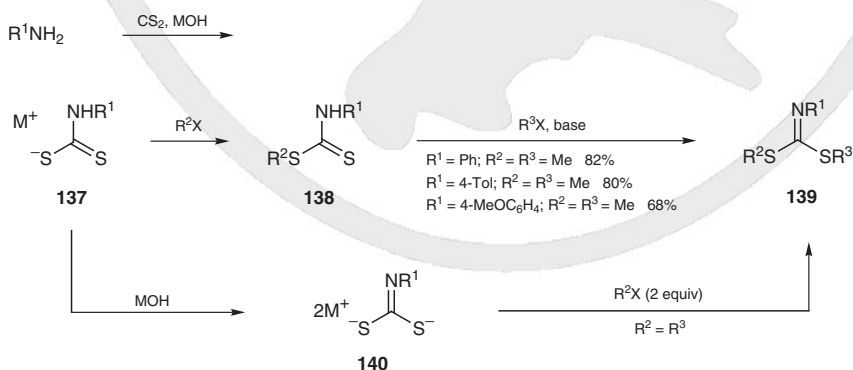
Scheme 61 Addition of Thiols to Thiocyanates^[266]**Diethyl Carbonimidodithioate Hydrochloride (136, $R^1 = R^2 = Et$); Typical Procedure:**^[266]

Dry HCl was bubbled for several h into a soln of EtSCN (43.5 g, 0.5 mol) and EtSH (31 g, 0.5 mol) in petroleum ether (bp 70–90 °C; 250 mL); the temperature of the mixture rose from 20 °C to about 35 °C during the introduction of the gas. The mixture was cooled, and an oil separated out; the petroleum ether was decanted from the oil, which was then stirred vigorously with more petroleum ether (2 × 200 mL). The oil slowly crystallized. The crystals were collected and dried in a vacuum desiccator over NaOH; yield: 72 g (78%); mp 91–93 °C.

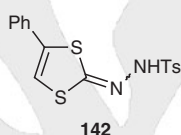
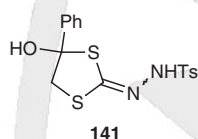
18.12.11.1.3

Method 3:**By the Alkylation of Dithiocarbamates**

The S-alkylation of dithiocarbamate esters **138** is the method most widely used for the preparation of carbonimidodithioates. Dithiocarbamates are in turn made from amines and carbon disulfide under basic conditions, via the salts **137** or **140**, so the method has several practical variations. These include “one-pot” procedures starting from compounds that incorporate the primary amino group, such as carboxamides, sulfonamides and cyanamides. The overall reaction sequence is outlined in Scheme 62.^[67,203,224,267–273] Either symmetrically substituted diesters or unsymmetrically substituted diesters **139** can be prepared by an appropriate choice of conditions. Phenacyl chloride reacts with the salt **137** ($R^1 = NHTs$; $M = K$) to give the 2-hydrazono-1,3-dithiolane **141** (yield 72%), which can be dehydrated to the dithiole **142** (Scheme 62); other α -halogenated ketones react similarly.^[267]

Scheme 62 Alkylation of Dithiocarbamates^[67,203,215,224,267–273]

R ¹	R ²	R ³	Starting Material	Reagents and Conditions	Yield (%) of 139	Ref
Ph	Me	Me	138	NaOH, MeI, rt	82	[268]
CN	Me	Me	140 (M = K)	MeI, 0 °C	60	[269]
CN	Me	Me	H ₂ NCN	1. CS ₂ , KOH, 0 °C; 2. Me ₂ SO ₄	53	[270]
CN	Me	4-O ₂ NC ₆ H ₄ CH ₂	140 (M = K)	1. MeI, 0 °C; 2. 4-O ₂ NC ₆ H ₄ CH ₂ Br	96	[224]
Bz	Me	Me	BzNH ₂	1. CS ₂ , KOH, 0 °C; 2. MeI	76	[203]
2-ClC ₆ H ₄ CO	Me	Me	2-ClC ₆ H ₄ CONH ₂	1. NaH, -10 to 0 °C; 2. CS ₂ ; 3. MeI	86	[271]
SO ₂ Ph	Me	Me	PhSO ₂ NH ₂	1. NaOH, CS ₂ , 5 °C; 2. Me ₂ SO ₄	60	[272]
Ts	CH ₂ CO ₂ Et	CH ₂ CO ₂ Et	TsNH ₂	1. NaOH, CS ₂ , 5 °C; 2. ClCH ₂ CO ₂ Et	66	[215]
CH ₂ Ts	Me	Me	138	MeOSO ₂ F, rt	93	[67]
carbazol-9-yl	Me	Me	carbazol-9-amine	1. KOH, CS ₂ , rt; 2. MeI, 70 °C	69	[273]



Dimethyl N-Arylcarbonimidodithioates **139 from Methyl N-Aryldithiocarbamates **138**;
General Procedure:**^[268]

CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

20 M NaOH (3 mL, 0.06 mol) was added at rt to a stirred soln of a methyl N-aryldithiocarbamate **138** (0.05 mol) in DMF (50 mL). After 1 h, MeI (8 g, 0.05 mol) was added dropwise. The mixture was stirred for 4 h, and then poured into H₂O (400 mL). The mixture was extracted with hexane (3 × 50 mL). The combined extracts were dried, and the solvent was concentrated under reduced pressure to leave the title compound.

Dimethyl N-(2-Thienylsulfonyl)carbonimidodithioate (139**, R¹ = 2-Thienylsulfonyl;
R² = R³ = Me) from Thiophene-2-sulfonamide; Typical Procedure:**^[272]

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

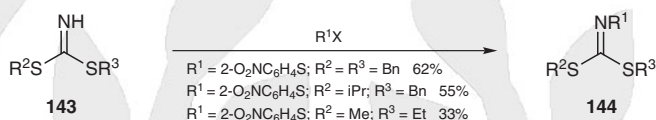
CAUTION: Dimethyl sulfate is corrosive and irritating to the skin, eyes, and respiratory system and is a probable human carcinogen.

Thiophene-2-sulfonamide (2.4 g, 14 mmol) in DMF (10 mL) was stirred and cooled in ice while 20 M NaOH (0.8 mL, 16 mmol) was added, followed by CS₂ (0.7 g, 9 mmol). The mixture developed a brick red color. After 20 min, more 20 M NaOH (0.4 mL, 8 mmol) and CS₂ (0.35 g, 4.5 mmol) were added and, 20 min later, further portions of 20 M NaOH (0.4 mL, 8 mmol) and CS₂ (0.35 g, 4.5 mmol) were added. The ice bath was removed and the mixture was stirred for 2 h at rt. It was again cooled in ice, and Me₂SO₄ (3.73 g, 29 mmol) was added dropwise. After 10 min, the addition was complete and the color of the mixture changed to yellow. The mixture was stirred at rt for 2 h, and then it was poured into H₂O (50 mL). The solid was collected by filtration, washed with H₂O, and dried under reduced pressure. The crude product (2.4 g) was crystallized (MeOH); yield: 2.24 g (60%); mp 121 °C.

18.12.11.1.4

Method 4:**From Other Carbonimidodithioates by Substitution on Nitrogen**

A few methyl carbonimidodithioates **144** are prepared from N-unsubstituted compounds **143** and electrophiles (Scheme 63) but this is not a method that is used frequently. The electrophiles (R^1X) used include aminosulfonyl chloride ($R^1 = SO_2NH_2$)^[199,274] and 2-nitrobenzenesulfonyl chloride ($R^1 = 2-O_2NC_6H_4S$)^[197]

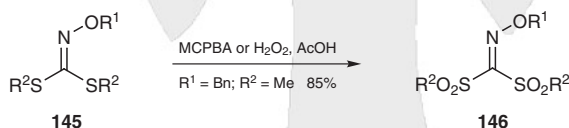
Scheme 63 Synthesis from Other Carbonimidodithioates by Substitution on Nitrogen^[197]**Dialkyl N-[(2-Nitrophenyl)sulfonyl]carbonimidodithioates 144 ($R^1 = 2-O_2NC_6H_4S$);****General Procedure:**^[197]

Pyridine (1.58 g, 20 mmol) was added to a soln of a dialkyl carbonimidodithioate **143** (as its HBr or HI salt) (10 mmol) in THF (20 mL) and the soln was cooled to -40°C . A soln of 2-nitrobenzenesulfonyl chloride (1.90 g, 10 mmol) in THF (20 mL) was added, before the mixture was warmed to rt, and stirred for 0.5 h. It was filtered and the filtrate was concentrated. The residue was redissolved in $CHCl_3$, the soln was filtered through Kieselgel, and then the solvent was removed. The residue was purified by two recrystallizations.

18.12.11.1.5

Method 5: **λ^6 -Sulfur Derivatives by S-Oxidation**

This method (Scheme 64) is used for the preparations of a few alkoxyiminobis(sulfonyl)-methanes **146** from the corresponding dialkyl carbonimidodithioates **145** [$R^1 = \text{Bn}$, THP; $R^2 = \text{Me}$, Ph; $R^2, R^2 = (CH_2)_2$].^[265]

Scheme 64 λ^6 -Sulfur Derivatives by S-Oxidation^[265]**Bis(methanesulfonyl)methanone O-Benzyl Oxime (146, $R^1 = \text{Bn}$; $R^2 = \text{Me}$);****Typical Procedure:**^[265]

35% aq H_2O_2 (2.1 mL, 25.5 mmol) was added dropwise with external cooling (0°C) to a soln of dimethyl N-(benzyloxy)carbonimidodithioate **145** ($R^1 = \text{Bn}$; $R^2 = \text{Me}$; 1.16 g, 5.09 mmol) in AcOH (5 mL). The mixture was stirred for 10 min at rt, and then heated at 100°C for 0.5 h. TLC showed a single new product. The mixture was cooled, diluted with CH_2Cl_2 (40 mL), and washed in turn with aq $Na_2S_2O_3$ (40 mL), aq $NaHCO_3$ (2×40 mL), and brine (40 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc/hexane 1:1) to give the title compound; yield: 1.26 g (85%); mp 75°C .

18.12.12 Product Subclass 12:
Carbonimidosenoethioic Diesters

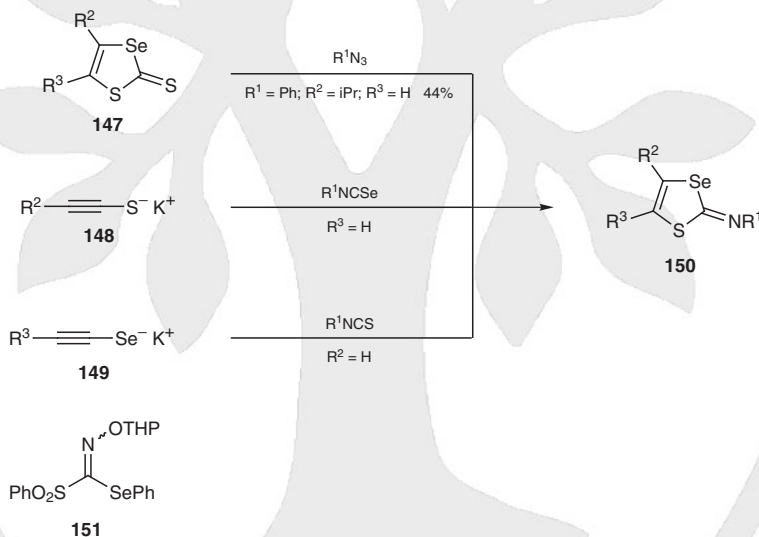
This subclass is confined almost entirely to 1,3-thiaselenol-2-imines, although the preparation of an acyclic compound (see Section 18.12.12.1.1) from the corresponding bromo compound and sodium benzeneselenolate^[101] indicates that this type of displacement method could probably be applied to other compounds.

18.12.12.1 Synthesis of Product Subclass 12

18.12.12.1.1 Method 1:
1,3-Thiaselenol-2-imines from 1,3-Thiaselenole-2-thiones and Azides

The imines **150** are prepared in two general ways, one from the corresponding 2-thiones **147** and an azide, the other from sodium or potassium alkynethiolates **148** and isoselenocyanates (or from the metal alkyneselenolates **149** and isothiocyantes). The routes are outlined in Scheme 65.^[275] When 5-alkyl-1,3-thiaselenole-2-thiones **147** are heated with azidobenzene or with ethyl azidoformate the corresponding imines **150** can be isolated in moderate yield.^[275] The acyclic imino ether **151** is formed from the corresponding bromo compound and sodium benzeneselenolate.^[101]

Scheme 65 Routes to 1,3-Thiaselenol-2-imines^[101,275]



5-Isopropyl-2-(phenylimino)-1,3-thiaselenole (150, R¹ = Ph; R² = iPr; R³ = H):^[275]

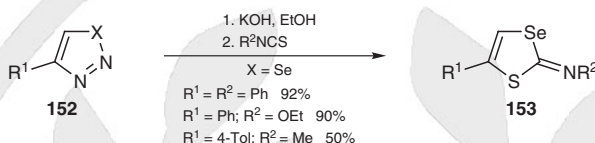
5-Isopropyl-1,3-thiaselenole-2-thione (**147**, R² = iPr; R³ = H; 2.23 g, 10 mmol) and azidobenzene (2 mL) were refluxed in xylene for 4 h. A further portion of azidobenzene (2 mL) was added and the soln was again refluxed for 10 h. The solvent was removed and the residue was purified by chromatography (silica gel, CHCl₃/petroleum ether 1:9) to give the title compound; yield: 1.25 g (44%); mp 59–60 °C (petroleum ether).

18.12.12.1.2 Method 2:
From Alkynethiolates or Alkyneselenolates

This method is used for the preparation of 4- and 5-substituted 1,3-thiaselenol-2-imines **153** bearing acyl or aryl groups on nitrogen^[276–279] and also for the ring-unsubstituted

compound **153** ($R^1 = H$; $R^2 = Ph$) (Scheme 66).^[280] The metal alkynethiolates and alkynesele-
nolates required are generated either from sodium arylalkynylides and elemental sulfur
or selenium,^[276] or by cleavage of the heterocycles **152** ($X = S, Se$) with a base such as po-
tassium hydroxide; they are then reacted with the appropriate selenium or sulfur reagent
(R^2NCSe or R^2NCS).^[278]

Scheme 66 Synthesis of 5-Aryl-1,3-thiaselenol-2-imines^[276–279]



2-(Acylimino)-5-aryl-1,3-thiaselenoles **153 ($R^2 = \text{Acyl}$); General Procedure:**^[278]

KOH (0.56 g, 0.01 mol) in EtOH (5 mL) was added to 4-aryl-1,2,3-selenadiazole **152** ($X = Se$, 0.01 mol) in dioxane (50 mL). When the evolution of N_2 had ceased, the precipitate was collected by filtration, washed with Et_2O and redissolved in THF (20 mL). The soln was stirred, cooled to $0^\circ C$, and a soln of an acyl isothiocyanate (0.01 mol) in THF (20 mL) was added. The mixture was stirred for 15 min at $0^\circ C$, and for 15 min at rt. The solvent was concentrated under reduced pressure, H_2O (50 mL) was added to the residue, and the mixture was extracted with $CHCl_3$ (2×50 mL). The combined extracts were dried (Na_2SO_4), filtered, and the filtrate concentrated. The residue was purified either by crystallization or by preparative layer chromatography (silica gel, $CHCl_3$ /petroleum ether 1:1).

18.12.13

Product Subclass 13:
Carbamimidothioic Esters (Isothioureas)

This is a large subclass of stable compounds. General methods for their preparation follow those described for earlier members of this class. S-Alkylation of thioureas is most commonly used, but displacement reactions, particularly those on activated carbonimidithioate esters, are also useful.

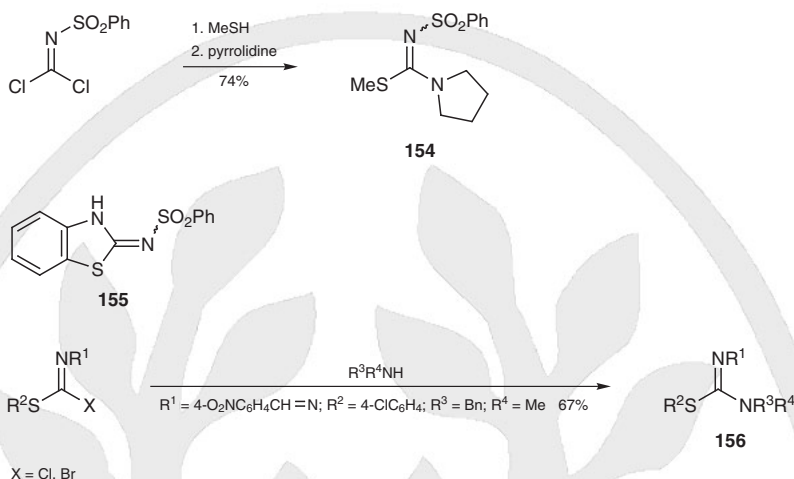
18.12.13.1

Synthesis of Product Subclass 13

18.12.13.1.1

Method 1:
From Carbonimidic Halides by Nucleophilic Displacement of Halide Ion

The successive displacement of chloride ion from carbonimidic dichlorides by sulfur and nitrogen nucleophiles is used only infrequently for the preparation of isothioureas;^[183,281] a successful example, the preparation of the isothiourea **154** from *N*-(phenylsulfonyl)carbonimidic dichloride, is illustrated in Scheme 67.^[183] If both nucleophiles are within the same molecule the method works well, as in the preparation of the dihydrobenzothiazol-2-imine **155** in high yield from 2-aminobenzenethiol and *N*-(phenylsulfonyl)carbonimidic dichloride.^[232] A more general procedure for isothioureas **156** is the displacement of halide ion from carbonohalidimidithioate esters by nitrogen nucleophiles (Scheme 67). In most cases the nucleophile is a primary or secondary amine,^[105,207,282] but azide ions,^[283] thiocyanate ions,^[126] and benzophenone imine^[123] are also used successfully.

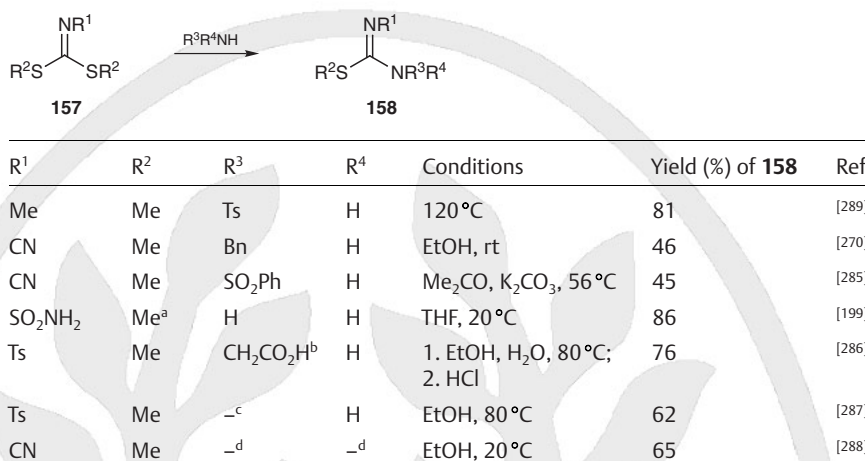
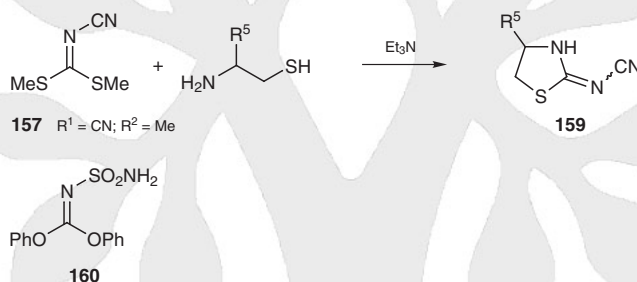
Scheme 67 Nucleophilic Displacement of a Halide Ion from Carbonimidic Halides^[105,123,126,179,207,232,281–283]**4-Chlorophenyl N-Benzyl-N-methyl-N'-(4-nitrobenzylidene)hydrazonothiocarbamate (156, $\text{R}^1 = 4\text{-O}_2\text{NC}_6\text{H}_4\text{CH}=\text{N}$; $\text{R}^2 = 4\text{-ClC}_6\text{H}_4$; $\text{R}^3 = \text{Bn}$; $\text{R}^4 = \text{Me}$); Typical Procedure:**^[207]

BnNHMe (0.242 mL, 2 mmol) was added to 4-nitrobenzaldehyde {bromo[(4-chlorophenyl)sulfanyl]methylene}hydrazone (0.398 g, 1 mmol) in benzene (40 mL) (**CAUTION: carcinogen**) and the soln was heated at 50 °C for 15 min. The precipitate of Bn(Me)NH₂Br (0.36 g, 80%) was removed by filtration, and the filtrate was concentrated to leave an oil. Extraction with petroleum ether (bp 60–80 °C) gave the isothiourea as a yellow solid; yield: 0.27 g (67%); mp 92–93 °C.

18.12.13.1.2

**Method 2:
From Carbonimidodithioate Diesters and Nitrogen Nucleophiles**

The displacement of an alkylsulfanyl substituent of a dialkyl carbonimidodithioate **157** by an amine or other nitrogen nucleophiles (Scheme 68) is an effective method that affords isothioureas **158** when the nitrogen substituent R^1 is an activating group (e.g., CN, SO₂Ph). Ammonia, primary and secondary amines and sulfonamides can be used as nucleophiles.^[199,270,284–288] When 2-sulfanylethylamine and related compounds are used as nucleophiles with the diester **157** ($\text{R}^1 = \text{CN}$; $\text{R}^2 = \text{Me}$) both sulfur substituents are displaced to give thiazolidin-2-imines **159**.^[289] A related double displacement of phenoxy groups in the carbonimide **160** by 2-sulfanylethylamine and other bidentate nucleophiles has been described.^[188]

Scheme 68 Synthesis from Carbonimidodithioate Diesters and Nitrogen Nucleophiles^[188,199,270,284–289]^a Starting material is (MeS)(PhS)C=NSO₂NH₂; SPh is displaced.^b Starting material is the Na salt.^c The amine is ethane-1,2-diamine; the product is a bis(thiourea).^d NR³R⁴ = pyrrolidin-1-yl; the nucleophile is 1-cyclohexen-1-ylpyrrolidine.

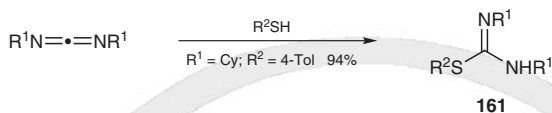
N'-Cyano-S-methyl-N-[(2-trifluoromethyl)phenylsulfonyl]isothiourea (158, R¹ = CN; R² = Me; R³ = 2-F₃CC₆H₄SO₂; R⁴ = H); Typical Procedure:^[285]

A mixture of 2-(trifluoromethyl)benzenesulfonamide (58.5 g, 0.26 mol), dimethyl N-cyano-carbonimidodithioate (38.0 g, 0.26 mol), and powdered anhyd K₂CO₃ (35.9 g, 0.26 mol) in acetone (420 mL) was refluxed for 17 h. The mixture was cooled to rt and filtered. The filtrate was concentrated to leave an amber-colored oil, which solidified when triturated with Et₂O. The solid was suspended in 2 M HCl (130 mL) and the suspension was stirred for 1.5 h. The solid was then collected by filtration and dried under vacuum to give the isothiourea; yield: 76.9 g (91%); mp 127 °C (dec).

18.12.13.1.3

Method 3:
By Addition of Thiols to Carbodiimides

Thiols add to carbodiimides at room temperature, or on mild heating, to give isothioureas **161** (Scheme 69).^[290–292] A related reaction, the addition of thiols to cyanamides, is a viable but infrequently used alternative.^[87,293]

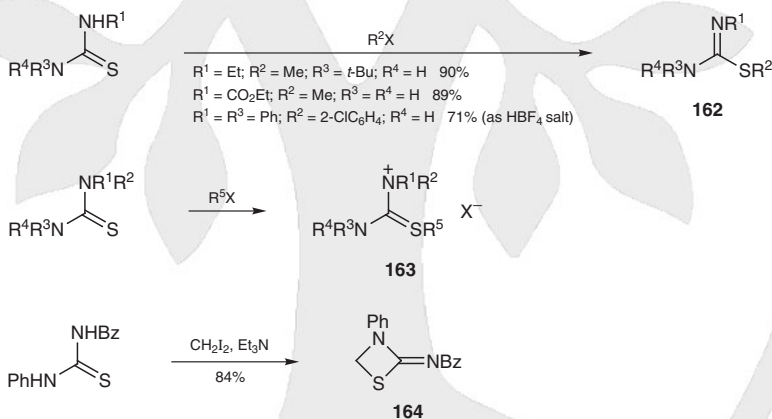
Scheme 69 Addition of Thiols to Carbodiimides^[290–292,294]***N,N'*-Dicyclohexyl-*S*-(4-tolyl)isourea (161, R¹ = Cy; R² = 4-Tol); Typical Procedure:**^[294]

4-Methylbenzenethiol (12.4 g, 0.1 mol) was added at 0 °C to a soln of DCC (20.6 g, 0.1 mol) in acetone (20 mL). The mixture was maintained at 0 °C for 10 h. The crystalline precipitate that had formed was then collected by filtration and washed with acetone (5 mL) at 0 °C. The mother liquors were reduced in volume and a further crop of crystals that separated was added to the first to give the isourea; yield: 31.0 g (94%); mp 71–72 °C (acetone).

18.12.13.1.4

**Method 4:
By the *S*-Alkylation of Thioureas**

This is the most general method for the preparation of isothiureas **162**. *S*-Alkylations of thioureas take place readily (Scheme 70)^[295,296] and several other types of *S*-substitution, including acylation^[297] and arylation,^[298] also give isothiureas from thioureas. The thioureas can be generated in situ from isothiocyanates.^[299] The alkylation of tetrasubstituted thioureas gives *S*-alkylisothiuronium salts **163**.^[300] The alkylation of *N,N'*-disubstituted thioureas with diiodomethane affords 1,3-thiazetidin-2-imines;^[301,302] for example, *N'*-benzoyl-*N*-phenylthiourea gives the 1,3-thiazetidine **164** (84%).^[301]

Scheme 70 *S*-Alkylation of Thioureas^[295–301]***N*-tert-Butyl-*N'*-ethyl-*S*-methylisothiurea 162 (R¹ = Et; R² = Me; R³ = *t*-Bu; R⁴ = H);****Typical Procedure:**^[295]

CAUTION: Dimethyl sulfate is corrosive and irritating to the skin, eyes, and respiratory system and is a probable human carcinogen.

Finely powdered *N*-tert-butyl-*N'*-ethylthiourea (24.0 g, 0.15 mol) and Me₂SO₄ (23 g, 0.18 mol) in H₂O (80 mL) were refluxed for 0.5 h. The soln was cooled and poured into aq Na₂CO₃ at 0–10 °C. The mixture was stirred for 1 h, and then extracted with Et₂O. The combined extracts were dried and concentrated to give the isothiurea as a colorless oil; yield: 23.5 g (90%).

***N*'-Ethoxycarbonyl-*S*-methylisothiourea (162, R¹ = CO₂Et; R² = Me; R³ = R⁴ = H);**

Typical Procedure:^[296]

CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

N-Ethoxycarbonylthiourea (3.5 g, 23 mmol) was added to a soln of NaOEt (1.56 g, 23 mmol) and MeI (5 mL) in EtOH (50 mL). After 1 h, the mixture was concentrated to dryness and the residue was extracted with Et₂O (100 mL). The combined extracts were filtered, and the filtrate was concentrated to leave a syrup that slowly crystallized; yield: 3.3 g (89%); mp 44–46 °C.

***S*-(2-Chlorophenyl)-*N,N'*-diphenylisourea (162, R¹ = R³ = Ph; R² = 2-ClC₆H₄; R⁴ = H);**

Typical Procedure:^[298]

2-Chlorobenzenediazonium tetrafluoroborate (2.3 g, 10 mmol) was added in portions to a soln of *N,N'*-diphenylthiourea (2.3 g, 10 mmol) in acetone (25 mL) at 40–50 °C. After evolution of gas had ceased, the soln was allowed to stand for 1 h. H₂O was then added to form an oil that was collected and allowed to crystallize slowly over 2–3 d. Recrystallization (EtOH) gave the product as the tetrafluoroborate salt; yield: 2.9 g (71%); mp 76–78 °C.

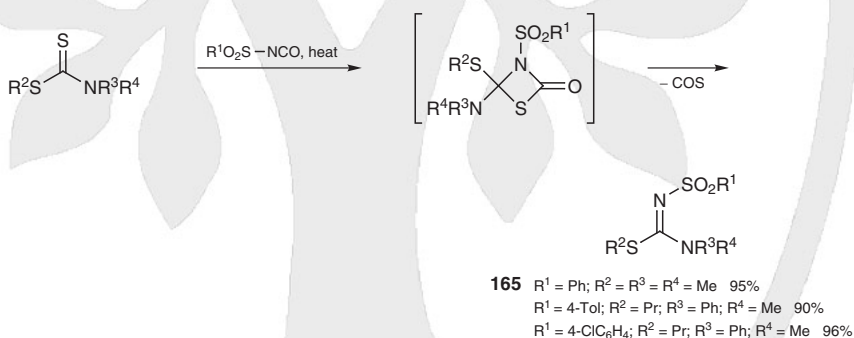
18.12.13.1.5

Method 5:

By the Cycloaddition of Arenesulfonyl Isocyanates to Dithiocarbamates

Arenesulfonyl isocyanates undergo [2+2]-cycloaddition reactions with dithiocarbamate esters to give *N'*-(arylsulfonyl)isoureas **165**, after the elimination of carbonyl sulfide (Scheme 71).^[303]

Scheme 71 Cycloaddition of Arenesulfonyl Isocyanates to Dithiocarbamates^[303]



***N'*-(Arylsulfonyl)isothioureas 165; General Procedure:**^[303]

An alkylidithiocarbamate (4.3 mmol) and an arenesulfonyl isocyanate (5.2 mmol) in toluene (11 mL) were refluxed for 6 h. The mixture was diluted with CH₂Cl₂ (100 mL) and the soln was washed with H₂O (50 mL), and then dried (Na₂SO₄). The solvent was distilled off under reduced pressure and the residue was purified by column chromatography (silica gel, hexane/EtOAc 2:1).

18.12.13.1.6

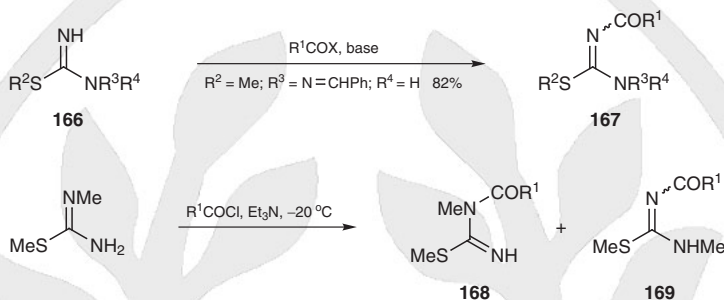
Method 6:

From Other Isothioureas by N-Acylation

Isoureas **166** with one or more free positions on nitrogen are normally acylated on nitrogen to give *N*-acylisoureas **167** (Scheme 72).^[87,304] The conditions for *N*-acylation are typical of those normally used for the acylation of nucleophilic nitrogen. Thus, *S*-methylisothiourea is benzoylated using benzoyl chloride and sodium hydroxide.^[305] and *N,S*-di-

methylisothiourea reacts with acetyl chloride or with benzoyl chloride below room temperature to give the *N*-acyl derivatives **168** ($R^1 = \text{Me, Ph}$).^[199] At or above room temperature the isomeric *N'*-acylisoureas **169** are also formed and these appear to be the more stable isomers.

Scheme 72 From Other Isothioureas by *N*-Acylation^[87,304,305]



***N'*-Acetyl-*N*-(benzylidenimino)-*S*-methylisothiourea (167, $R^1 = R^2 = \text{Me}$; $R^3 = \text{N=CHPh}$; $R^4 = \text{H}$); Typical Procedure:**^[304]

N-(Benzylidenimino)-*S*-methylisothiourea (**166**, $R^2 = \text{Me}$; $R^3 = \text{N=CHPh}$; $R^4 = \text{H}$; 2.5 g, 12.95 mmol) was added to Ac_2O (10 mL) and the soln was stirred at rt for 2 h. The soln was poured into ice water and the mixture was allowed to stand overnight. The precipitate that formed was collected by filtration and crystallized (EtOH) to give the title compound; yield: 2.5 g (82%); mp 86–88 °C.

18.12.14

Product Subclass 14:
Imides with a Sulfur and a Phosphorus Substituent

Members of the subclass are known with both λ^3 -phosphorus and λ^5 -phosphorus substituents. The general methods available for their preparations are analogous to some of those used for isothioureas, although with much fewer examples.

18.12.14.1

Synthesis of Product Subclass 14

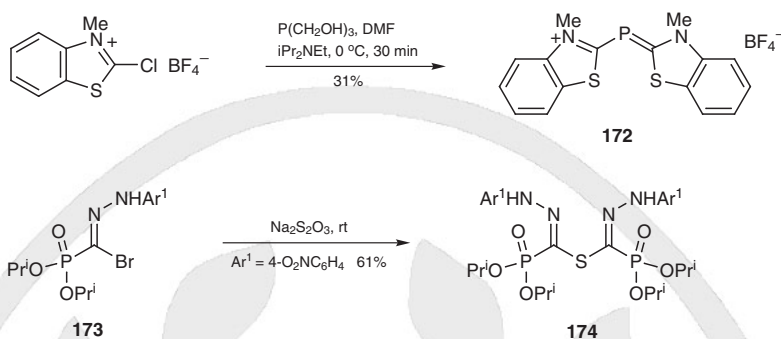
18.12.14.1.1

Method 1:
From Carbonimidic Halides by Nucleophilic Displacement of a Halide Ion

Some examples of the displacement of halide ion to give members of this subclass are shown in Scheme 73, but none represents a general procedure. The reactions of tris(trimethylsilyl)phosphine with the iminium chloride **170** give new iminium salts **171**.^[306] The benzothiazolium salt **172** and analogous compounds are prepared from the corresponding 2-chlorobenzothiazolium salts and tris(hydroxymethyl)phosphine.^[307,308] The displacement of a halide ion from a phosphorus-bearing precursor is exemplified by the reaction of the bromohydrazone **173** with sodium thiosulfate to give the sulfide **174**.^[309]

Scheme 73 Nucleophilic Displacement of a Halide Ion from Carbonimidic Halides^[306–309]





{Bis[2-(N-methylbenzothiazole)]phosphamethine}cyanine Tetrafluoroborate (172);

Typical Procedure:^[308]

Tris(hydroxymethyl)phosphine (1.25 g, 10 mmol) in DMF (10 mL) was added under N₂ to an ice-cold soln of 2-chloro-3-methylbenzothiazolium tetrafluoroborate (5.43 g, 20 mmol) in DMF (20 mL), and then iPr₂NEt (3.90 g, 30 mmol) was added slowly dropwise. After 30 min, the mixture was diluted with H₂O (70 mL) and the precipitate of the salt **172** that had formed was collected, and washed with BuOH (20 mL), and then with Et₂O (20 mL); yield: 1.3 g (31%); mp 224–227 °C (dec).

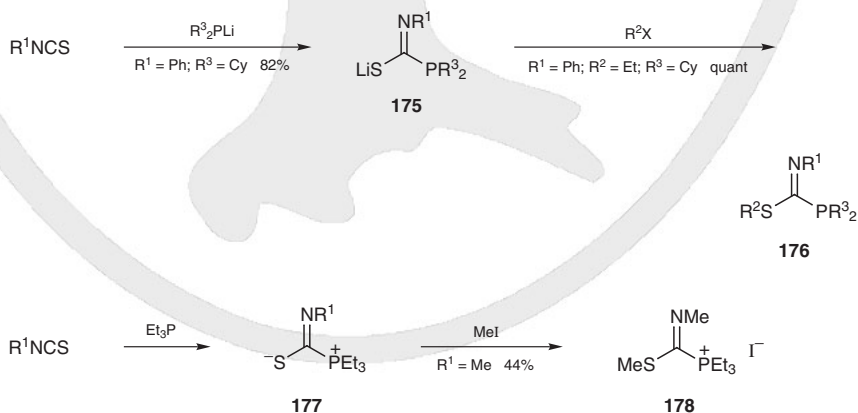
18.12.14.1.2

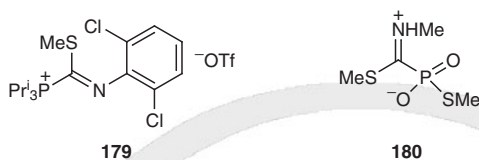
Method 2:

By Addition of Phosphorus Nucleophiles to Isothiocyanates and Related Procedures

This method parallels those used to prepare isothiureas from isothiocyanates and from dithiocarbamate esters. Thus, lithium salts **175** of 1-(phosphino)thioformamides are prepared by the addition of lithium salts of dialkylphosphines, or diarylphosphines, to isothiocyanates (Scheme 74). These salts can be alkylated on sulfur to give the imines **176**.^[310,311] Triethylphosphine adds to isothiocyanates to give the internal salts **177**, and S-methylation of the zwitterion **177** (R¹ = Me) yields the phosphonium iodide **178**.^[312] Related S-methylation procedures are described for the preparation of compounds **179**^[313] and **180**.^[314]

Scheme 74 Addition of Phosphorus Nucleophiles to Isothiocyanates and Related Procedures^[310–314]





S-Ethyl C-(Dicyclohexylphosphinyl)-N-phenylcarbonimidothioate (176, R¹ = Ph; R² = Et; R³ = Cy); Typical Procedure:^[315]

Lithium dicyclohexylphosphide (6.0 g, 29.4 mmol) was suspended in Et₂O (30 mL) and PhNCS (3.9 g, 28.9 mmol) in Et₂O (20 mL) was added. The lithium phosphide dissolved when the mixture was warmed. The soln was cooled in a dry ice/MeOH bath and the lithium salt **175** (R¹ = Ph; R³ = Cy) crystallized out. It was collected by filtration, washed, and dried under vacuum; yield: 8.0 g (82%).

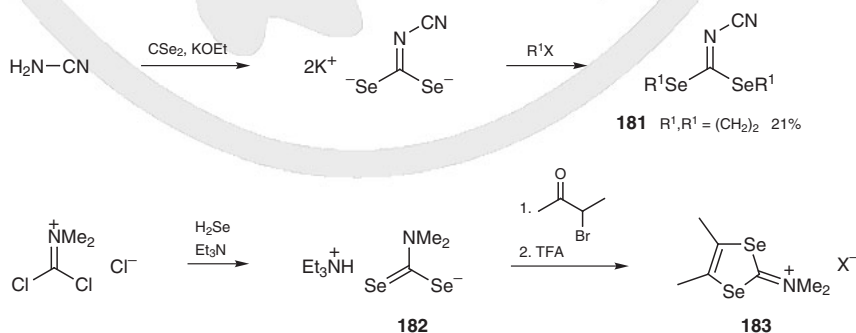
The lithium salt **175** (R¹ = Ph; R³ = Cy; 3.1 g, 9.1 mmol) and EtI (1.4 g, 9.0 mmol) in Et₂O (100 mL) were refluxed for 0.5 h. On cooling H₂O (50 mL) was added, and the Et₂O layer was separated, dried, and concentrated, and the residue was crystallized to give the ester **176** (R¹ = Ph; R² = Et; R³ = Cy); yield: nearly quant; mp 81 °C (EtOH).

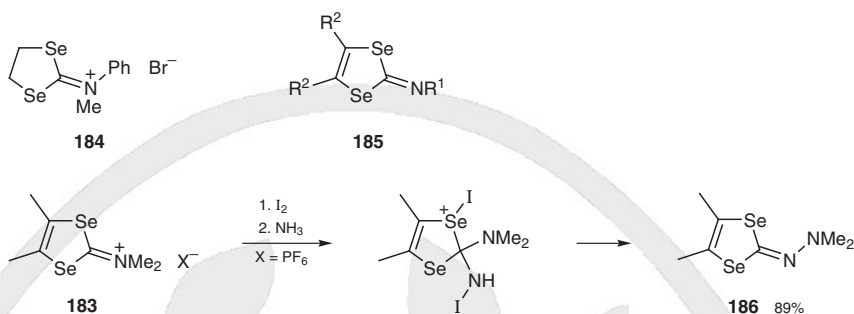
**18.12.15 Product Subclass 15:
Carbonimidodiselenoic Diesters**

18.12.15.1 Synthesis of Product Subclass 15

There are so few members of this product subclass that general methods of preparation cannot be described; however, most of the methods used for the known compounds (Scheme 75) are Se-alkylation reactions, mechanistically similar to those employed for earlier subclasses particularly carbamimidodithioic diesters (Section 18.12.11) and carbamimidoselenothioic diesters (Section 18.12.12). A few dialkyl *N*-cyanocarbonimidodiselenoic diesters **181** are available from cyanamide, carbon diselenide and an alkylating agent^[316] but, since carbon diselenide is extremely unpleasant to work with, an alternative method for the formation of a diselenocarbamate salt **182** has been devised from dichlorodimethyliminium chloride, hydrogen selenide, and triethylamine. The salt **182** is then converted into the 1,3-diselenolium salt **183** (X = CO₂CF₃) by a reaction with 3-bromobutan-2-one and trifluoroacetic acid.^[317] The iminium salt **184** and some related salts may be prepared by the alkylation of dimethyltin diselenocarbamates with dibromoalkanes.^[318] Several 1,3-diselenol-2-imines **185** are known and these are prepared by methods exactly analogous to those used for 1,3-thioselenol-2-imines **150** (see Scheme 65, Section 18.12.12.1.1).^[276–280,319] An exception is the dimethylhydrazone **186**, which is made by an unusual nitrogen insertion reaction on the hexafluorophosphate **183** (X = PF₆).^[320]

Scheme 75 Routes to Carbonimidodiselenoic Diesters^[276–280,316–320]





2-(Cyanoimino)-1,3-diselenolidine [181, R¹, R¹ = (CH₂)₂]; Typical Procedure:^[316]

CSe₂ (4.25 g, 25 mmol) in dioxane (10 mL) was added at 0 °C under N₂ to a stirred soln of H₂N-CN (1.05 g, 25 mmol) in dioxane (10 mL) and EtOH (5 mL) to which KOH (1.40 g, 25 mmol) in H₂O (2 mL) had been added. A further portion of KOH (1.40 g, 25 mmol) was added, after the addition of CSe₂ was complete. EtOH (100 mL) was then added, and dipotassium *N*-cyanodiselenocarbamate separated as a yellow solid. A further crop of this solid was obtained by the addition of Et₂O. The combined solids were purified by dissolution in H₂O (2.5 mL) and reprecipitation by the addition of EtOH; yield: 4.32 g (60%).

1,2-Dibromoethane (376 mg, 2 mmol) was added to a soln of the dipotassium salt (576 mg, 2 mmol) in DMF (10 mL) containing 10–20% H₂O at 0 °C. The soln was allowed to stand at rt for 5 h, and then H₂O (60 mL) was added, and the soln was heated to boiling. Activated carbon was added and the mixture was filtered. When the filtrate was cooled 2-(cyanoimino)-1,3-diselenolidine [**181**, R¹, R¹ = (CH₂)₂] separated as a colorless crystalline solid (70 mg). A further crop (30 mg) was obtained by extraction of the mother liquors to give a total yield: 100 mg (21%); mp 80–80.5 °C [benzene (CAUTION: carcinogen)/heptane 3:1].

4,5-Dimethyl-1,3-diselenol-2-one *N,N*-Dimethylhydrazone (186):^[320]

Aq NH₃ (5 mL) was added to a mixture of 2-(dimethylamino)-4,5-dimethyl-1,3-diselenolium hexafluorophosphate (50 mg, 0.12 mmol) and I₂ (46 mg, 0.18 mmol) in MeCN (100 mL) at 20 °C. (CAUTION: I₂/NH₃ mixtures can be explosive). The mixture slowly decolorized from black to orange-yellow. It was stirred for 2 h, and then it was poured into H₂O (200 mL) and extracted with CH₂Cl₂ (2 × 50 mL). The combined extracts were dried (MgSO₄) and the solvent was removed to leave the title compound as a yellow solid; yield: 30 mg (89%); mp 71–74 °C.

18.12.16

Product Subclass 16: Carbamimidoseleenoic Esters (Isoselenoureas)

Most of the known acyclic isoselenoureas [R¹SeC(NH₂)=NH] are unsubstituted on nitrogen and are prepared from selenourea by Se-alkylation or Se-arylation. A few *N*-substituted selenoureas are converted into isoselenoureas by alkylation. Methods for the synthesis of cyclic isoselenoureas also commonly involve a Se-alkylation step.

18.12.16.1

Synthesis of Product Subclass 16

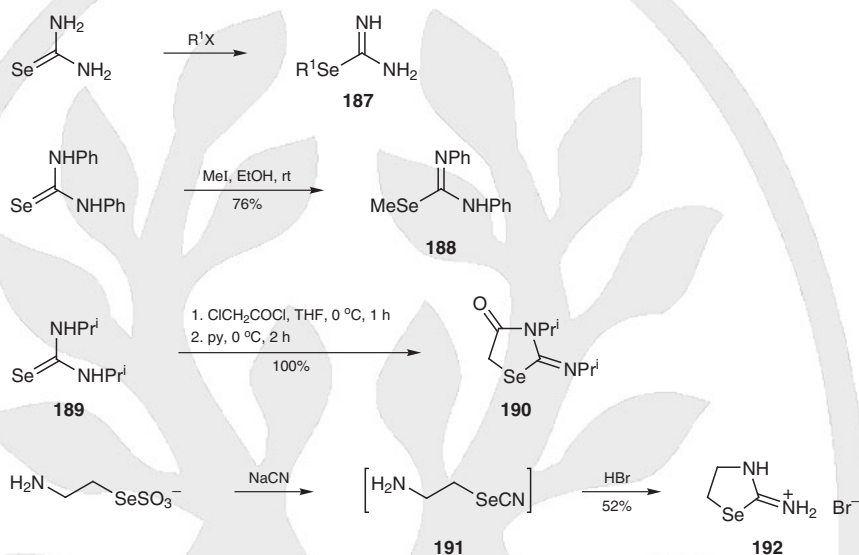
18.12.16.1.1

Method 1: Se-Alkylation of Selenoureas

Selenourea is easily alkylated on selenium by haloalkanes, such as bromoethane^[321] and 2-bromoethylamine,^[322] to afford the acyclic isoselenoureas **187** (Scheme 76). Selenourea is also substituted by dihaloalkanes^[323] and Se-arylated by arenediazonium salts.^[324] *N,N'*-

Diphenylselenourea is methylated by iodomethane to give the isoselenourea **188**.^[325] An example of alkylation that leads to a cyclic isoselenourea is the preparation of the selenazolidinone **190** from the selenourea **189** and chloroacetyl chloride.^[326] An exception to the alkylation of a selenourea is a preparation of 1,3-selenazolidin-2-iminium bromide (**192**) by the cyclization of a transient selenocyanate **191** (Scheme 76).^[327]

Scheme 76 Se-Alkylation of Selenoureas^[322–327]



***N,N'*-Diphenyl-Se-methylisoselenourea (188)**.^[325]

CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

N,N'-Diphenylselenourea (0.83 g, 3 mmol) in EtOH (25 mL) was mixed with a soln of MeI (0.43 g, 3 mmol) in EtOH (10 mL). The soln was left to stand overnight at rt, and then filtered to remove a small amount of an insoluble material. The filtrate was concentrated (to ca. 10 mL) and aq NaHCO₃ (1%; 100 mL) was added. A crystalline precipitate of the isoselenourea was collected by filtration, washed with H₂O, and dried; yield: 0.66 g (76%); mp 94–95 °C (EtOH).

3-Isopropyl-2-(isopropylimino)-1,3-selenazolidin-4-one (190); Typical Procedure:^[326]

Chloroacetyl chloride (0.08 mL, 1.0 mmol) was added to a stirred soln of *N,N'*-diisopropylselenourea (0.42 g, 2.0 mmol) in dry THF (20 mL) at 0 °C under argon. The mixture was stirred for 1 h at 0 °C, and then anhyd pyridine (0.09 mL, 1.0 mmol) was added, and the mixture was stirred for a further 2 h at 0 °C. The mixture was extracted with CH₂Cl₂ (100 mL), and the combined extracts were washed with H₂O (30 mL), dried (Na₂SO₄), and concentrated to dryness. The residue was purified by column chromatography (silica gel, CH₂Cl₂) to give a colorless liquid; yield: 0.25 g (100%).

18.12.17

Product Subclass 17:
(Dihalomethylene)phosphines (Dihalophosphaalkenes)

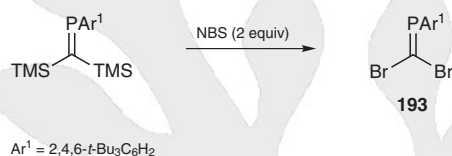
Representatives of this subclass are known that bear fluoro, chloro, bromo, and iodo substituents. The most comprehensive previous review of the subclass, and of other phosphalkenes in this product class, is by Romanenko.^[328] Several simple members of this subclass have been generated as transient intermediates; some of them have been character-

ized spectroscopically or intercepted (for example, in cycloaddition reactions^[329]) but not isolated. Most of the known difluorophosphaalkenes are of this type; thus, (difluoromethylene)(trifluoromethyl)phosphine ($F_2C=PCF_3$) dimerizes slowly in solution at room temperature and polymerizes rapidly in the condensed phase.^[330] Relatively few compounds are stable enough to be isolated and characterized, and all bear a large carbon or nitrogen substituent on phosphorus that provides steric protection.

18.12.17.1 Synthesis of Product Subclass 17

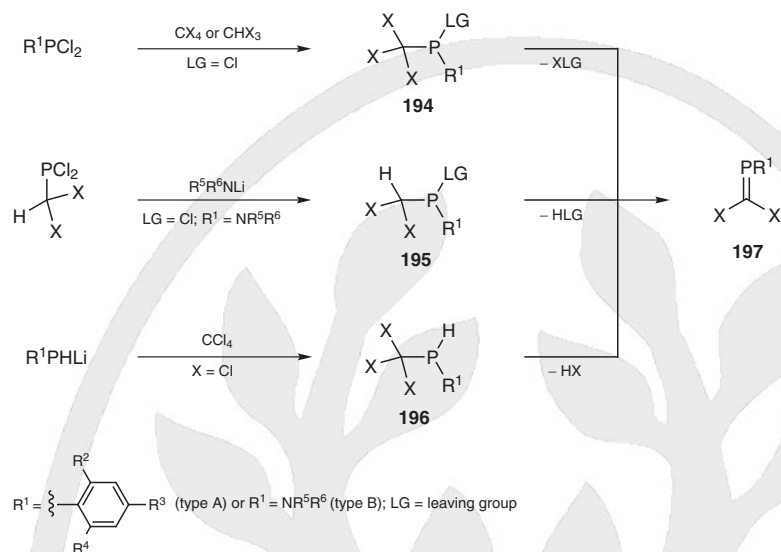
Only the methods that lead to isolable compounds are described here; routes to the transient members of the subclass are detailed in other reviews.^[6,328] Most of the stable compounds are produced by liquid-phase elimination of halogens or of hydrogen halides from phosphines. A preparation of the dibromophosphaalkene **193** by a displacement method (Scheme 77) has been described, but without experimental details; the method cannot be extended to the corresponding dichlorophosphaalkene.^[331]

Scheme 77 A Dibromophosphaalkane by the Displacement of Trimethylsilyl Substituents^[331]



18.12.17.1.1 Method 1: From Di- and Trihalomethylphosphines by Elimination

This method involves elimination, usually of halogen or hydrogen halide, from a phosphine that is normally generated in situ. Phosphines **194–196** of various types are used as precursors (Scheme 78). The nature of the phosphorus substituent (R^1) is the most important factor in determining the stability of the phosphalkene **197**. For example, in a series of compounds **197** ($X=\text{I}$) the stability decreases in line with the steric bulk of the 2,4,6-trisubstituted aryl substituent R^1 ; thus, whereas the phosphalkene **197** ($R^1=2,4,6\text{-}t\text{-Bu}_3\text{C}_6\text{H}_2$) is a stable solid in the absence of air, the analogues **197** ($R^1=2,4,6\text{-Et}_3\text{C}_6\text{H}_2$ or Mes) cannot be isolated.^[332] There is some indication that the stability of the phosphalkenes decreases across the series where the carbon substituent (X) is chloro, bromo, or iodo; for example, only the liquid phosphalkene **197** ($R^1=\text{Mes}$; $X=\text{Cl}$) can be distilled.^[333] Stable compounds have two types of substituent (R^1) on phosphorus; in one group (Type A) the substituent is a very bulky aryl group, usually a 2,4,6-trisubstituted phenyl group. In the second (Type B), it is a bulky dialkylamino or trimethylsilylamino group. The known (and characterized) compounds of this subclass are shown in Scheme 78. Some can be prepared by more than one method; but only one, usually the most efficient, is included in the Scheme.^[332–343]

Scheme 78 Synthetic Routes to Phosphaalkenes^[332–343]

Type	X	R ²	R ³	R ⁴	R ⁵	R ⁶	Reagents and Conditions	Yield (%) of 197	Ref
A	Cl	Me	Me	Me	–	–	R ¹ P(CCl ₃) ₂ , TMSCl, (Et ₂ N) ₃ P, –50 to 20 °C	82	[333]
A	F	<i>t</i> -Bu	<i>t</i> -Bu	<i>t</i> -Bu	–	–	R ¹ P(Cl)CF ₃ , BuLi, –80 °C to rt	64	[334]
A	Cl	<i>t</i> -Bu	<i>t</i> -Bu	<i>t</i> -Bu	–	–	R ¹ PCl ₂ , CHCl ₃ , BuLi, –100 °C	73	[335]
A	Br	<i>t</i> -Bu	<i>t</i> -Bu	<i>t</i> -Bu	–	–	R ¹ PCl ₂ , CHBr ₃ , BuLi, –100 °C	55	[335]
A	I	<i>t</i> -Bu	<i>t</i> -Bu	<i>t</i> -Bu	–	–	R ¹ PCl ₂ , CHI ₃ , LDA, –100 °C	93	[336]
A	– ^a	<i>t</i> -Bu	<i>t</i> -Bu	<i>t</i> -Bu	–	–	R ¹ P(Br)CHClBr, DBU, 20 °C	79	[334]
A	Cl	CF ₃	CF ₃	CF ₃	–	–	R ¹ PCl ₂ , CHCl ₂ Li, CdCl ₂ , –130 °C	65	[337]
A	Cl	<i>t</i> -Bu	<i>t</i> -Bu	Me	–	–	R ¹ PHLi, CCl ₄ , DBU, –126 °C	41	[338]
A	Cl	Mes	Me	Mes	–	–	R ¹ PCl ₂ , CHCl ₃ , BuLi, –110 °C	86	[339]
A	Cl	2-MeOC ₆ H ₄	Me	2-MeOC ₆ H ₄	–	–	R ¹ PCl ₂ , CHCl ₃ , BuLi, –110 °C	85	[339]
B	Cl	–	–	–	<i>t</i> -Bu	<i>t</i> -Bu	R ¹ P(Cl)CCl ₃ , (Et ₂ N) ₃ P, 0 °C	96	[340]
B	Br	–	–	–	<i>t</i> -Bu	<i>t</i> -Bu	R ¹ PCl ₂ , CBr ₄ , <i>t</i> -Bu ₃ P, –40 °C	40	[341]
B	Cl	–	–	–	CMe ₂ (CH ₂) ₃ CMe ₂	–	R ¹ P(CCl ₃) ₂ , TMSCl, (Et ₂ N) ₃ P, 0–20 °C	85	[333]
B	Br	–	–	–	CMe ₂ (CH ₂) ₃ CMe ₂	–	R ¹ PCl ₂ , CBr ₄ , <i>t</i> -Bu ₃ P, –40 °C	67	[341]
B	Cl	–	–	–	TMS	TMS	(TMS ₂ N) ₂ PH, CCl ₄ , Et ₃ N, 30 °C	43	[342]
B	Br	–	–	–	TMS	TMS	Br ₂ CHPCl ₂ , LiHMDS, –70 °C to rt	70	[343]
B	Cl	–	–	–	<i>t</i> -Bu	TMS	Cl ₂ CHPCl ₂ , <i>t</i> -Bu(TMS)NLi, –70 °C to rt	58	[343]

^a X₂ = ClBr.

18.12.17.1.1

**Variation 1:
From Dichlorophosphines and Trihalomethanes**

This procedure is used to synthesize several phosphaalkenes **197** of Type A (see Scheme 78; Section 18.12.17.1.1). Most reactions are carried out at very low temperatures and with butyllithium as a base; lithium diisopropylamide can also be used.^[336] Preparations are

also described using tri-*tert*-butylphosphine in diethyl ether at room temperature.^[344] Compounds **197** of Type B ($R^5 = R^6 = \text{TMS}$) are prepared from dihalo(dihalomethyl)phosphines and 2 molecular equivalents of sodium hexamethyldisilazide, one of which acts as a nucleophile to displace halide ion, and the second as a base to generate the phosphalkene from the intermediates **195**.^[343,345]

(Dichloromethylene)(2,4,6-tri-*tert*-butylphenyl)phosphine (197, $R^1 = 2,4,6\text{-}t\text{-Bu}_3\text{C}_6\text{H}_2$; $X = \text{Cl}$); **Typical Procedure**:^[335]

1.6 M BuLi (40 mmol) in hexane (25 mL) was added during 0.5 h at -100°C to a soln of 2,4,6-*t*-Bu₃C₆H₂PCl₂ (6.94 g, 20 mmol) and CHCl₃ (1.6 mL, 2.38 g, 20 mmol) in THF (150 mL). The soln was slowly warmed to rt, and the solvent was concentrated under reduced pressure at rt to give a residue that was extracted with pentane (200 mL). The title compound was obtained as colorless crystals; yield: 5.2 g (73%); mp 148°C (pentane).

18.12.17.1.1.2 Variation 2: From Dichlorophosphines and Tetrahalomethanes

This variation has been used to prepare phosphalkenes **197** of both Types A and B (see Scheme 78; Section 18.12.17.1.1).^[333,340,341,344,346] Tri-*tert*-butylphosphine or hexaethylphosphorous triamide are typical coreagents that bring about the elimination of halogen from an intermediate **194**.

(Dibromomethylene)(di-*tert*-butylamino)phosphine (197, $R^1 = \text{Nt-Bu}_2$; $X = \text{Br}$); **Typical Procedure**:^[341]

t-Bu₃P (8.09 g, 0.04 mol) was added to a soln of CBr₄ (6.63 g, 0.02 mol) and (di-*tert*-butylamino)dichlorophosphine (4.60 g, 0.02 mol) in Et₂O (200 mL) at -70°C . The mixture was stirred for 0.5 h at -40°C then warmed to rt. A precipitate that formed was separated off in a dry inert atmosphere, and it was washed with Et₂O (2×40 mL). The filtrate and washings were cooled to -10°C and MeOH (30 mL) was added. The soln was concentrated (to ca. 100 mL) and a precipitate that formed was again removed by filtration. The solvents were removed from the filtrate and the residue was distilled to give the dibromophosphalkene; yield: 2.65 g (40%); bp $105\text{--}107^\circ\text{C}/0.03$ Torr.

18.12.17.1.1.3 Variation 3: From Monosubstituted Phosphines and Tetrachloromethane

This variation, which involves an intermediate of the type **196** (see Scheme 78; Section 18.12.17.1.1), has been used less often than the other procedures. An example is a preparation of (dichloromethylene)(2,4-di-*tert*-butyl-6-methylphenyl)phosphine (**197**, $R^1 = 2,4\text{-}t\text{-Bu}_2\text{-6-MeC}_6\text{H}_2$; $X = \text{Cl}$) from (2,4-di-*tert*-butyl-6-methylphenyl)phosphine, butyllithium, and carbon tetrachloride.^[338] The dichlorophosphalkene **197** [$R^1 = \text{N}(\text{TMS})_2$, $X = \text{Cl}$] is also prepared in a similar way from the corresponding primary aminophosphine and carbon tetrachloride, with triethylamine as the base.^[342]

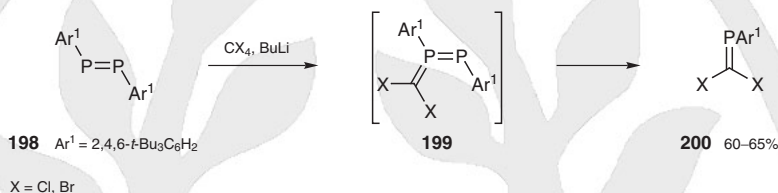
[Bis(trimethylsilyl)amino](dichloromethylene)phosphine [197, $R^1 = \text{N}(\text{TMS})_2$; $X = \text{Cl}$]:^[342]

CCL₄ (4.2 g, 27 mmol) (**CAUTION: toxic**) was added to a soln of [bis(trimethylsilyl)amino]phosphine (5.2 g, 27 mmol) and Et₃N (5.5 g, 54 mmol) in Et₂O (20 mL) at 0°C . The mixture was then refluxed for 60 h. The precipitate of Et₃N•HCl was removed by filtration and the solvent was removed from the filtrate. Fractional distillation of the residue gave the title compound; yield: 3.2 g (43%); bp $49\text{--}52^\circ\text{C}/0.05$ Torr.

18.12.17.1.2

Method 2:**From Diaryldiphosphines and Tetrahalomethanes**

The diphosphene **198** ($R^1 = 2,4,6\text{-}t\text{-Bu}_3\text{C}_6\text{H}_2$) is used in preparations of dichloro- and dibromophosphaalkenes **200** ($R^1 = 2,4,6\text{-}t\text{-Bu}_3\text{C}_6\text{H}_2$; $X = \text{Cl}, \text{Br}$).^[347,348] It is likely that the reactions involve the addition of dichlorocarbene or dibromocarbene (generated from the corresponding tetrahalomethanes) to give intermediates **199** ($R^1 = 2,4,6\text{-}t\text{-Bu}_3\text{C}_6\text{H}_2$; $X = \text{Cl}, \text{Br}$), which then break down to give the phosphoalkenes (Scheme 79).^[347]

Scheme 79 Reaction of Diphosphenes and Tetrahalomethanes^[347,348]

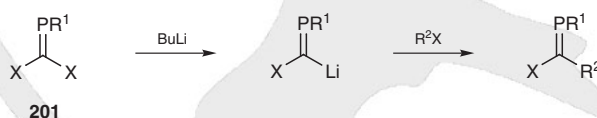
(Dichloromethylene)(2,4,6-tri-*tert*-butylphenyl)phosphine (200, $R^1 = 2,4,6\text{-}t\text{-Bu}_3\text{C}_6\text{H}_2$; $X = \text{Cl}$):^[348]

CCl_4 (0.050 mL, 0.52 mmol) (**CAUTION: toxic**) was added to the diphosphene **198** ($R^1 = 2,4,6\text{-}t\text{-Bu}_3\text{C}_6\text{H}_2$; 54.5 mg, 0.099 mmol) in THF (8 mL) at -78°C . BuLi (0.52 mmol) in hexane was added slowly. After the addition was complete, the cooling bath was removed and the mixture was allowed to warm to rt. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, pentane) to give the dichlorophosphaalkene; yield: 21.3–23.1 mg (60–65%); ^{31}P NMR (THF, δ): 233.4.

18.12.17.2

Applications of Product Subclass 17 in Organic Synthesis

The stable dihalophosphaalkenes **201** are useful precursors for several classes of unusual organophosphorus compounds. The most important reaction is halogen–metal exchange by butyllithium; the intermediates can then be reacted with electrophiles to give a variety of other phosphoalkenes bearing hydrogen, carbon, silicon, or other metal functional groups (Scheme 80).^[331,335,349–352] Cycloaddition reactions to the $\text{C}=\text{P}$ bond also provide novel organophosphorus compounds; these include examples of both [4+2] and [2+2] cycloadditions.^[2,353]

Scheme 80 Halogen–Lithium Exchange Reactions^[331,335,349–352]

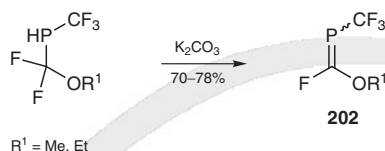
18.12.18

Product Subclass 18:**[Alkoxy(halo)methylene]phosphines [Alkoxy(halo)phosphaalkenes]**

18.12.18.1

Synthesis of Product Subclass 18

There are no examples of this subclass that are stable at room temperature. The alkoxy-fluorophosphaalkenes **202** ($R^1 = \text{Me}, \text{Et}$) are prepared by an elimination method (Scheme 81); they can be obtained in the pure state at -20°C .^[354]

Scheme 81 Alkoxy(fluoro)phosphaalkenes by Elimination^[354] $R^1 = \text{Me, Et}$

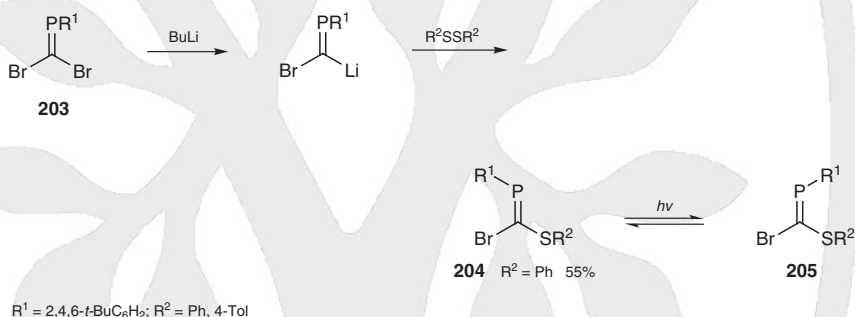
18.12.19

Product Subclass 19:**[Arylsulfanyl(halo)methylene]phosphines****[Arylsulfanyl(halo)phosphaalkenes]**

18.12.19.1

Synthesis of Product Subclass 19

The first stable examples of this subclass were prepared by exchange reactions from the dibromophosphaalkene **203** (Scheme 82).^[355,356] The sequence leads specifically to the *Z*-isomers **204**, but compound **204** ($R^2 = \text{Ph}$) forms an equilibrium mixture with its *E*-isomer **205** under UV irradiation.

Scheme 82 Arylsulfanyl(bromo)phosphaalkenes from Dibromophosphaalkenes^[355,356] $R^1 = 2,4,6\text{-}t\text{-Bu}_3\text{C}_6\text{H}_2; R^2 = \text{Ph, 4-Tol}$ **[Bromo(phenylsulfanyl)methylene](2,4,6-tri-*tert*-butylphenyl)phosphine**
(**204**, $R^1 = 2,4,6\text{-}t\text{-Bu}_3\text{C}_6\text{H}_2$; $R^2 = \text{Ph}$):^[351,355]

1.63 M BuLi (0.358 mmol) in hexane was added to (dibromomethylene)(2,4,6-tri-*tert*-butylphenyl)phosphine (**203**; 157 mg, 0.351 mmol) in THF (12 mL) at -78°C . $(\text{PhS})_2$ (111 mg, 0.508 mmol) was added, the soln was stirred for 1 h, and then warmed to rt. The solvent was removed, the residue was extracted with Et_2O , and the combined extracts were dried, and concentrated. Column chromatography (silica gel) gave the title compound as colorless needles, which were recrystallized (MeOH); yield: 92 mg (55%); mp $74\text{--}75^\circ\text{C}$ (dec); ^{31}P NMR (δ): 272.8.

18.12.20

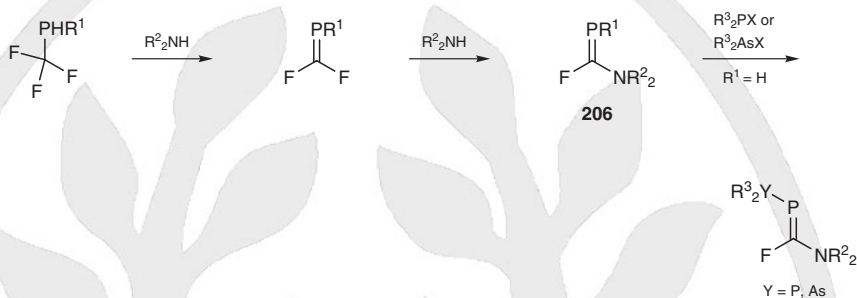
Product Subclass 20:**[Dialkylamino(halo)methylene]phosphines****[Dialkylamino(halo)phosphaalkenes]**

This subclass consists of fluoro substituted phosphaalkenes **206** that bear a disubstituted amino group on carbon and a variety of substituents [H ,^[357] CF_3 ,^[358,359] CO_2Me ,^[360] PR_2 , AsR_2 ^[361]] on phosphorus. Most are only characterized by spectroscopy, but a few [those bearing CF_3 or $\text{P}(\text{CF}_3)_2$ groups on phosphorus] are stable at room temperature; for example, the trifluoromethyl compounds **206** ($R^2 = \text{Me}$, or $\text{NR}_2 = \text{pyrrolidin-1-yl}$, piperidino) are colorless solids with melting points of 3, 54, and 56°C , respectively.

18.12.20.1 **Synthesis of Product Subclass 20**

The known compounds are made either by displacement of fluoride ion from difluorophosphaalkenes or by P-substitution of phosphoalkenes bearing a hydrogen on phosphorus (Scheme 83). The phosphoalkenes **172** are mainly or exclusively the *Z*-isomers.

Scheme 83 Routes to Dialkylamino(fluoro)phosphaalkenes^[357–361]



Dialkylamino(trifluoromethyl)phosphaalkenes 206 ($R^1 = CF_3$); General Procedure:^[359]

Using a standard vacuum apparatus (difluoromethylene)(trifluoromethyl)phosphine (1–2 mmol) was transferred under high vacuum at $-78^\circ C$ to an ampoule containing a soln of a secondary amine (2–4 mmol) in CH_2Cl_2 , $CHCl_3$, pentane, or toluene. A brown ring immediately formed at the point of contact, indicating the start of the reaction. When the mixture was melted at $-40^\circ C$ the conversion was quantitative in terms of the difluorophosphaalkene. The phosphoalkenes **206** ($R^2 = Me$ or Et) were isolated by fractional distillation and condensation (bath temperature in the range -196 to $-78^\circ C$). For phosphoalkenes derived from other secondary alkylamines the solvent and excess amine was first pumped off and the residue was then transferred to a Schlenk tube. The products were isolated by sublimation under reduced pressure, followed by column chromatography (50–70 mesh silica gel, $CHCl_3$).

18.12.21

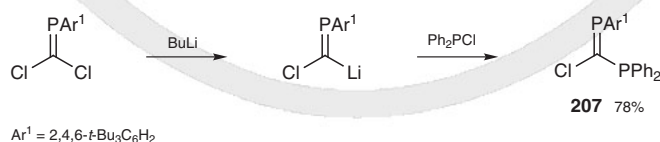
Product Subclass 21:
(Halomethylene)phosphines [(Halo)phosphaalkenes] Bearing
a Phosphorus Substituent

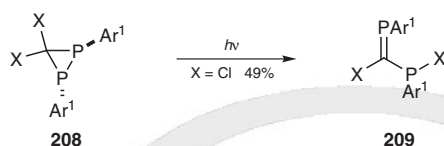
18.12.21.1

Synthesis of Product Subclass 21

The two routes to compounds of this subclass are illustrated in Scheme 84. The first, a substitution reaction, is represented by a single example **207**.^[351,362] There are two examples of the second method, the photolysis of phosphiranes **208** ($X = Cl, Br$) which produces the phosphoalkenes **209** ($X = Cl, Br$) as the major products.^[363]

Scheme 84 Routes to (Halomethylene)phosphines Bearing a Phosphorus Substituent^[351,362,363]





$\text{Ar}^1 = 2,4,6\text{-}t\text{-Bu}_3\text{C}_6\text{H}_2$; $\text{X} = \text{Cl}, \text{Br}$

(Z)-[Chloro(diphenylphosphino)methylene](2,4,6-tri-*tert*-butylphenyl)phosphine (207):^[351,362]

1.63 M BuLi (0.358 mmol) in hexane was added to (dichloromethylene)(2,4,6-tri-*tert*-butylphenyl)phosphine (126 mg; 0.351 mmol) in THF (12 mL) at -78°C . Ph_2PCl (112 mg, 0.508 mmol) was added; the soln was stirred for 1 h, and then warmed to rt. The solvent was removed, the residue was extracted with Et_2O , and the combined extracts were dried, and concentrated. Column chromatography (silica gel, hexane/toluene 5:1) gave the phosphalkene; yield: 78%; ^{31}P NMR (δ): 302.4.

(Z)-{Chloro[chloro-2,4,6-tri-*tert*-(butylphenyl)phosphino]methylene}(2,4,6-tri-*tert*-butylphenyl)phosphine (209, $\text{Ar}^1 = 2,4,6\text{-}t\text{-Bu}_3\text{C}_6\text{H}_2$; $\text{X} = \text{Cl}$):^[363]

The *trans*-diphosphirane **208** ($\text{X} = \text{Cl}$; 200 mg, 0.32 mmol) in degassed toluene (4 mL) was irradiated at 300 nm for 5 h. The soln was concentrated to dryness under reduced pressure. Pentane was added and the suspension was filtered through Celite. The phosphalkene was obtained as yellow crystals; yield: 100 mg (49%); mp 184°C (pentane).

18.12.22

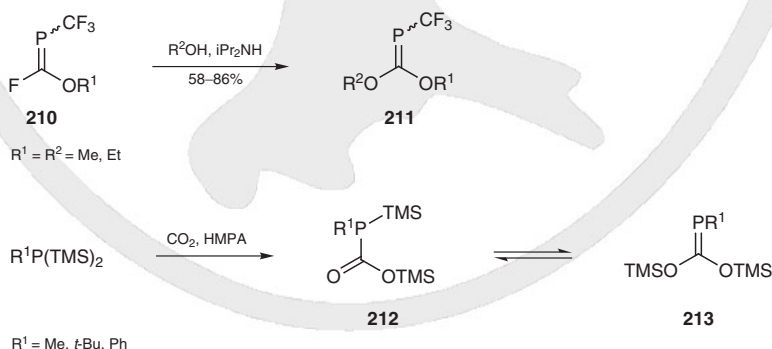
**Product Subclass 22:
Dioxymethylenephosphines (Dialkoxyposphalkenes)**

18.12.22.1

Synthesis of Product Subclass 22

There are very few examples of this subclass. Three dialkoxymethylenephosphines **211** are prepared by displacement reactions from the fluorophosphalkenes **210** ($\text{R}^1 = \text{Me}, \text{Et}$) and methanol or ethanol in the presence of diisopropylamine; they can be isolated at -20°C and characterized by spectroscopy.^[360] The trimethylsilyl esters **212** and **213** ($\text{R}^1 = \text{Me}, t\text{-Bu}, \text{Ph}$) exist as equilibrium mixtures for which spectroscopic data are also available (Scheme 85).^[364]

Scheme 85 Dioxymethylenephosphines and Related Compounds^[360,364]



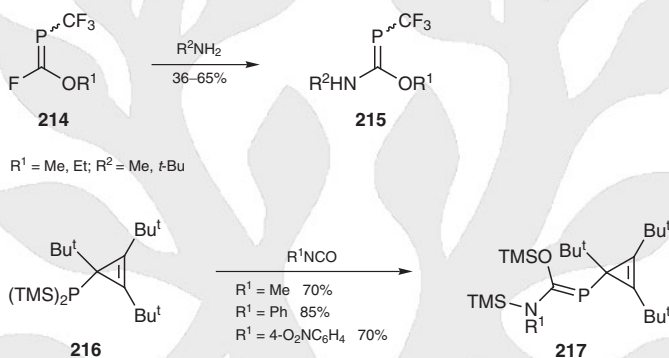
18.12.23

Product Subclass 23:**[(Amino)(oxy)methylene]phosphines [Alkoxy(amino)phosphaalkenes]**

18.12.23.1

Synthesis of Product Subclass 23

Three labile members **215** ($R^1 = \text{Me, Et}$; $R^2 = \text{Me, Bu}$) of this subclass are prepared by displacement reactions in which the appropriate trifluoromethylphosphaalkene **214** is treated with a primary amine; these compounds are obtained spectroscopically pure at -50°C .^[360] More stable members of the subclass are the sterically hindered cyclopropenes **217**, which are prepared by the addition of the bis(trimethylsilyl)phosphines **216** to isocyanates (Scheme 86).^[365,366] Several of these compounds can be isolated in the crystalline form and as single isomers that are probably the *E*-isomers.^[365]

Scheme 86 [(Amino)(oxy)methylene]phosphines^[360,365,366]**[(Amino)(trimethylsiloxy)methylene](1,2,3-tri-*tert*-butylcyclopropenyl)phosphines **217**; General Procedure:**^[365]

MeNCO (or an aryl isocyanate) (2.0 mmol) in pentane (5 mL) was added to the cyclopropenylphosphine **216** (750 mg, 2.0 mmol) in pentane (5 mL), and the mixture was stirred for 8 h at 25°C . The solvent was concentrated at 30°C and 10^{-2} Torr to leave an oily residue that crystallized when triturated with pentane at -78°C and, if necessary, was further purified by recrystallization with the same solvent.

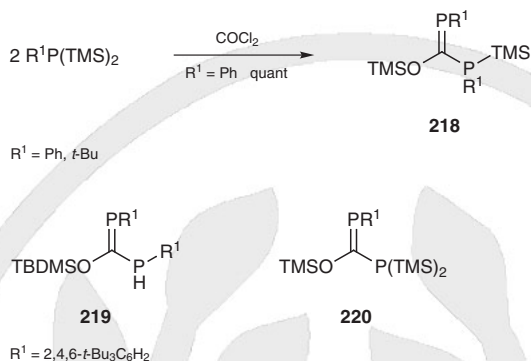
18.12.24

Product Subclass 24:**Methylenephosphines (Phosphaalkenes) with an Oxygen and a Phosphorus Substituent**

18.12.24.1

Synthesis of Product Subclass 24

Several isolable members of this subclass are known, all with trialkylsilyl substituents on oxygen. The reactions of bis(trimethylsilyl)phosphines with phosgene lead to the formation of the silyl ethers **218** (Scheme 87).^[367,368] Related preparations of the silyl ethers **219**^[369] and **220**,^[370,371] both bearing the bulky 2,4,6-tri-*tert*-butylphenyl group on phosphorus, are described.

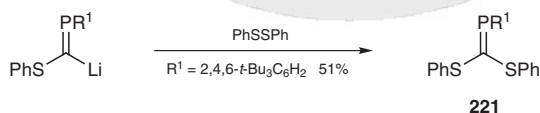
Scheme 87 Methylene phosphines with an Oxygen and a Phosphorus Substituent^[367–371]**Phosphaalkene 218 ($R^1 = Ph$):**^[367]

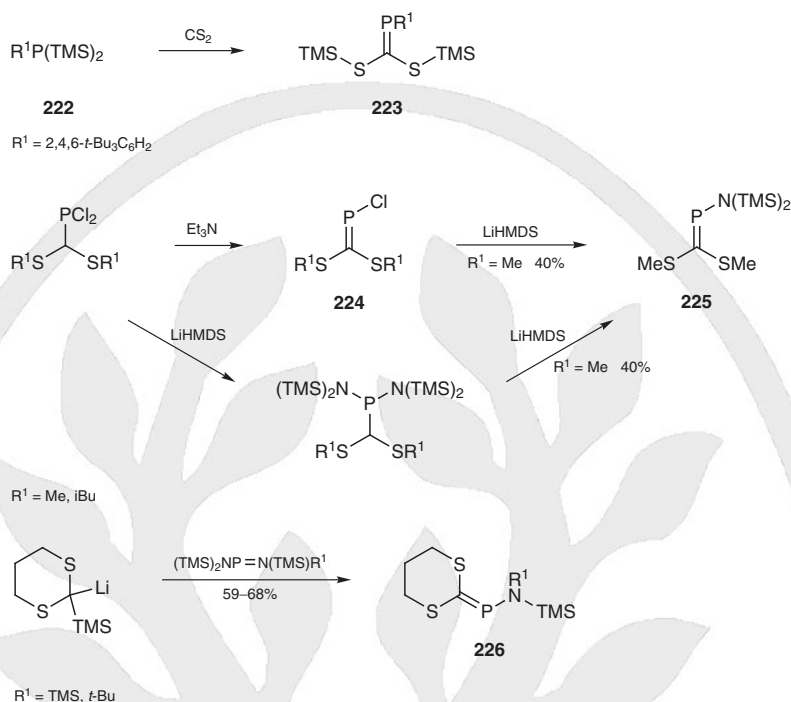
CAUTION: Phosgene is a severe respiratory irritant and very toxic by inhalation.

$COCl_2$ (10.7 g, 108 mmol) was condensed over 6 h into a stirred soln of $PhP(TMS)_2$ (50.8 g, 200 mmol) in pentane (400 mL) at 0 °C in an evacuated vessel. After 12 h at rt, the soln was concentrated (to ca. 100 mL) and stirred for a further 12 h. The mixture was filtered and the filtrate was concentrated to leave the phosphaalkene as a yellow oil in an almost quantitative yield. The compound cannot be distilled without decomposition, but it is stable for several weeks at 0 °C in the absence of O_2 and moisture; ^{31}P NMR (benzene- d_6 , 85% H_3PO_4 , δ): +164.0 (d, $J = 72.8$), -37.0 (d, $J = 72.8$).

18.12.25**Product Subclass 25:
Disulfanylmethylenephosphines (Disulfanylphosphaalkenes)****18.12.25.1****Synthesis of Product Subclass 25**

Several methods, illustrated in Scheme 88, are used to produce the relatively small number of compounds in this subclass. One example in which a displacement method is used is the synthesis of the stable and crystalline bis(phenylsulfanyl)phosphaalkene **221**.^[355] The reaction of the arylbis(trimethylsilyl)phosphine **222** with carbon disulfide gives the phosphaalkene **223**.^[372] Other members of this subclass are produced by elimination and by P-substitution methods. P-Chlorobis(alkylsulfanyl)phosphaalkenes **224** can be generated by base-induced elimination and the P-chloro substituent is then displaced by either nitrogen or phosphorus nucleophiles;^[373–375] an example is the preparation of the P-[bis(trimethylsilyl)amino]phosphaalkene **225**, which is available by either elimination or P-displacement methods.^[373] As with other phosphaalkenes of this type, the stability of the compounds is increased when the substituents on phosphorus and on carbon are bulky; thus, the compounds **224** ($R^1 = Me, iBu$) are only stable in solution below 0 °C, whereas the phosphaalkene **225** can be distilled. The dithianes **226** are also prepared by a P-displacement method.^[376]

Scheme 88 Disulfanylphosphaalkenes^[355,372–376]



[Bis(trimethylsilyl)amino][bis(methylsulfanyl)methylene]phosphine (225);

Typical Procedure:^[373]

$LiHMDS$ (1.67 g, 0.01 mol) in THF (5 mL) was added with stirring to $Cl_2PCH(SMe)_2$ (2.08 g, 0.01 mol) in THF (5 mL) at $-30^\circ C$. The mixture was allowed to warm to rt. After 1 h, the solvent was distilled off at 10 Torr, and the residue was filtered to remove $LiCl$. Fractional distillation of the oily residue gave the phosphine $[(TMS)_2N]_2PCH(SMe)_2$; yield: 1.67 g (50%); bp $128-132^\circ C/0.03$ Torr; ^{31}P NMR (δ): 129.7. $LiHMDS$ (1.67 g, 0.01 mol) in THF (5 mL) was added to a soln of this phosphine (3.34 g, 0.01 mol) in THF (10 mL), and the mixture was left for 50 h at rt. The solvent was then removed under reduced pressure, $LiCl$ was removed by filtration and the residue was distilled to give the methylenephosphine as a yellow oil; yield: 1.19 g (40%); bp $80-85^\circ C/0.05$ Torr; ^{31}P NMR (δ): 258.3.

References

- [1] Appel, R.; Knoll, F.; Ruppert, I., *Angew. Chem.*, (1981) **93**, 771; *Angew. Chem. Int. Ed. Engl.*, (1981) **20**, 731.
- [2] Grobe, J.; Le Van, D.; Schulze, J.; Szameitat, J., *Phosphorus, Sulfur Silicon Relat. Elem.*, (1986) **28**, 239.
- [3] Markovskii, L. N.; Romanenko, V. D., *Zh. Obshch. Khim.*, (1986) **56**, 253; *J. Gen. Chem. USSR (Engl. Transl.)*, (1986) **56**, 221.
- [4] Markovskii, L. N.; Romanenko, V. D., *Zh. Obshch. Khim.*, (1987) **57**, 1; *J. Gen. Chem. USSR (Engl. Transl.)*, (1987) **57**, 1.
- [5] Markovski, L. N.; Romanenko, V. D., *Tetrahedron*, (1989) **45**, 6019.
- [6] Gaumont, A. C.; Denis, J. M., *Chem. Rev.*, (1994) **94**, 1413.
- [7] Weber, L., *Eur. J. Inorg. Chem.*, (2000), 2425.
- [8] Gilchrist, T. L., In *Comprehensive Organic Functional Group Transformations*, Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds.; Pergamon: Oxford, (1995); Vol. 6, p 601.
- [9] Kühle, E.; Anders, B.; Zumach, G., *Angew. Chem.*, (1967) **79**, 663; *Angew. Chem. Int. Ed. Engl.*, (1967) **6**, 649.
- [10] Ulrich, H., *The Chemistry of Imidoyl Halides*, Plenum: New York, (1968).
- [11] Kühle, E.; Anders, B.; Zumach, G., In *Newer Methods of Preparative Organic Chemistry*, Foerst, W., Ed.; VCH: Weinheim, Germany, (1971); Vol. VI, p 127.
- [12] Ulrich, H.; Richter, W., In *The Chemistry of Cyanates and Their Thio Derivatives*; Patai, S., Ed.; Wiley-Interscience: Chichester, UK, (1977); p 969.
- [13] Tanaka, J.; Higa, T., *J. Nat. Prod.*, (1999) **62**, 1339.
- [14] Musman, M.; Tanaka, J.; Higa, T., *J. Nat. Prod.*, (2001) **64**, 111.
- [15] Kehraus, S.; König, G. M.; Wright, A. D., *J. Nat. Prod.*, (2001) **64**, 939.
- [16] Petrov, K. A.; Neimysheva, A. A., *Zh. Obshch. Khim.*, (1959) **29**, 2165; *J. Gen. Chem. USSR (Engl. Transl.)*, (1959) **29**, 2131.
- [17] Klauke, E., *Angew. Chem.*, (1966) **78**, 829; *Angew. Chem. Int. Ed. Engl.*, (1966) **5**, 848.
- [18] El-Abadelah, M. M., *Chem. Ind. (London)*, (1976), 164.
- [19] Chiarino, D.; Napoletano, M.; Sala, A., *Synth. Commun.*, (1988) **18**, 1171.
- [20] Halling, K.; Thomsen, I.; Torrsell, K. B. G., *Liebigs Ann. Chem.*, (1989), 985.
- [21] Hanson, R. N.; Mohamed, F. A., *J. Heterocycl. Chem.*, (1997) **34**, 345.
- [22] Vyas, D. M.; Chiang, Y.; Doyle, T. W., *Tetrahedron Lett.*, (1984) **25**, 487.
- [23] Wade, P. A.; Berezna, J. F.; Palfey, B. A.; Carroll, P. J.; Dailey, W. P.; Sivasubramanian, S., *J. Org. Chem.*, (1990) **55**, 3045.
- [24] Rohloff, J. C.; Robinson, J.; Gardner, J. O., *Tetrahedron Lett.*, (1992) **33**, 3113.
- [25] Bach, K. K.; El-Seedi, H. R.; Jensen, H. M.; Nielsen, H. B.; Thomsen, I.; Torrsell, K. B. G., *Tetrahedron*, (1994) **50**, 7543.
- [26] Foti, F.; Grassi, G.; Risitano, F., *Tetrahedron Lett.*, (1999) **40**, 2605.
- [27] Koldobskii, A. B.; Lunin, V. V., *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1991), 533; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1991), 462.
- [28] Nagarajan, S.; Ho, T. L.; Dubois, G. E., *Synth. Commun.*, (1992) **22**, 1191.
- [29] Johnstone, R. A. W.; Price, P. J., *J. Chem. Soc., Perkin Trans. 1*, (1987), 1069.
- [30] Vandort, M.; Neubig, R.; Counsell, R. E., *J. Med. Chem.*, (1987) **30**, 1241.
- [31] Rouot, B.; Leclerc, G., *Bull. Soc. Chim. Fr.*, (1979), II-520.
- [32] Bunnenberg, R.; Jochims, J. C.; Härle, H., *Chem. Ber.*, (1982) **115**, 3587.
- [33] Alves, J. A. C.; Johnstone, R. A. W., *Synth. Commun.*, (1997) **27**, 2645.
- [34] Neidlein, R.; Haussmann, W., *Chem. Ber.*, (1966) **99**, 239.
- [35] Lidy, W.; Sundermeyer, W., *Chem. Ber.*, (1976) **109**, 1491.
- [36] Dergach, G. I.; Liptuga, N. I., *Zh. Obshch. Khim.*, (1966) **36**, 461; *J. Gen. Chem. USSR (Engl. Transl.)*, (1966) **36**, 480.
- [37] Hassel, T.; Müller, H. P., *Angew. Chem.*, (1987) **99**, 368; *Angew. Chem. Int. Ed. Engl.*, (1987) **26**, 359.
- [38] Sheppard, W. A., *J. Am. Chem. Soc.*, (1965) **87**, 4338.
- [39] Gompper, R.; Kunz, R., *Chem. Ber.*, (1966) **99**, 2900.
- [40] Janousek, Z.; Viehe, H. G., In *Iminium Salts in Organic Chemistry, Part 1*; Böhme, H.; Viehe, H. G., Eds.; Wiley: New York, (1976); Vol. 9, p 343.
- [41] Viehe, H. G.; Janousek, Z., *Angew. Chem.*, (1971) **83**, 614; *Angew. Chem. Int. Ed. Engl.*, (1971) **10**, 573.
- [42] Guillot, N.; Marin, B.; Janousek, Z.; Viehe, H. G., *Synth. Commun.*, (1989) **19**, 2825.

- [43] Vilkas, M.; Qasmi, D., *Synth. Commun.*, (1990) **20**, 2769.
- [44] Kukhar', V. P.; Pasternak, V. I.; Povolotskii, M. I.; Pavlenko, N. G., *Zh. Org. Khim.*, (1974) **10**, 449; *J. Org. Chem. USSR (Engl. Transl.)*, (1974) **10**, 454.
- [45] McAdam, D. P.; Stick, R. V., *Aust. J. Chem.*, (1988) **41**, 563.
- [46] Drach, B. S.; Sinitsa, A. D., *Zh. Obshch. Khim.*, (1968) **38**, 1325; *J. Gen. Chem. USSR (Engl. Transl.)*, (1968) **38**, 1276.
- [47] Grohe, K.; Degener, E.; Holtschmidt, H.; Heitzer, H., *Justus Liebigs Ann. Chem.*, (1969) **730**, 133.
- [48] Reimlinger, H.; Billiau, F.; Merényi, R., *Chem. Ber.*, (1978) **111**, 1619.
- [49] Holtschmidt, H.; Degener, E.; Schmelzer, H.-G., *Justus Liebigs Ann. Chem.*, (1967) **701**, 107.
- [50] Holtschmidt, H., *Angew. Chem.*, (1962) **74**, 848; *Angew. Chem. Int. Ed. Engl.*, (1962) **1**, 632.
- [51] Holtschmidt, H.; Degener, E.; Schmelzer, H.-G.; Tarnow, H.; Zecher, W., *Angew. Chem.*, (1968) **80**, 942; *Angew. Chem. Int. Ed. Engl.*, (1968) **7**, 856.
- [52] Baldwin, J. E.; Patrick, J. E., *Chem. Commun.*, (1968), 968.
- [53] Szönyi, F.; Cambon, A., *Tetrahedron Lett.*, (1992) **33**, 2339.
- [54] Seyferth, D.; Damrauer, R.; Shih, H.; Tronich, W.; Smith, W. E.; Mui, J. Y.-P., *J. Org. Chem.*, (1971) **36**, 1786.
- [55] Wiberg, N.; Uhlenbrock, W., *Chem. Ber.*, (1971) **104**, 3989.
- [56] Sologub, L. S.; Kisilenko, A. A.; Kukhar, V. P.; Vdovenko, S. I., *Khim. Geterotsikl. Soedin.*, (1983), **19**, 798; *Chem. Heterocycl. Compd. (Engl. Transl.)*, (1983) **19**, 641.
- [57] Savchenko, T. I.; Kolesnikova, I. V.; Petrova, T. D.; Platonov, V. E., *J. Fluorine Chem.*, (1983) **22**, 439.
- [58] Lentz, D.; Graske, K.; Preugschat, D., *Chem. Ber.*, (1988) **121**, 1445.
- [59] Petrov, V. A., *J. Fluorine Chem.*, (2001) **109**, 123.
- [60] Petrov, K. A.; Neimysheva, A. A., *Zh. Obshch. Khim.*, (1959) **29**, 2695; *J. Gen. Chem. USSR (Engl. Transl.)*, (1959) **29**, 2662.
- [61] Lam, W. Y.; DesMarteau, D. D., *J. Fluorine Chem.*, (1981) **18**, 441.
- [62] Bürger, H.; Pawelke, G., *J. Chem. Soc., Chem. Commun.*, (1988), 105.
- [63] Barton, D. H. R.; Harris, R. L.; Hesse, R. H.; Pechet, M. M.; Urban, F. J., *J. Chem. Soc., Perkin Trans. 1*, (1974), 2344.
- [64] Krumm, B.; Vij, A.; Kirchmeier, R. J.; Shreeve, J. M.; Oberhammer, H., *Angew. Chem.*, (1995) **107**, 645; *Angew. Chem. Int. Ed. Engl.*, (1995) **34**, 586.
- [65] Klich, M.; Teutsch, G., *Tetrahedron*, (1986) **42**, 2677.
- [66] Houwing, H. A.; Van Leusen, A. M., *J. Heterocycl. Chem.*, (1981) **18**, 1127.
- [67] Baudler, M.; Simon, J., *Chem. Ber.*, (1987) **120**, 421.
- [68] Currie, K. S.; Tennant, G., *J. Chem. Soc., Chem. Commun.*, (1995), 2295.
- [69] Bergemann, M.; Neidlein, R., *Synthesis*, (1996), 975.
- [70] Ruppert, I., *Tetrahedron Lett.*, (1980) **21**, 4893.
- [71] Pawellek, D., *Angew. Chem.*, (1966) **78**, 908; *Angew. Chem. Int. Ed. Engl.*, (1966) **5**, 845.
- [72] Fuks, R.; Hartemink, M., *Tetrahedron*, (1973) **29**, 297.
- [73] Hagemann, D.; Alt, D.; Ugi, I., *Angew. Chem.*, (1969) **81**, 572; *Angew. Chem. Int. Ed. Engl.*, (1969) **8**, 606.
- [74] Beger, J.; Günther, K.; Vogel, J., *J. Prakt. Chem.*, (1969) **311**, 15.
- [75] Arlt, D., *Synthesis*, (1970), 20.
- [76] Klauke, E.; Kühle, E., DE 1 235 291, (1967); *Chem. Abstr.*, (1967) **67**, 2916.
- [77] Thrasher, J. S.; Nielsen, J. B.; Bott, S. G.; McClure, D. J.; Morris, S. A.; Atwood, J. L., *Inorg. Chem.*, (1988) **27**, 570.
- [78] Thrasher, J. S.; Seppelt, K., *Inorg. Chem.*, (1985) **24**, 4171.
- [79] Mitsch, R. A.; Ogden, P. H., *J. Org. Chem.*, (1966) **31**, 3833.
- [80] Cabiddu, S.; Gaudiano, G.; Quilico, A., *Gazz. Chim. Ital.*, (1962) **92**, 501.
- [81] Geevers, J.; Trompen, W. P., *Tetrahedron Lett.*, (1974), 1691.
- [82] Birckenbach, L.; Sennewald, K., *Justus Liebigs Ann. Chem.*, (1931) **489**, 7.
- [83] Prevezentseva, N. F.; Chelebov, F. N.; Kruglyak, Y. L.; Martynov, I. V., *Zh. Obshch. Khim.*, (1972) **42**, 305; *J. Gen. Chem. USSR (Engl. Transl.)*, (1972) **42**, 296.
- [84] Kühle, E.; Anders, B.; Klauke, E.; Tarnow, H.; Zumach, G., *Angew. Chem.*, (1969) **81**, 18; *Angew. Chem. Int. Ed. Engl.*, (1969) **8**, 20.
- [85] Baldwin, J. E.; Adlington, R. M.; O'Neil, I. A.; Russell, A. T.; Smith, M. L., *Chem. Commun. (Cambridge)*, (1996), 41.
- [86] Schmuck, A.; Seppelt, K., *Angew. Chem.*, (1987) **99**, 138; *Angew. Chem. Int. Ed. Engl.*, (1987) **26**, 134.
- [87] Kühle, E., In *Houben-Weyl*, (1983); Vol. E 4, p 522.

- [88] Petrova, T. D.; Kolesnikova, I. V.; Savchenko, T. I.; Platonov, V. E., *Zh. Org. Khim.*, (1984) **20**, 1197; *J. Org. Chem. USSR (Engl. Transl.)*, (1984) **20**, 1088.
- [89] Thrasher, J. S.; Clifford, A. F., *J. Fluorine Chem.*, (1982) **19**, 411.
- [90] Hegarty, A. F.; Dignam, K. J., *J. Chem. Soc., Perkin Trans. 2*, (1975), 1046.
- [91] Ried, W.; Merkel, W.; Schweitzer, R., *Chem. Ber.*, (1975) **108**, 2290.
- [92] Gontar, A. F.; Bykhovskaya, E. G.; Sizov, Y. A.; Knunyants, I. L., *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1976), 2381; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1976), 2224.
- [93] Andreev, V. G.; Kolomiets, A. F.; Sokolskii, G. A., *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1990), 1643; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1990), 1493.
- [94] Roesky, H. W., *Angew. Chem.*, (1969) **81**, 119; *Angew. Chem. Int. Ed. Engl.*, (1969) **8**, 136.
- [95] Olijnsma, T.; Engberts, J. B. F. N., *Synth. Commun.*, (1973) **3**, 1.
- [96] Grigat, E., *Angew. Chem.*, (1969) **81**, 623; *Angew. Chem. Int. Ed. Engl.*, (1969) **8**, 607.
- [97] Shevchenko, V. I.; Kulibaba, N. K.; Kirsanov, A. V., *Zh. Obshch. Khim.*, (1969) **39**, 1689; *J. Gen. Chem. USSR (Engl. Transl.)*, (1969) **39**, 1656.
- [98] Grigat, E., *Angew. Chem.*, (1972) **84**, 1008; *Angew. Chem. Int. Ed. Engl.*, (1972) **11**, 949.
- [99] Martin, D.; Weise, A., *Chem. Ber.*, (1967) **100**, 3736.
- [100] Neidlein, R.; Haussmann, W.; Heukelbach, E., *Chem. Ber.*, (1966) **99**, 1252.
- [101] Kim, S.; Cheong, J. H., *Chem. Commun. (Cambridge)*, (1998), 1143.
- [102] Makarov, S. P.; Englin, M. A.; Shpanskii, V. A.; Ermakova, I. V., *Zh. Obshch. Khim.*, (1969) **39**, 199; *J. Gen. Chem. USSR (Engl. Transl.)*, (1969), **39**, 183.
- [103] Gielow, P.; Haas, A., *Z. Anorg. Allg. Chem.*, (1972) **394**, 53.
- [104] Harley-Mason, J., *Nature*, (1945) **155**, 515.
- [105] Alimov, P. I.; Levkova, L. N., *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1964), 1889; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1964), 1793.
- [106] Acton, E. M.; Ryan, K. J., *J. Org. Chem.*, (1984) **49**, 528.
- [107] Petrova, T. D.; Platonov, V. E.; Shchegoleva, L. N.; Maksimov, A. M.; Haas, A.; Schelvis, M.; Lieb, M., *J. Fluorine Chem.*, (1996) **79**, 13.
- [108] Ottmann, G.; Hooks, H., *Angew. Chem.*, (1965) **77**, 427; *Angew. Chem. Int. Ed. Engl.*, (1965) **4**, 432.
- [109] Ottmann, G.; Hooks, H., *J. Org. Chem.*, (1966) **31**, 838.
- [110] Dahms, G.; Haas, A.; Klug, W., *Chem. Ber.*, (1971) **104**, 2732.
- [111] Neidlein, R.; Leinberger, P.; Gieren, A.; Dederer, B., *Chem. Ber.*, (1978) **111**, 698.
- [112] Appel, R.; Giesen, K., *Chem. Ber.*, (1976) **109**, 810.
- [113] Eilingsfeld, H.; Möbius, L., *Chem. Ber.*, (1965) **98**, 1293.
- [114] Neidlein, R.; Bottler, R., *Arch. Pharm. (Weinheim, Ger.)*, (1975) **308**, 379.
- [115] Bossio, R.; Marcaccini, S.; Pepino, R., *Heterocycles*, (1986) **24**, 2003.
- [116] Bossio, R.; Marcaccini, S.; Pepino, R., *Tetrahedron Lett.*, (1986) **27**, 4643.
- [117] Bossio, R.; Marcaccini, S.; Pepino, R., *Heterocycles*, (1986) **24**, 2411.
- [118] Bossio, R.; Marcaccini, S.; Pepino, R.; Torroba, T.; Valle, G., *Synthesis*, (1987), 1138.
- [119] Bossio, R.; Marcaccini, S.; Pepino, R.; Polo, C.; Valle, G., *Synthesis*, (1989), 641.
- [120] Morel, G.; Marchand, E.; Thi, K. H. N.; Foucaud, A., *Tetrahedron*, (1984) **40**, 1075.
- [121] Morel, G.; Marchand, E.; Foucaud, A., *J. Org. Chem.*, (1985) **50**, 771.
- [122] Morel, G.; Marchand, E.; Haquin, C.; Foucaud, A., *J. Org. Chem.*, (1986) **51**, 4043.
- [123] Morel, G.; Marchand, E.; Foucaud, A.; Toupet, L., *J. Org. Chem.*, (1989) **54**, 1185.
- [124] Morel, G.; Marchand, E.; Foucaud, A.; Toupet, L., *J. Org. Chem.*, (1990) **55**, 1721.
- [125] Havlik, A. J.; Wald, M. M., *J. Am. Chem. Soc.*, (1955) **77**, 5171.
- [126] Goerdeler, J.; Panshiri, F. M.; Vollrath, W., *Chem. Ber.*, (1975) **108**, 3071.
- [127] Wiberg, N.; Hübler, G., *Z. Naturforsch.*, B, (1977) **32**, 1003.
- [128] Bossio, R.; Marcaccini, S.; Paoli, P.; Pepino, R.; Polo, C., *Heterocycles*, (1990) **31**, 1855.
- [129] Liebscher, J.; Hartmann, H., *Tetrahedron Lett.*, (1975), 2977.
- [130] Kristinsson, H., *Tetrahedron Lett.*, (1973), 4489.
- [131] Vrijland, M. S. A., *Tetrahedron Lett.*, (1974), 837.
- [132] Berrée, F.; Malvaut, Y.; Marchand, E.; Morel, G., *J. Org. Chem.*, (1993) **58**, 6022.
- [133] Kantelehner, W., In *Iminium Salts in Organic Chemistry*; Böhme, H.; Viehe, H. G., Eds.; Wiley: New York, (1979); Vol. 2, p 173.
- [134] Berrée, F.; Marchand, E.; Morel, G., *Tetrahedron Lett.*, (1992) **33**, 6155.
- [135] Spitzner, R.; Andersch, J.; Schröth, W., *Liebigs Ann. Chem.*, (1989), 931.
- [136] Kühle, E.; Eue, L., GB 888 646, (1959); *Chem. Abstr.*, (1962) **57**, 13696.

- [137] Kolesnikova, I. V.; Petrova, T. D.; Platonov, V. E.; Mikhailov, V. A.; Popov, A. A.; Savelova, V. A., *J. Fluorine Chem.*, (1988) **40**, 217.
- [138] Knunyants, I. L.; Gontar, A. F.; Tilkunova, N. A.; Vinogradov, A. S.; Bihovskaja, E. G., *J. Fluorine Chem.*, (1980) **15**, 169.
- [139] Schroth, W.; Spitzner, R.; Andersch, J., DD 258 223, (1988); *Chem. Abstr.*, (1989) **110**, 134 895.
- [140] Quintela, J. M.; Moreira, M. J.; Peinador, C., *Tetrahedron*, (1996) **52**, 3037.
- [141] Himbert, G.; Schwickerath, W., *Liebigs Ann. Chem.*, (1982), 2105.
- [142] Van Broeck, D.; Janousek, Z.; Viehe, H. G., *Angew. Chem.*, (1979) **91**, 355; *Angew. Chem. Int. Ed. Engl.*, (1979) **18**, 333.
- [143] George, P.; Viehe, H. G., *Chimia*, (1975) **29**, 209.
- [144] Eilingsfeld, H.; Neubauer, G.; Seefelder, M.; Weidinger, H., *Chem. Ber.*, (1964) **97**, 1232.
- [145] Bock, G., *Chem. Ber.*, (1967) **100**, 2870.
- [146] Lwowski, W.; Kanemasa, S.; Murray, R. A.; Ramakrishnan, V. T.; Thiruvengadam, T. K.; Yoshida, K.; Subbaraj, A., *J. Org. Chem.*, (1986) **51**, 1719.
- [147] Zielinski, W.; Kudelko, A.; Holt, E. M., *Heterocycles*, (1998) **48**, 319.
- [148] Appel, R.; Ziehn, K.-D.; Warning, K., *Chem. Ber.*, (1973) **106**, 2093.
- [149] Appel, R.; Warning, K.; Ziehn, K.-D., *Chem. Ber.*, (1974) **107**, 698.
- [150] Ulrich, H.; Tilley, J. N.; Sayigh, A. A. R., *J. Org. Chem.*, (1964) **29**, 2401.
- [151] Roesky, H. W.; Tutkunkardes, S., *Z. Anorg. Allg. Chem.*, (1970) **374**, 147.
- [152] Ulrich, H.; Tucker, B.; Sayigh, A. A. R., *Tetrahedron*, (1966) **22**, 1565.
- [153] Hartke, K.; Palou, E., *Chem. Ber.*, (1966) **99**, 3155.
- [154] Brady, W. T.; Owens, R. A., *J. Org. Chem.*, (1977) **42**, 3220.
- [155] Brederick, K.; Richter, R., *Chem. Ber.*, (1966) **99**, 2454.
- [156] Ried, W.; Dietschmann, H.; Erle, H.-E., *Synthesis*, (1980), 619.
- [157] Ried, W.; Schöpke, K., *Liebigs Ann. Chem.*, (1986), 1997.
- [158] Schindler, N., *Chem. Ber.*, (1973) **106**, 56.
- [159] Kosinskaya, I. M.; Pisanenko, N. P.; Shevchenko, V. I., *Zh. Obshch. Khim.*, (1974) **44**, 1264; *J. Gen. Chem. USSR (Engl. Transl.)*, (1974) **44**, 1242.
- [160] Shevchenko, V. I.; Pisanenko, N. P.; Kosinskaya, I. M., *Zh. Obshch. Khim.*, (1978) **48**, 1179; *J. Gen. Chem. USSR (Engl. Transl.)*, (1978) **48**, 1078.
- [161] Katritzky, A. R.; Rogovoy, B.; Klein, C.; Insuasty, H.; Vvedensky, V.; Insuasty, B., *J. Org. Chem.*, (2001) **66**, 2854.
- [162] Schnell, M.; Gross, H.; Costisella, B., *Z. Chem.*, (1989) **29**, 405.
- [163] Hund, H.; Rosenthaler, G. V., *Phosphorus, Sulfur Silicon Relat. Elem.*, (1993) **75**, 209.
- [164] Sokolov, M. P.; Mavrin, G. V.; Gazizov, I. G.; Ivanova, V. N.; Zyblikova, T. A., *Zh. Obshch. Khim.*, (1989) **59**, 53; *J. Gen. Chem. USSR (Engl. Transl.)*, (1989) **59**, 45.
- [165] Buzykin, B. I.; Sokolov, M. P.; Ivanova, V. N., *Zh. Obshch. Khim.*, (1989) **59**, 714; *J. Gen. Chem. USSR (Engl. Transl.)*, (1989) **59**, 631.
- [166] Buzykin, B. I.; Sokolov, M. P.; Pavlov, V. A.; Ivanova, V. N.; Chertanova, L. F.; Zyblikova, T. A., *Zh. Obshch. Khim.*, (1990) **60**, 546; *J. Gen. Chem. USSR (Engl. Transl.)*, (1990) **60**, 475.
- [167] Sokolov, M. P.; Buzykin, B. I.; Mavrin, G. V., *Zh. Obshch. Khim.*, (1990) **60**, 1986; *J. Gen. Chem. USSR (Engl. Transl.)*, (1990) **60**, 1773.
- [168] Buzykin, B. I.; Sokolov, M. P., *Zh. Obshch. Khim.*, (1990) **60**, 1980; *J. Gen. Chem. USSR (Engl. Transl.)*, (1990) **60**, 1767.
- [169] Sokolov, M. P.; Buzykin, B. I.; Pavlov, V. A., *Zh. Obshch. Khim.*, (1990) **60**, 223; *J. Gen. Chem. USSR (Engl. Transl.)*, (1990) **60**, 195.
- [170] Pavlov, V. A.; Aristova, N. V.; Moskva, V. V.; Makhayeva, G. F.; Yankovskaya, V. L.; Malygin, V. V., *Khim.-Farm. Zh.*, (1991) **25**, 31; *Pharm. Chem. J. (Engl. Transl.)*, (1991) **4**, 255.
- [171] Shagidullin, R. R.; Pavlov, V. A.; Buzykin, B. I.; Aristova, N. V.; Chertanova, L. F.; Vandyukova, I. I.; Plyamovatyi, A. K.; Enikeev, K. M.; Sokolov, M. P.; Moskva, V. V., *Zh. Obshch. Khim.*, (1991) **61**, 1590; *J. Gen. Chem. USSR (Engl. Transl.)*, (1991) **61**, 1459.
- [172] Buzykin, B. I.; Sokolov, M. P., *Zh. Obshch. Khim.*, (1992) **62**, 2266; *J. Gen. Chem. USSR (Engl. Transl.)*, (1992) **62**, 1868.
- [173] Doroshenko, V. A.; Stukalo, V. A.; Shokol, V. A.; Kozhushko, B. N., *Zh. Obshch. Khim.*, (1971) **41**, 2155; *J. Gen. Chem. USSR (Engl. Transl.)*, (1971) **41**, 2180.
- [174] Silina, E. B.; Kozhushko, B. N.; Shokol, V. A., *Zh. Obshch. Khim.*, (1989) **59**, 571; *J. Gen. Chem. USSR (Engl. Transl.)*, (1989) **59**, 505.
- [175] Stevens, T. E., *J. Org. Chem.*, (1961) **26**, 3451.

- [176] Patel, N. R.; Kirchmeier, R. L.; Shreeve, J. M., *J. Fluorine Chem.*, (1990) **48**, 395.
- [177] Zheng, Y. Y.; John, E. O.; Kirchmeier, R. L.; Shreeve, J. M., *J. Fluorine Chem.*, (1992) **57**, 293.
- [178] Guirado, A.; Zapata, A.; Galvez, J., *Tetrahedron Lett.*, (1994) **35**, 2365.
- [179] Guirado, A.; Zapata, A.; Jones, P. G., *Tetrahedron*, (1995) **51**, 3641.
- [180] Buschauer, A., *Arch. Pharm. (Weinheim, Ger.)*, (1987) **320**, 377.
- [181] Würthwein, E. U.; Kupfer, R.; Meier, S.; Krestel, M.; Allmann, R., *Chem. Ber.*, (1988) **121**, 991.
- [182] Dergach, G. I.; Samarai, L. I., *Zh. Obshch. Khim.*, (1964) **34**, 1161; *J. Gen. Chem. USSR (Engl. Transl.)*, (1964) **34**, 1152.
- [183] Neidlein, R.; Haussmann, W., *Arch. Pharm. (Weinheim, Ger.)*, (1967) **300**, 553.
- [184] Hoppe, D.; Beckmann, L., *Liebigs Ann. Chem.*, (1980), 1751.
- [185] Schaumann, E.; Dietz, J.; Kausch, E.; Schmerse, G. C., *Chem. Ber.*, (1987) **120**, 339.
- [186] Kantlehner, W.; Maier, T.; Löffler, W.; Kapassakalidis, J. J., *Liebigs Ann. Chem.*, (1982), 507.
- [187] Webb, R. L.; Labaw, C. S., *J. Heterocycl. Chem.*, (1982) **19**, 1205.
- [188] Haake, M.; Schümmelfeder, B., *Synthesis*, (1991), 753.
- [189] Krestel, M.; Kupfer, R.; Allmann, R.; Würthwein, E. U., *Chem. Ber.*, (1987) **120**, 1271.
- [190] Kupfer, R.; Meier, S.; Würthwein, E. U., *Chem. Ber.*, (1992) **125**, 2487.
- [191] Lopyrev, V. A.; Kurochkin, V. N.; Titova, I. A.; Voronkov, M. G., *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1989), 2363; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1989), 2174.
- [192] Martin, D.; Mücke, W., *Chem. Ber.*, (1965) **98**, 2059.
- [193] Martin, D.; Rackow, S., *Chem. Ber.*, (1965) **98**, 3662.
- [194] Houben, J.; Zivadinovitsch, E., *Ber. Dtsch. Chem. Ges.*, (1936) **69**, 2352.
- [195] Martin, D.; Berger, A.; Niclas, H.-J., *J. Prakt. Chem.*, (1973) **315**, 289.
- [196] Kupfer, R.; Würthwein, E. U.; Krestel, M.; Allmann, R., *Chem. Ber.*, (1986) **119**, 3236.
- [197] Meese, C. O.; Walter, W., *Chem. Ber.*, (1976) **109**, 3129.
- [198] Dergach, G. I.; Liptuga, N. I., *Zh. Obshch. Khim.*, (1968) **38**, 1779; *J. Gen. Chem. USSR (Engl. Transl.)*, (1968) **38**, 1734.
- [199] Michael, J. D.; Ross, B. C.; Rees, P. M., *Tetrahedron Lett.*, (1985) **26**, 4149.
- [200] Michael, J. D., *Synthesis*, (1987), 170.
- [201] Schmidpeter, A.; Zeiss, W., *Chem. Ber.*, (1971) **104**, 1199.
- [202] Étlis, V. S.; Sineokov, A. P.; Razuvaev, G. A., *Zh. Obshch. Khim.*, (1964) **34**, 4090; *J. Gen. Chem. USSR (Engl. Transl.)*, (1964) **34**, 4149.
- [203] Burkhardt, J.; Feinauer, R.; Gulbins, E.; Hamann, K., *Chem. Ber.*, (1966) **99**, 1912.
- [204] Copeland, C.; Stick, R. V., *Aust. J. Chem.*, (1984) **37**, 1483.
- [205] Beger, J., *J. Prakt. Chem.*, (1969) **311**, 549.
- [206] Hans, M.; Dehne, H.; Hartwig, R., *Z. Chem.*, (1986) **26**, 204.
- [207] Donovan, J.; Cronin, J. A.; Scott, F. L.; Hegarty, A. F., *J. Chem. Soc., Perkin Trans. 2*, (1972), 1050.
- [208] Hassaneen, H. M.; Abdelhamid, A. O.; Fahmi, A. A.; Shawali, A. S., *J. Heterocycl. Chem.*, (1985) **22**, 395.
- [209] Diekmann, J., *J. Org. Chem.*, (1965) **30**, 2272.
- [210] Grigat, E.; Pütter, R., *Chem. Ber.*, (1964) **97**, 3022.
- [211] Jensen, K. A.; Due, M.; Holm, A.; Wentrup, C., *Acta Chem. Scand.*, (1966) **20**, 2091.
- [212] Tanaka, K., *Bull. Chem. Soc. Jpn.*, (1972) **45**, 834.
- [213] Kulka, M., *Can. J. Chem.*, (1981) **59**, 1557.
- [214] Atkins, P. R.; Glue, S. E. J.; Kay, I. T., *J. Chem. Soc., Perkin Trans. 1*, (1973), 2644.
- [215] Gompper, R.; Hägele, W., *Chem. Ber.*, (1966) **99**, 2885.
- [216] Rüfenacht, K., *Helv. Chim. Acta*, (1974) **57**, 23.
- [217] Selby, T. P.; Lepone, G. E., *J. Heterocycl. Chem.*, (1984) **21**, 61.
- [218] Chen, L.; Thompson, T. R.; Hammer, R. P.; Barany, G., *J. Org. Chem.*, (1996) **61**, 6639.
- [219] Walter, W.; Ruback, W., *Liebigs Ann. Chem.*, (1982), 231.
- [220] Hlawatschek, H.; Gattow, G., *Z. Anorg. Allg. Chem.*, (1983) **501**, 176.
- [221] Hlawatschek, H.; Gattow, G., *Z. Anorg. Allg. Chem.*, (1983) **501**, 169.
- [222] Oba, M.; Yoshihara, M.; Nagatsuka, J.; Nishiyama, K., *Heterocycles*, (1997) **45**, 1913.
- [223] Bernat, J.; Kristian, P.; Imrich, J.; Mazagova, D.; Cernak, J.; Busova, T.; Lipkowski, J., *Synth. Commun.*, (1995) **25**, 3973.
- [224] Krapivin, G. D.; Jurašek, A.; Kovac, J.; Kulnevich, V. G., *Coll. Czech. Chem. Commun.*, (1984) **49**, 2285.
- [225] Shachat, N.; Bagnell, J. J., Jr., *J. Org. Chem.*, (1963) **28**, 991.
- [226] Sakai, S.; Niimi, H.; Kobayashi, Y.; Ishii, Y., *Bull. Chem. Soc. Jpn.*, (1977) **50**, 3271.

- [227] Fest, C., DE 3 841 185, (1990); *Chem. Abstr.*, (1990) **113**, 190 956.
- [228] Maeda, H.; Kambe, N.; Sonoda, N.; Fujiwara, S.; Shin-Ike, T., *Tetrahedron*, (1996) **52**, 12 165.
- [229] Le Maréchal, A. M.; Robert, A.; Leban, I., *J. Chem. Soc., Perkin Trans. 1*, (1993), 351.
- [230] Weber, M.; Hartmann, H., *Z. Chem.*, (1987) **27**, 95.
- [231] Bakibaev, A. A.; Shtrykova, V. V., *Russ. Chem. Rev. (Engl. Transl.)*, (1995) **64**, 929.
- [232] Neidlein, R.; Krull, H., *Arch. Pharm. (Weinheim, Ger.)*, (1971) **304**, 763.
- [233] Fukada, N.; Hayashi, M.; Suzuki, Y., *Bull. Chem. Soc. Jpn.*, (1985) **58**, 3379.
- [234] Dergach, G. I.; Narbut, A. V.; Kirsanov, A. V., *Zh. Obshch. Khim.*, (1963) **33**, 3062; *J. Gen. Chem. USSR (Engl. Transl.)*, (1963) **33**, 2988.
- [235] Kosinskaya, I. M.; Pisanenko, N. P.; Shevchenko, V. I., *Zh. Obshch. Khim.*, (1976) **46**, 47; *J. Gen. Chem. USSR (Engl. Transl.)*, (1976) **46**, 47.
- [236] Prietzel, H., DE 1 948 370, (1971); *Chem. Abstr.* (1971) **74**, 124 906.
- [237] Zmitek, J.; Jenko, B.; Milivojevic, D.; Anzel, J., *Org. Prep. Proced. Int.*, (1991) **23**, 721.
- [238] Garratt, P. J.; Hobbs, C. J.; Wrigglesworth, R., *J. Org. Chem.*, (1989) **54**, 1062.
- [239] Bertinaria, M.; Sorba, G.; Medana, C.; Cena, C.; Adami, M.; Morini, G.; Pozzoli, C.; Coruzzi, G.; Gasco, A., *Helv. Chim. Acta*, (2000) **83**, 287.
- [240] Buschauer, A., *Arzneim.-Forsch.*, (1987) **37**, 1003.
- [241] Meyer, R. F., *J. Org. Chem.*, (1963) **28**, 2902.
- [242] Däbritz, E., *Angew. Chem.*, (1966) **78**, 483; *Angew. Chem. Int. Ed. Engl.*, (1966) **5**, 470.
- [243] Schmidt, E.; Moosmüller, F., *Justus Liebigs Ann. Chem.*, (1956) **597**, 235.
- [244] Schmidt, E.; Däbritz, E.; Thulke, K.; Grassmann, E., *Justus Liebigs Ann. Chem.*, (1965) **685**, 161.
- [245] Jaeger, R., *Synthesis*, (1991), 465.
- [246] Rink, H.; Riniker, B., *Helv. Chim. Acta*, (1974) **57**, 831.
- [247] Goerdeler, J.; Raddatz, S., *Chem. Ber.*, (1980) **113**, 1095.
- [248] Forman, S. E.; Erickson, C. A.; Adelman, H., *J. Org. Chem.*, (1963) **28**, 2653.
- [249] Donetti, A.; Bellova, E., *J. Org. Chem.*, (1972) **37**, 3352.
- [250] Giuliano, R. M.; Duong, T. T.; Deisenroth, T. W.; McMahon, W. G.; Boyko, W. J., *Synthesis*, (1991), 86.
- [251] Moss, R. A.; Wilk, B. K.; Hadel, L. M., *Tetrahedron Lett.*, (1987) **28**, 1969.
- [252] Moss, R. A.; Kim, H. R., *Tetrahedron Lett.*, (1990) **31**, 4715.
- [253] Moss, R. A.; Johnson, L. A.; Merrer, D. C.; Lee, G. E., *J. Am. Chem. Soc.*, (1999) **121**, 5940.
- [254] Grigat, E.; Pütter, R., *Chem. Ber.*, (1964) **97**, 3027.
- [255] Moss, R. A.; Perez, L. A.; Wlostowska, J.; Guo, W.; Krogh-Jespersen, K., *J. Org. Chem.*, (1982) **47**, 4177.
- [256] Janus, J. W., *J. Chem. Soc.*, (1955), 3551.
- [257] Meerwein, H.; Florian, W.; Schön, N.; Stopp, G., *Justus Liebigs Ann. Chem.*, (1961) **641**, 1.
- [258] Mathias, L. J., *Synthesis*, (1979), 561.
- [259] Romanenko, V. D.; Volkov, G. I.; Markovskii, L. N., *Zh. Obshch. Khim.*, (1982) **52**, 926; *J. Gen. Chem. USSR (Engl. Transl.)*, (1982) **52**, 808.
- [260] Fuchs, E.; Breit, B.; Bergsträsser, U.; Hoffmann, J.; Heydt, H.; Regitz, M., *Synthesis*, (1991), 1099.
- [261] Sokolov, M. P.; Buzynkin, B. I.; Molodykh, Z. V., *Zh. Obshch. Khim.*, (1990) **60**, 222; *J. Gen. Chem. USSR (Engl. Transl.)*, (1990) **60**, 194.
- [262] Batyeva, É. S.; Girfanova, Y. N.; Zamaletdinova, G. U.; Pudovik, A. N., *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1976), 455; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1976), 440.
- [263] Well, M.; Schmutzler, R., *Phosphorus, Sulfur Silicon Relat. Elem.*, (1990) **54**, 151.
- [264] Beak, P.; Yamamoto, J.; Upton, C. J., *J. Org. Chem.*, (1975) **40**, 3052.
- [265] Kim, S.; Yoon, J. Y., *J. Am. Chem. Soc.*, (1997) **119**, 5982.
- [266] Sasse, K., DE 1 252 656, (1965); *Chem. Abstr.*, (1968) **68**, 104 748.
- [267] Bittner, S.; Moradpour, A.; Krief, P., *Synthesis*, (1989), 132.
- [268] Garin, J.; Melendez, E.; Merchán, F. L.; Tejel, C.; Tejero, T., *Synthesis*, (1983), 375.
- [269] Gattow, G.; Klaeser, K., *Z. Anorg. Allg. Chem.*, (1977) **434**, 115.
- [270] Shimada, K.; Fujisaki, H.; Oketani, K.; Murakami, M.; Shoji, T.; Wakabayashi, T.; Ueda, K.; Ema, K.; Hashimoto, K.; Tanaka, S., *Chem. Pharm. Bull.*, (1984) **32**, 4893.
- [271] Sato, M.; Fukada, N.; Kurauchi, M.; Takeshima, T., *Synthesis*, (1981), 554.
- [272] Maybhate, S. P.; Rajamohanam, P. P.; Rajappa, S., *Synthesis*, (1991), 220.
- [273] Gante, J.; Mohr, G., *Z. Naturforsch., B*, (1970) **25**, 655.
- [274] Cousins, S. J.; Ross, B. C.; Maw, G. N.; Michael, J. D., *Tetrahedron Lett.*, (1985) **26**, 1105.
- [275] Shafiee, A.; Vosooghi, M.; Asgharian, R., *J. Heterocycl. Chem.*, (1980) **17**, 117.

- [276] Spies, H.; Gewald, K.; Mayer, R., *J. Prakt. Chem.*, (1971) **313**, 804.
- [277] Laishiev, V. Z.; Petrov, M. L.; Petrov, A. A., *Zh. Org. Khim.*, (1982) **18**, 514; *J. Org. Chem. USSR (Engl. Transl.)*, (1982) **18**, 450.
- [278] Shafiee, A.; Fanaii, G., *Synthesis*, (1984), 512.
- [279] Zmitrovich, N. I.; Petrov, M. L.; Petrov, A. A., *Zh. Org. Khim.*, (1991) **27**, 1394; *J. Org. Chem. USSR (Engl. Transl.)*, (1991) **27**, 1219.
- [280] Zmitrovich, N. I.; Petrov, M. L., *Zh. Org. Khim.*, (1996) **32**, 1870; *Russ. J. Org. Chem. (Engl. Transl.)*, (1996) **32**, 1812.
- [281] Neidlein, R.; Klotz, U. J., *Monatsh. Chem.*, (1985) **116**, 651.
- [282] Hans, M.; Gulube, A.; Dehne, H., *J. Prakt. Chem.*, (1991) **333**, 187.
- [283] Neidlein, R.; Haussmann, W., *Tetrahedron Lett.*, (1966), 5401.
- [284] Tanaka, T.; Azuma, T.; Fang, X.; Uchida, S.; Iwata, C.; Ishida, T.; In, Y.; Maezaki, N., *Synlett*, (2000), 33.
- [285] Kleschick, W. A.; Dunbar, J. E.; Snider, S. W.; Vinogradoff, A. P., *J. Org. Chem.*, (1988) **53**, 3120.
- [286] Gante, J., *Angew. Chem.*, (1967) **79**, 858; *Angew. Chem. Int. Ed. Engl.*, (1967) **6**, 862.
- [287] Fukada, N.; Takano, M.; Nakai, K.; Kuboike, S.; Takeda, Y., *Bull. Chem. Soc. Jpn.*, (1993) **66**, 148.
- [288] Neidlein, R.; Askani, U., *Arch. Pharm. (Weinheim, Ger.)*, (1977) **310**, 820.
- [289] Metzger, C.; Wegler, R., *Chem. Ber.*, (1968) **101**, 1131.
- [290] Kurzer, F.; Sanderson, P. M., *J. Chem. Soc.*, (1962), 230.
- [291] Burdon, M. G.; Moffatt, J. G., *J. Am. Chem. Soc.*, (1966) **88**, 5855.
- [292] Goerdeler, J.; Lohmann, H., *Chem. Ber.*, (1977) **110**, 2996.
- [293] Fuchs, J. J., US 3 882 160, (1972); *Chem. Abstr.*, (1976) **84**, 16858.
- [294] Vowinkel, E.; Claussen, G., *Chem. Ber.*, (1974) **107**, 898.
- [295] Schlack, P.; Keil, G., *Justus Liebigs Ann. Chem.*, (1963) **661**, 164.
- [296] Tam, S. Y.-K.; Klein, R. S.; Wempen, I.; Fox, J. J., *J. Org. Chem.*, (1979) **44**, 4547.
- [297] Pratt, R. F.; Bruice, T. C., *J. Am. Chem. Soc.*, (1972) **94**, 2823.
- [298] Kopylova, B. V.; Khasanova, M. N., *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1971), 1809; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1971), 1701.
- [299] Oba, M.; Yoshihara, M.; Nishiyama, K., *Heterocycles*, (1997) **45**, 1405.
- [300] Hartke, K.; Salamon, G., *Chem. Ber.*, (1970) **103**, 133.
- [301] Ried, W.; Möisinger, O., *Chem. Ber.*, (1978) **111**, 143.
- [302] Ried, W.; Möisinger, O., *Chem. Ber.*, (1978) **111**, 155.
- [303] Iwakawa, T.; Tamura, H.; Sato, T.; Hayase, Y., *Chem. Pharm. Bull.*, (1988) **36**, 4755.
- [304] Toyooka, K.; Kubota, S., *Chem. Pharm. Bull.*, (1988) **36**, 96.
- [305] Davidson, J. S., *Chem. Ind. (London)*, (1972), 464.
- [306] Schmidpeter, A.; Willhalm, A., *Angew. Chem.*, (1984) **96**, 901; *Angew. Chem. Int. Ed. Engl.*, (1984) **23**, 903.
- [307] Dimroth, K.; Hoffmann, P., *Angew. Chem.*, (1964) **76**, 433; *Angew. Chem. Int. Ed. Engl.*, (1964) **3**, 384.
- [308] Dimroth, K.; Hoffmann, P., *Chem. Ber.*, (1966) **99**, 1325.
- [309] Buzykin, B. I.; Sokolov, M. P.; Chertanova, L. F., *Zh. Obshch. Khim.*, (1990) **60**, 2703; *J. Gen. Chem. USSR (Engl. Transl.)*, (1990) **60**, 2422.
- [310] Antoniadis, A.; Bruns, A.; Kunze, U., *Phosphorus Sulfur Relat. Elem.*, (1983) **15**, 317.
- [311] Kunze, U.; Bruns, A.; Hiller, W.; Mohyla, J., *Chem. Ber.*, (1985) **118**, 227.
- [312] Akiba, K.; Yoneyama, T.; Hamada, H.; Inamoto, N., *Bull. Chem. Soc. Jpn.*, (1976) **49**, 1970.
- [313] Gololobov, Y. G.; Galkina, M. A.; Dovgan, O. V.; Krasnova, I. Y.; Petrovskii, P. V.; Antipin, M. Y.; Voronov, I. L.; Lyssenko, K. A.; Schmutzler, R., *Russ. Chem. Bull.*, (2001) **50**, 279.
- [314] Tashma, Z., *J. Org. Chem.*, (1983) **48**, 3966.
- [315] Issleib, K.; Harzfeld, G., *Chem. Ber.*, (1964) **97**, 3430.
- [316] Jensen, K. A.; Henriksen, L., *Acta Chem. Scand.*, (1970) **24**, 3213.
- [317] Wudl, F.; Nalewajek, D., *J. Chem. Soc., Chem. Commun.*, (1980), 866.
- [318] Tanaka, K.; Tanaka, T., *Bull. Chem. Soc. Jpn.*, (1972) **45**, 489.
- [319] Zmitrovich, N. I.; Petrov, M. L.; Petrov, A. A., *Zh. Org. Khim.*, (1990) **26**, 179; *J. Org. Chem. USSR (Engl. Transl.)*, (1990) **26**, 157.
- [320] Chesney, A.; Bryce, M. R.; Yoshida, S.; Perepichka, I. F., *Chem.-Eur. J.*, (2000) **6**, 1153.
- [321] Pavlova, L. V.; Rachinskii, F. Y., *Zh. Obshch. Khim.*, (1965) **35**, 493; *J. Gen. Chem. USSR (Engl. Transl.)*, (1965) **35**, 492.
- [322] Chu, S.-H.; Mautner, H. G., *J. Org. Chem.*, (1962) **27**, 2899.

- [323] Senning, A.; Sørensen, O. N., *Acta Chem. Scand.*, (1966) **20**, 1445.
- [324] Nesynov, E. P.; Aldokhina, T. F., *Zh. Obshch. Khim.*, (1976) **46**, 1098; *J. Gen. Chem. USSR (Engl. Transl.)*, (1976) **46**, 1090.
- [325] Warner, J. S.; Page, T. F., *J. Org. Chem.*, (1966) **31**, 606.
- [326] Koketsu, M.; Nada, F.; Ishihara, H., *Synthesis*, (2002), 195.
- [327] Klayman, D. L., *J. Org. Chem.*, (1965) **30**, 2454.
- [328] Romanenko, V. D.; Sanchez, M.; Lamande, L., In *Comprehensive Organic Functional Group Transformations*, Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds.; Pergamon, Oxford, (1995); Vol. 6, p 677.
- [329] Grobe, J.; Hegemann, M.; Le Van, D., *Z. Naturforsch., B*, (1990) **45**, 148.
- [330] Grobe, J.; Le Van, D., *Angew. Chem.*, (1984) **96**, 716; *Angew. Chem. Int. Ed. Engl.*, (1984) **23**, 710.
- [331] Appel, R.; Casser, C.; Immenkeppel, M., *Tetrahedron Lett.*, (1985) **26**, 3551.
- [332] Goede, S. J.; Dam, M. A.; Bickelhaupt, F., *Recl. Trav. Chim. Pays-Bas*, (1994) **113**, 278.
- [333] Marchenko, A. P.; Koidan, G. N.; Baram, G. O.; Chernega, A. N.; Pinchuk, A. M.; Romanenko, E. A., *Zh. Obshch. Khim.*, (1994) **64**, 913; *Russ. J. Gen. Chem. (Engl. Transl.)*, (1994) **64**, 821.
- [334] Appel, R.; Immenkeppel, M., *Z. Anorg. Allg. Chem.*, (1987) **553**, 7.
- [335] Goede, S. J.; Bickelhaupt, F., *Chem. Ber.*, (1991) **124**, 2677.
- [336] Goede, S. J.; van Schaik, H. P.; Bickelhaupt, F.; Kooijman, H.; Spek, A. L., *Organometallics*, (1992) **11**, 3844.
- [337] Dillon, K. B.; Goodwin, H. P., *J. Organomet. Chem.*, (1994) **469**, 125.
- [338] Baudler, M.; Simon, J., *Chem. Ber.*, (1988) **121**, 281.
- [339] Rigon, L.; Ranaivonjatovo, H.; Escudie, J., *Phosphorus, Sulfur Silicon Relat. Elem.*, (1999) **152**, 153.
- [340] Marchenko, A. P.; Koidan, G. N.; Oleinik, V. A.; Pinchuk, A. M., *Zh. Obshch. Khim.*, (1988) **58**, 1923; *J. Gen. Chem. USSR (Engl. Transl.)*, (1988) **58**, 1717.
- [341] Koidan, G. N.; Oleinik, V. A.; Marchenko, A. P.; Pinchuk, A. M., *Zh. Obshch. Khim.*, (1989) **59**, 1198; *J. Gen. Chem. USSR (Engl. Transl.)*, (1989) **59**, 1061.
- [342] Niecke, E.; Guth, W.; Lysek, M., *Z. Naturforsch., B*, (1985) **40**, 331.
- [343] Prishchenko, A. A.; Gromov, A. V.; Luzikov, Y. N.; Borisenko, A. A.; Lazhko, E. I.; Klaus, K.; Lutsenko, I. F., *Zh. Obshch. Khim.*, (1984) **54**, 1520; *J. Gen. Chem. USSR (Engl. Transl.)*, (1984) **54**, 1354.
- [344] Koidan, G. N.; Oleinik, V. A.; Marchenko, A. P.; Pinchuk, A. M., *Zh. Obshch. Khim.*, (1989) **59**, 1902; *J. Gen. Chem. USSR (Engl. Transl.)*, (1989) **59**, 1700.
- [345] Prishchenko, A. A.; Lutsenko, I. F., *Zh. Obshch. Khim.*, (1981) **51**, 2630; *J. Gen. Chem. USSR (Engl. Transl.)*, (1981) **51**, 2268.
- [346] Marchenko, A. P.; Koidan, G. N.; Baram, G. O.; Oleinik, V. A.; Pinchuk, A. M., *Zh. Obshch. Khim.*, (1992) **62**, 948; *J. Gen. Chem. USSR (Engl. Transl.)*, (1992) **62**, 778.
- [347] Etemad-Moghadam, G.; Bellan, J.; Tachon, C.; Koenig, M., *Tetrahedron*, (1987) **43**, 1793.
- [348] Yoshifuji, M.; Sasaki, S.; Inamoto, N., *Tetrahedron Lett.*, (1989) **30**, 839.
- [349] VanderSluis, M.; Bickelhaupt, F.; Veldman, N.; Kooijman, H.; Spek, A. L.; Eisefeld, W.; Regitz, M., *Chem. Ber.*, (1995) **128**, 465.
- [350] VanderSluis, M.; Wit, J. B. M.; Bickelhaupt, F., *Phosphorus, Sulfur Silicon Relat. Elem.*, (1996) **110**, 585.
- [351] Yoshifuji, M.; Ito, S.; Toyota, K.; Yasunami, M., *Bull. Chem. Soc. Jpn.*, (1995) **68**, 1206.
- [352] Ito, S.; Toyota, K.; Yoshifuji, M., *J. Organomet. Chem.*, (1998) **553**, 135.
- [353] Grobe, J.; Le Van, D.; Broschk, B.; Hegemann, M.; Lüth, B.; Becker, G.; Böhringer, M.; Würthwein, E.-U., *J. Organomet. Chem.*, (1997) **529**, 177.
- [354] Grobe, J.; Le Van, D.; Althoff, U.; Lange, G., *Chem. Ber.*, (1992) **125**, 567.
- [355] Ito, S.; Yoshifuji, M., *Chem. Lett.*, (1998), 651.
- [356] Ito, S.; Yoshifuji, M., *Chem. Lett.*, (2000), 1390.
- [357] Grobe, J.; Le Van, D.; Luth, B.; Hegemann, M., *Chem. Ber.*, (1990) **123**, 2317.
- [358] Grobe, J.; Le Van, D.; Nientiedt, J., *Z. Naturforsch., B*, (1986) **41**, 149.
- [359] Grobe, J.; Le Van, D.; Nientiedt, J.; Krebs, B.; Dartmann, M., *Chem. Ber.*, (1988) **121**, 655.
- [360] Grobe, J.; Le Van, D.; Lange, G., *Z. Naturforsch., B*, (1993) **48**, 58.
- [361] Grobe, J.; Le Van, D.; Winnemoller, J.; Krebs, B.; Lage, M., *Z. Naturforsch., B*, (1996) **51**, 778.
- [362] Ito, S.; Yoshifuji, M., *Chem. Commun. (Cambridge)*, (2001), 1208.
- [363] Gouygou, M.; Tachon, C.; Koenig, M.; Dubourg, A.; Declercq, J. P.; Jaud, J.; Etemad-Moghadam, G., *J. Org. Chem.*, (1990) **55**, 5750.
- [364] Appel, R.; Laubach, B.; Siray, M., *Tetrahedron Lett.*, (1984) **25**, 4447.

- [365] Wegmann, T.; Hafner, M.; Regitz, M., *Chem. Ber.*, (1993) **126**, 2525.
- [366] Sinitsa, A. D.; Parkhomenko, N. A.; Povolotskii, M. I.; Markovskii, L. N., *Zh. Obshch. Khim.*, (1984) **54**, 715; *J. Gen. Chem. USSR (Engl. Transl.)*, (1984) **54**, 633.
- [367] Appel, R.; Barth, V., *Angew. Chem.*, (1979) **91**, 497; *Angew. Chem. Int. Ed. Engl.*, (1979) **18**, 469.
- [368] Appel, R.; Paulen, W., *Chem. Ber.*, (1983) **116**, 109.
- [369] Yoshifuji, M.; Toyota, K.; Inamoto, N., *J. Chem. Soc., Chem. Commun.*, (1984), 689.
- [370] Appel, R.; Folling, P.; Schuhn, W.; Knoch, F., *Tetrahedron Lett.*, (1986) **27**, 1661.
- [371] Appel, R.; Niemann, B.; Schuhn, W.; Knoch, F., *Angew. Chem.*, (1986) **98**, 934; *Angew. Chem. Int. Ed. Engl.*, (1986) **25**, 932.
- [372] Appel, R.; Folling, P.; Krieger, L.; Siray, M.; Knoch, F., *Angew. Chem.*, (1984) **23**, 970; *Angew. Chem. Int. Ed. Engl.*, (1984) **23**, 970.
- [373] Kukhar', V. P.; Shevchenko, I. V.; Kolodyazhnyi, O. I., *Zh. Obshch. Khim.*, (1985) **55**, 264; *J. Gen. Chem. USSR (Engl. Transl.)*, (1985) **55**, 230.
- [374] Kolodyazhnyi, O. I.; Shevchenko, I. V.; Kukhar, V. P., *Zh. Obshch. Khim.*, (1985) **55**, 1862; *J. Gen. Chem. USSR (Engl. Transl.)*, (1985) **55**, 1655.
- [375] Kolodyazhnyi, O. I.; Shevchenko, I. V.; Povolotskii, M. I.; Boldeskul, I. E.; Kukhar', V. P., *Zh. Obshch. Khim.*, (1985) **55**, 2797; *J. Gen. Chem. USSR (Engl. Transl.)*, (1985) **55**, 2489.
- [376] Romanenko, V. D.; Polyachenko, L. K.; Markovskii, L. N., *Zh. Obshch. Khim.*, (1984) **54**, 965; *J. Gen. Chem. USSR (Engl. Transl.)*, (1984) **54**, 860.

Product Class 13: Guanidine Derivatives

R. G. S. Berlinck, M. H. Kossuga, and A. M. Nascimento

General Introduction

Guanidine and guanidine derivatives are among the strongest organic bases known (pK_a of conjugate acids ~ 12.5), owing to resonance or “Y” stabilization after guanidine protonation.^[1] Several reviews on guanidine chemistry have been published.^[2–12] Guanidine derivatives are generally very basic and, as such, soluble in polar solvents such as water, dimethyl sulfoxide, methanol, and dimethylformamide, and less frequently in acetonitrile, ethyl acetate, and chloroform. Therefore, a major problem in the synthesis of guanidines is the reaction workup. The solubility in organic solvents can be improved if the guanidine group is substituted with two or more alkyl groups, or if it is protected with *tert*-butoxycarbonyl, trifluoromethanesulfonyl, benzyloxycarbonyl, or other amine-protecting groups. After removal of the protecting groups, in general the reaction workup involves counterion exchange or purification by chromatography (usually reversed phase or ion exchange). Guanidine compounds are generally very stable to oxidation, thermal degradation, or acidic conditions. Guanidines can be degraded in basic aqueous solution to give the corresponding urea derivatives. Some natural products bearing a guanidine group, such as saxitoxin and tetrodotoxin, are reported to be unstable in pH above 7.0. Alkyl- and arylguanidine derivatives are very often synthesized from an amine and an amidine derivative bearing a leaving group, a reaction which is also called *guanylation*.^[8] Less frequently, guanidines have also been obtained by guanidine alkylation with alkyl or aryl halides (a reaction named *guanidinylation*^[8]), guanidine acylation, or even condensation of guanidine with saturated or unsaturated alcohols, aldehydes, ketones, and esters. These latter reactions have also been performed under mild conditions with urea and thiourea derivatives replacing guanidine, followed by subsequent reaction with ammonia, an amine, or an amide to give the corresponding substituted guanidine. Physical and spectroscopic properties of guanidine compounds have been briefly reviewed.^[10] Synthetic guanidine derivatives have not been reported as hazardous or toxic. However, due to the biological activities frequently observed for these compounds, careful handling is often advisable. One example is the microcystins, liposoluble hepatotoxins from cyanobacteria, which are readily absorbed through the skin.^[13–15] Guanidine derivatives have been reported as environmentally friendly catalysts^[16,17] and fuel stabilizers.^[18]

Product Subclass 1: Substituted Guanidines

The synthesis of substituted guanidines follows two general approaches: either the reaction of a substituted amine with an amidine source, or the reaction of a guanidine, urea, or thiourea derivative with an alkyl halide, an alcohol, or a carbonyl derivative. The first approach is the most commonly employed and of a more general application. In this section, it will be shown that a variety of methods are described for the synthesis of guanidines from amines and an amidine source. On the other hand, the alkylation or condensation of a guanidine, urea, or thiourea derivative is more often used in the synthesis of biologically active guanidine-containing natural products.^[9–12] In the past, guanidines have been synthesized from amines and cyanamide or cyanogen bromide, which are

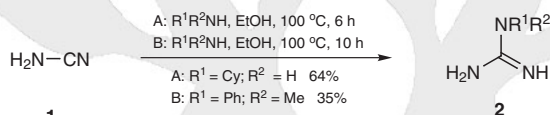
very hazardous reagents. However, these methods are still employed in guanidine synthesis. More recently, guanidines have been prepared from an amine and a “protected amine” source. These reactions are easy to carry out, with no need for an inert atmosphere, and in some cases even in water as a solvent. Frequently, good to excellent yields are obtained. Reaction byproducts, such as dimethyl sulfide or other sulfides, can be hazardous but in recent years these sulfur reagents have been replaced by alternatives less hazardous to health and the environment.

18.13.1.1 Synthesis of Product Subclass 1

18.13.1.1.1 Method 1: Reaction of Amines with Cyanamides

The synthesis of guanidine (**2**, $R^1 = R^2 = H$) and its derivatives using cyanamide (**1**) dates from the dawn of organic synthesis. However, since cyanamide itself is a harmful reagent, the method has not been widely used. The yields reported for the reaction of cyanamide with both alkyl and aryl primary amines are moderate to low (Scheme 1).^[19] Also, a substituted cyanamide was used in the total synthesis of the bis-guanidine alkaloid, martinelllic acid.^[20]

Scheme 1 Reaction of Cyanamide with Alkyl- and Arylamines^[19]



Guanidines **2** by Reaction of Cyanamide with Alkyl- and Arylamines; General Procedure:^[19]

CAUTION: Cyanamide is caustic and irritating to the eyes, skin, and respiratory tract of humans. Contact with cyanamide in dust or liquid form causes severe irritation of the eyes and ulceration of moist skin.

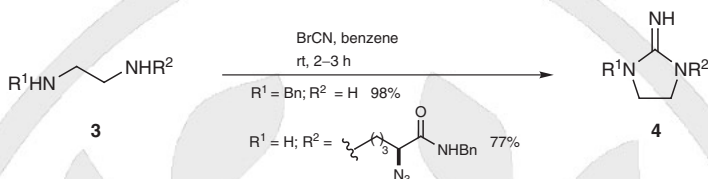
The amine hydrochloride salt (0.074–0.34 mol) and cyanamide (0.107–0.41 mol) in EtOH (100 mL) was refluxed at 100 °C for 6 or 10 h. The solvent was evaporated to 50 mL under atmospheric pressure after which, upon cooling, crystals were formed. After filtration, the solid material was washed with Et_2O and dried in vacuo. Usually, compounds were recrystallized (acetone).

18.13.1.1.1 Variation 1: Reaction of Amines with Cyanogen Bromide

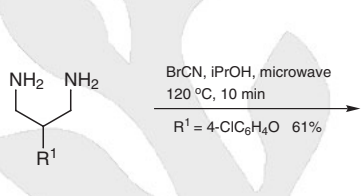
Cyanogen bromide has been more widely used in the synthesis of guanidine derivatives than cyanamide. In general, the reaction yields are moderate to excellent.^[21–23] Within the synthesis of 1-substituted or 1,3-disubstituted imidazolidin-2-imines **4**, it has been observed that the addition of *N*-benzylethane-1,2-diamine (**3**, $R^1 = Bn$; $R^2 = H$) or *N*-(diphenylmethyl)ethane-1,2-diamine (**3**, $R^1 = CHPh_2$; $R^2 = H$) to the benzene solution of cyanogen bromide avoids the formation of the corresponding diamine hydrobromide salt (Scheme 2).^[24] Similar reactions to give products **5** proceed in moderate yields using a microwave-assisted system (Scheme 3).^[22] Moderate to good yields have also been obtained in the solid-phase synthesis of trisubstituted 1-[2-(2-iminoimidazolidin-1-yl)-1-methylethyl]imidazolidin-2-imines **6** (Scheme 4), using a 4-methylbenzhydrylamine resin (MBHA).^[25] Applications of the synthesis of guanidines from amines and cyanogen bromide include the

synthesis of chiral guanidines,^[23] synthesis of noncompetitive *N*-methyl-D-aspartate receptor antagonists,^[26,27] and in the synthesis of several natural products.^[28–30]

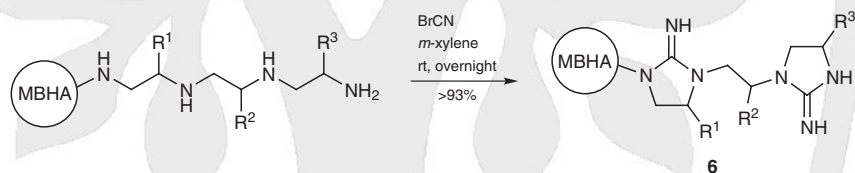
Scheme 2 Preparation of 1-Substituted or 1,3-Disubstituted Imidazolidin-2-imines from Cyanogen Bromide and *N*-Monosubstituted or *N,N'*-Disubstituted Alkanediamines^[21,24]



Scheme 3 Preparation of 5-Alkyltetrahydropyrimidin-2(1*H*)-imines or 5-Phenoxytetrahydropyrimidin-2(1*H*)-imines from Cyanogen Bromide and 2-Alkyl or 2-Phenoxy Monosubstituted 1,3-Diamines^[22]



Scheme 4 Solid-Phase Synthesis of Trisubstituted 1-[2-(2-Iminoimidazolidin-1-yl)-1-methylethyl]imidazolidin-2-imines from Cyanogen Bromide and Trisubstituted Tetramines^[25]



R^1	R^2	R^3	HPLC Purity of 6 (%)	Ref
Ph	Bn	Me	75	[25]
Bn	4-ClC ₆ H ₄ CH ₂	Me	55	[25]

1-Benzylimidazolidin-2-imine (4, $R^1 = \text{Bn}; R^2 = \text{H}$); Typical Procedure:^[24]

CAUTION: Cyanogen bromide reacts violently with water and with mineral and organic acids. It may decompose when exposed to heat, moist air, or water, producing toxic fumes of hydrogen cyanide and hydrogen bromide. Cyanogen bromide may be fatal if inhaled or swallowed and causes severe irritation.

To a soln of BrCN (4.5 g, 40 mmol) in benzene (150 mL) (**CAUTION:** carcinogen) was added dropwise a soln of *N*-benzylethane-1,2-diamine (**3**, $R^1 = \text{Bn}; R^2 = \text{H}$; 6.0 g, 40 mmol) in benzene (50 mL) with stirring at rt. The mixture was stirred at rt over a period of 2–3 h. A solid separated out and was collected by filtration; the product was obtained as its hydrobromide salt; yield: 9.8 g (98%).

1,3-Disubstituted Imidazolidin-2-imines 4; General Procedure:^[21]

CAUTION: Cyanogen bromide reacts violently with water and with mineral and organic acids. It may decompose when exposed to heat, moist air, or water, producing toxic fumes of hydrogen cyanide and hydrogen bromide. Cyanogen bromide may be fatal if inhaled or swallowed and causes severe irritation.

BrCN (112 mg, 1.10 mmol) was dissolved in benzene (3.0 mL) (**CAUTION: carcinogen**) and stirred at rt. Next, the diamine dissolved in benzene (1.0 mL) was added dropwise over 5 min to the BrCN soln. The formation of the product was characterized by precipitation of the insoluble HBr salt. The mixture was stirred for a minimum of 3 h, after which time the benzene was removed under reduced pressure and the product was purified by reversed phase HPLC. Purification of about 400 mg of crude product was effected by elution at a flow rate of 6 mL·min⁻¹ using a linear gradient of 3–35% of 0.084% TFA in MeCN in 0.1% aq TFA over 1 h and monitoring the effluent by UV absorbance at 254 nm.

5-(4-Chlorophenoxy)-3,4,5,6-tetrahydropyrimidin-2(1H)-ium Bromide (5, R¹ = 4-ClC₆H₄O); Typical Procedure:^[22]

CAUTION: Cyanogen bromide reacts violently with water and with mineral and organic acids. It may decompose when exposed to heat, moist air, or water, producing toxic fumes of hydrogen cyanide and hydrogen bromide. Cyanogen bromide may be fatal if inhaled or swallowed and causes severe irritation.

To a soln of BrCN (127 mg, 1.2 mmol) in iPrOH (2.5 mL) was added 2-(4-chlorophenoxy)propane-1,3-diamine (200 mg, 1.0 mmol) and the mixture was heated under microwave irradiation at 120 °C for 10 min. iPr₂O (2.5 mL) was added and the precipitate was collected by filtration, washed with iPr₂O, and dried in vacuo (P₄O₁₀) to give the product as a white solid; yield: 61%.

Trisubstituted 1-[2-(2-Iminoimidazolidin-1-yl)-1-methylethyl]imidazolidin-2-imines 6; General Procedure:^[25]

CAUTION: Cyanogen bromide reacts violently with water and with mineral and organic acids. It may decompose when exposed to heat, moist air, or water, producing toxic fumes of hydrogen cyanide and hydrogen bromide. Cyanogen bromide may be fatal if inhaled or swallowed and causes severe irritation.

The resin-bound tetramine was treated with 0.02 M BrCN (2.2 equiv) in *m*-xylene overnight under N₂, followed by washes with *m*-xylene (2 ×), CH₂Cl₂ (2 ×), iPrOH (2 ×), and CH₂Cl₂ (3 ×). The resin-bound product was cleaved using anhyd HF in the presence of PhOMe at 0 °C for 1.5 h, and the cleaved product was extracted with AcOH/H₂O (95:5) and lyophilized.

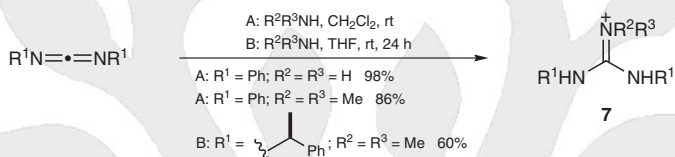
18.13.1.1.1.2

**Variation 2:
Reaction of Amines with Carbodiimides**

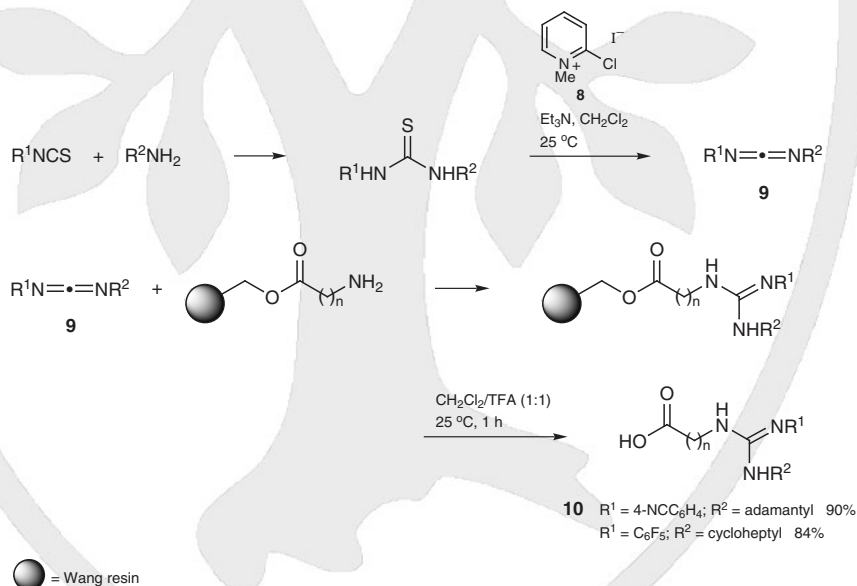
Carbodiimides are stable guanylating agents of primary and secondary amines, which can be generated following different approaches. The reaction is performed under mild conditions, and the yields of products **7** are usually good to excellent (Scheme 5).^[31–33] The method is also of application in solid-phase synthesis of guanidines.^[34–36] In this particular case, the use of 2-chloro-1-methylpyridinium iodide (2-CMPI, Mukaiyama's reagent, **8**) as the reagent for carbodiimide formation proves to be particularly efficient (Schemes 6 and 7).^[34] Two solid-phase approaches have been developed. In the first case, a suitable carbodiimide **9** is initially synthesized and then reacted with a resin-bound amine (Scheme 6). In an alternative approach, the carbodiimide is generated within the resin,

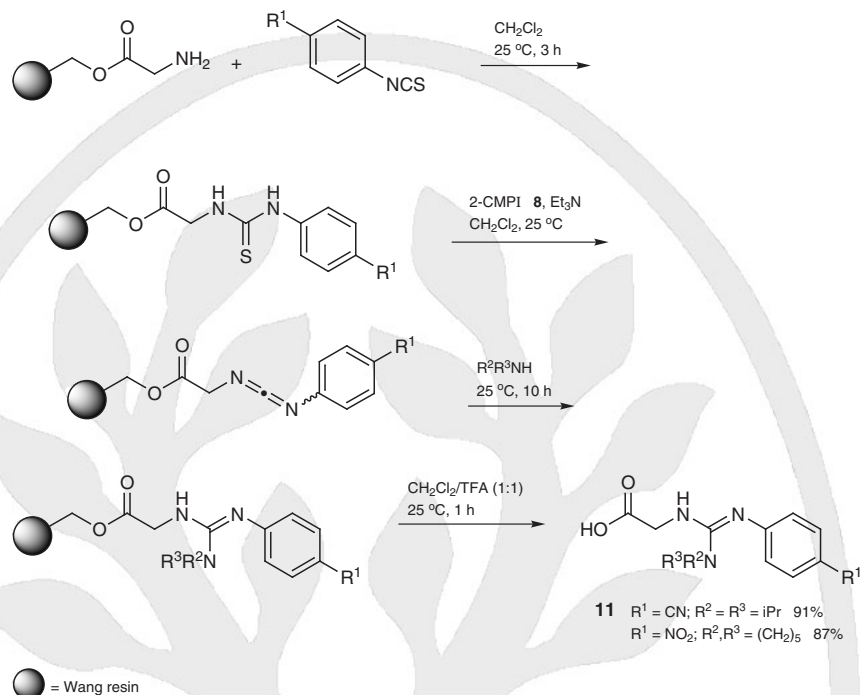
which is subsequently reacted with a suitable amine (Scheme 7). In both cases, the yields for guanidine formation are good to very good, with a respectable degree of purity. The use of triphenylphosphine as the carbodiimide-generating reagent from the corresponding thiourea gives the product in lower yields than Mukaiyama's reagent; nevertheless, the resin-free guanidines are obtained with an excellent degree of purity.^[37] Therefore, the solid-phase synthesis of guanidines appears to be a suitable method for the generation of libraries of guanidine-bearing compounds such as **10** and **11**. The synthesis of guanidines from carbodiimides is used in the synthesis of 3,5-dihydro-4*H*-imidazol-4-ones,^[38] in the solid-phase synthesis of guanidines through iminophosphoranes,^[39] in the synthesis of larger aromatic bis(guanidines),^[40] the synthesis of 2,3-dihydro-6*H*-pyrimido[2,1-*b*]-quinazolin-4[1*H*]-ones,^[35] biguanides,^[36] guanidinium oligomers,^[41] and 3,4-dihydroquinazolines,^[42] and in the synthesis of an advanced precursor of tetrodotoxin,^[43] of 11-deoxy-tetrodotoxin,^[44,45] and of naturally derived leucettamine B.^[46]

Scheme 5 Synthesis of 1,1,2,3-Tetrasubstituted Guanidines from Disubstituted Carbodiimides and Secondary Amines^[31–33]



Scheme 6 Solid-Phase Synthesis of N,N'-Disubstituted Guanidino Carboxylic Acids^[34]



Scheme 7 Solid-Phase Synthesis of N,N,N'-Trisubstituted Guanidinoacetic Acids^[34]

1,1,2,3-Tetrasubstituted Guanidines **7** from Disubstituted Carbodiimides and Secondary Amines; General Procedure:^[31]

To a soln of the bis(carbodiimide) (0.34 mmol) in anhyd CH_2Cl_2 (15 mL) was added the amine (1.02 mmol). The resultant mixture was stirred at rt for 15–30 min and then the solvent was removed under reduced pressure. The solid residue was treated with Et_2O , filtered, and air dried to give the corresponding bis(guanidine), which was recrystallized from an appropriate solvent. In the case of the reaction with NH_3 , it was bubbled through a soln of the bis(carbodiimide) in anhyd CH_2Cl_2 at rt for 20–30 min and worked up similarly.

Alternative Synthesis of 1,1,2,3-Tetrasubstituted Guanidines **7** from Disubstituted Carbodiimides and Secondary Amines; General Procedure:^[33]

A soln of the carbodiimide (1 mmol) and amine (10 mmol) in THF (10 mL) was stirred at rt for 24 h. The solvent was evaporated at reduced pressure and the remaining amine was removed under vacuum (0.1 Torr). The crude guanidine was dissolved in Et_2O (20 mL) and extracted with 2 M HCl (3 \times 10 mL). The combined aqueous layers were neutralized with NaOH, extracted with Et_2O (3 \times 15 mL), and the organic layers were dried (Na_2SO_4). Evaporation under reduced pressure yielded guanidines, which were purified by Kugelrohr distillation.

Guanidino Carboxylic Acids **10** via Reaction of Supported Amines with Carbodiimides; General Procedure:^[34]

The carbodiimides **9** were prepared by mixing equal amounts of a primary amine and an isothiocyanate (usually 0.5 mmol) in CH_2Cl_2 (10 mL). The formation of the thiourea was generally rapid (TLC), except for aromatic amines, in which case the reactions proceeded at a more convenient rate at 40 °C. After complete formation of the thiourea (TLC), the solvent was removed and the resulting solid was washed several times with Et_2O /petroleum

ether (1:1) and then dried in vacuo. The thiourea thus obtained was typically obtained in a high state of purity and was used as such in the next synthetic step.

The thioureas prepared as above were dissolved in CH_2Cl_2 (10 mL). Et_3N (5 equiv) and then 2-CMPI (**8**; 1 equiv) were added, and the mixture was briefly sonicated. The solvent was then removed, and a small amount of hexanes (or petroleum ether) was added. The carbodiimide, but not the byproducts, was generally soluble in this solvent. The hexanes soln was then passed through a short pad of silica gel packed in a pipet. This effectively removed impurities and give practically pure carbodiimide as a viscous liquid or a low-melting solid. For the 4-nitrophenyl derivatives, the carbodiimides were not soluble in petroleum ether or hexanes; in those situations Et_2O /hexanes (1:4) was used in place of pure hexanes.

For the reaction of the resin-bound amines with the carbodiimides, Fmoc-Gly-Wang resin (ChemImpex) or Fmoc- β -Ala-Wang resin (homemade) was deprotected by 20% piperidine in DMF. After washing and drying, the resin was suspended in DMF and the necessary carbodiimide (3–4 equiv) dissolved in DMF was added. The reaction was completed in 1 h, as checked by the ninhydrin test. Compounds having the 1-adamantyl substituent and no strong electron-withdrawing group on the carbodiimide had to be heated to 50 °C with longer reaction times. After the reaction was completed, the resin was washed and dried. The cleavage was accomplished by treating the resin with TFA/ CH_2Cl_2 (1:1) at rt for 1 h. The product was obtained by evaporation of solvents.

N,N,N'-Trisubstituted Guanidinoacetic Acids **11 via Resin-Bound Carbodiimide Intermediates; General Procedure:**^[34]

Fmoc-Gly-Wang resin (ChemImpex) was deprotected with 20% piperidine in DMF. After washing and drying, the resin was suspended in dry CH_2Cl_2 and treated with the corresponding isothiocyanate (2–3 equiv). After 3 h of agitation at rt, the resin was washed and dried. It was then suspended in DMF/ CH_2Cl_2 (1:1), and Et_3N (5 equiv) was added. 2-CMPI (**8**; 2 equiv) was then added, and the resin was briefly agitated (ca. 1 min). A suitable amine (5 equiv) was then added, and the resin was agitated for 10 h at rt (in case of $\text{R}^1 = \text{Cl}$, the reaction was carried out at 50 °C). This was then washed and dried. The cleavage was accomplished by treating the resin with TFA/ CH_2Cl_2 (1:1) at rt for 1 h, and the product was collected after evaporation of the solvents.

18.13.1.1.2

Method 2:

Reaction of Amines with Substituted Thioureas

The synthesis of substituted guanidines **13** from substituted thioureas **12** is frequently employed and of wide application. Simple alkyl- and arylguanidines can be obtained from the corresponding thioureas in the presence of a base, usually triethylamine, and a catalyst such as mercury(II) chloride,^[47] sodium metaperiodate or sodium chlorite,^[48] copper(II) sulfate/silica gel,^[49] or lac sulfur adsorbed on alumina.^[50] In general, the yields of such reactions are moderately good to excellent, giving the corresponding guanidine free of the sulfur byproduct (Scheme 8). The syntheses of mono- or bis(*tert*-butoxycarbonyl)-protected guanidines (e.g., **14**) are successfully achieved from the corresponding mono- or bis(*tert*-butoxycarbonyl)-protected thioureas (Scheme 9),^[51–53] using mercury(II) chloride or copper(II) chloride as catalyst,^[51] or alternatively 2-chloro-1-methylpyridinium iodide (2-CMPI, **8**).^[52] In both cases, yields are generally excellent. Deprotection with trifluoroacetic acid in either aqueous or organic solvents is fast and clean, with high yields of products **15**. In the case of 2-chloro-1-methylpyridinium iodide, it has been suggested that the reaction occurs through a carbodiimide intermediate.^[52] An additional example of the synthesis of guanidines from bis(*tert*-butoxycarbonyl)-protected thioureas and amines involves the use of the polymer-supported *N*-cyclohexyl-*N'*-propylcarbodiimide

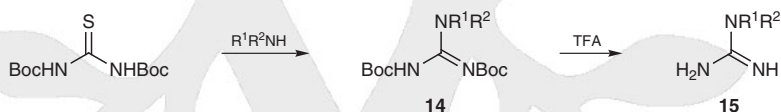
16 as the reaction catalyst and the polymer-supported *N,N*-bis(2-aminoethyl)-*N'*-methylethane-1,2-diamine **17** as a reaction scavenger.^[53]

Scheme 8 Synthesis of 1,1,3-Tri- or 1,1,2,3-Tetrasubstituted Guanidines from 1,3-Disubstituted Thioureas and Primary or Secondary Amines^[47–50]



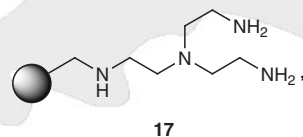
R ¹	R ²	R ³ R ⁴ NH	Conditions	Yield (%) of 13	Ref
Cy	CONHBn	1,2,3,4-tetrahydroisoquinoline	Et ₃ N, HgCl ₂ , DMF, rt, 1.5 h	67	[47]
Ph	H	PhNH ₂	NaIO ₄ , DMF, H ₂ O, 80–85 °C, 0.75 h	76	[48]
Ph	H	PhNH ₂	NaClO ₂ , DMF, H ₂ O, 80–85 °C, 2.0 h	80	[48]
2-Tol	CH ₂ CH ₂ OH	2-TolNH ₂	CuSO ₄ , silica gel, Et ₃ N, THF, rt, 55 min	75	[49]
Ph	Ph	Et ₂ NH	alumina/S, [HO(CH ₂) ₂] ₃ N, THF, heat, 1.0 h	82	[50]

Scheme 9 Synthesis of Mono- or Bis(*tert*-butoxycarbonyl)-Protected Guanidines from Mono- or Bis(*tert*-butoxycarbonyl)-Protected Thioureas and Primary or Secondary Amines^[51–53]



R ¹ R ² NH	Conditions	Yield (%) of 14	Yield (%) of 15 from 14	Ref
(<i>S</i>)-benzyl proline	HgCl ₂ , Et ₃ N, DMF, 0 °C, 20 min	90	–	[51]
(<i>S</i>)-benzyl proline	CuCl ₂ , Et ₃ N, DMF, 0 °C, 0.5 h, then rt, 0.5 h	62	–	[51]
(H ₂ C=CHCH ₂) ₂ NH	2-CMPI 8 , DMF	–	86	[52]

Me(CH ₂) ₉ NH ₂	<p>16</p>	–	94	[53]
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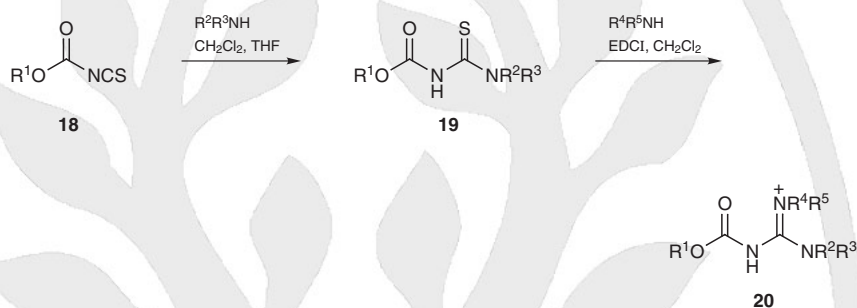


CH₂Cl₂, rt, 16 h

A report on the synthesis of 1,1-disubstituted guanidines from mono(*tert*-butoxycarbonyl)-protected thioureas using *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide (EDCI) hydrochloride as catalyst in the presence of triethylamine in dimethylformamide, and either hydrochloric acid in dioxane or trimethylsilyl trifluoromethanesulfonate in dichloromethane as deprotecting reagents, gives no experimental details.^[54] A single example of

the synthesis of 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) protected guanidines from the corresponding Pbf-protected thioureas in the presence of Hünig's base (ethyldiisopropylamine) and 2-chloro-1-methylpyridinium iodide has been reported, with very good yields.^[55] Finally, the synthesis of (alkoxycarbonyl)guanidines **20** ($R^1 = \text{alkyl}$) from (alkoxycarbonyl)thioureas **19** [$(R^1 = \text{alkyl})$] preparable from alkyl isothiocyanatoformates **18** ($R^1 = \text{alkyl}$) has been developed, including two high-yielding examples (Scheme 10).^[7,56,57] The removal of the alkoxycarbonyl protecting group (not shown in Scheme 10) is achieved in the presence of bromotrimethylsilane.^[57] Several applications of the synthesis of guanidines from thioureas are known.^[58–69]

Scheme 10 Synthesis of (Alkoxycarbonyl)guanidines from (Alkoxycarbonyl)thioureas and Primary or Secondary Amines^[7,56,57]



1,1,3-Tri- or 1,1,2,3-Tetrasubstituted Guanidines 13 from 1,3-Disubstituted Thioureas 12 and Primary or Secondary Amines Using Mercury(II) Chloride; General Procedure:^[47]

CAUTION: Mercury(II) chloride is a poison by ingestion and is toxic by skin contact. When heated to decomposition it emits toxic fumes of mercury.

The thiourea **12** (1.1 equiv), amine (1.1 equiv), and Et_3N (2.2 equiv) were dissolved in DMF ($5\text{ mL} \cdot \text{mmol}^{-1}$ substrate) at rt. The mixture was cooled in an ice bath. $HgCl_2$ (1.1 equiv) was added and the mixture was stirred for 20 min, after which it was allowed to react at rt. When completed (TLC), the mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed with H_2O and brine, and the organic phase was dried ($MgSO_4$). The crude product was purified by flash chromatography (silica gel).

1,1,3-Tri- or 1,1,2,3-Tetrasubstituted Guanidines 13 from 1,3-Disubstituted Thioureas 12 and Primary or Secondary Amines Using Sodium Metaperiodate; General Procedure:^[48]

An aqueous soln (10 mL) of $NaIO_4$ (2.34 g, 11 mmol) was added dropwise to a vigorously stirred mixture of thiourea **12** (10 mmol), DMF (5 mL), H_2O (5 mL), and the amine (15 mmol) at rt. In other procedures, the mixture was heated to $80\text{--}85^\circ\text{C}$. After completion of the reaction (TLC), 10% aq NaOH (10 mL) was added, with stirring for an additional 20 min at rt. The product was collected by filtration, washed with H_2O , and dried. Crystallization of the crude product (hexane/ $CHCl_3$ 1:4) yielded the pure guanidine.

1,1,3-Tri- or 1,1,2,3-Tetrasubstituted Guanidines 13 from 1,3-Disubstituted Thioureas 12 and Primary or Secondary Amines Using Copper(II) Sulfate and Silica Gel; General Procedure:^[49]

A mixture consisting of a THF soln of a substituted thiourea **12** (15 mL, 1 mmol), Et_3N (1 mmol), and anhyd $CuSO_4$ /silica gel (1 g/1.3 g) was gently stirred at rt. After 30 min, a soln of an amine in THF (5 mL) was added to the mixture, and the stirring was continued for 30 min. Filtration and washing the inorganic residue with THF ($2 \times 5\text{ mL}$) yielded an organic filtrate which was evaporated to give the corresponding guanidine product.

1,1-Diethyl-2,3-Diphenylguanidine (13, $R^1 = R^2 = \text{Ph}$; $R^3 = R^4 = \text{Et}$) Using Lac Sulfur**Adsorbed on Alumina; Typical Procedure:**^[50]

A THF soln of 1,3-diphenylthiourea (**12**, $R^1 = R^2 = \text{Ph}$; 15 mL, 10 mmol), triethanolamine (2 mL, 10 mmol), and lac sulfur (1 g) adsorbed on alumina (1.5 g) was stirred before adding Et_2NH (10 mmol). The mixture was stirred under gentle reflux. The guanidine formation was completed in 2 h. After filtration and washing the residue with THF ($2 \times 5 \text{ mL}$), the filtrate and washings were evaporated to give the product; yield: 82%.

L-Benzyl 1-[[*tert*-Butoxycarbonyl]amino][*tert*-butoxycarbonyl]imino]methyl-L-prolinate [14, $\text{NR}^1\text{R}^2 = (\text{S})$ -2-(Benzyloxycarbonyl)pyrrolidin-1-yl] Using Mercury(II) Chloride;**Typical Procedure:**^[51]

CAUTION: Mercury(II) chloride is a poison by ingestion and is toxic by skin contact. When heated to decomposition it emits toxic fumes of mercury.

To a mixture of benzyl L-prolinate hydrochloride (241.8 mg, 1 mmol), 1,3-bis(*tert*-butoxycarbonyl)thiourea (276.4 mg, 1 mmol), and Et_3N (333.3 mg, 3.3 mmol) in DMF (2 mL) at 0°C was added HgCl_2 (298.6 mg, 1.1 mmol) with stirring. The resulting mixture was stirred at 0°C for 20 min, diluted with EtOAc (20 mL), and filtered through a pad of Celite. The filtrate soln was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, hexane/EtOAc 3:1); yield: 402 mg (90%).

Mono- or Bis(*tert*-butoxycarbonyl)-Protected Guanidines 14 from Mono- or Bis(*tert*-butoxycarbonyl)-Protected Thioureas and Primary or Secondary Amines Using 2-Chloro-1-methylpyridinium Iodide; General Procedure:^[52]

To a soln of an amine (0.366 mmol) in anhyd DMF (120 μL) were added 1,3-bis(*tert*-butoxycarbonyl)thiourea (121 mg, 0.439 mmol) and Et_3N (113 μL , 0.806 mmol). A suspension of 2-CMPI (**8**; 112 mg, 0.439 mmol) in anhyd DMF (240 μL) was added dropwise via syringe, and the mixture was stirred at 25°C . When the reaction had reached completion (TLC), the mixture was diluted with H_2O (360 μL) and extracted with Et_2O ($3 \times 360 \mu\text{L}$). The combined organic layers were dried (Na_2SO_4) and evaporated to afford the crude guanidine, which was purified by flash chromatography.

Mono- or Bis(*tert*-butoxycarbonyl)-Protected Guanidines 14 from Mono- or Bis(*tert*-butoxycarbonyl)-Protected Thioureas in the Presence of Catalyst 16 and Scavenging Agent 17; General Procedure:^[53]

To five tubes of a Quest 210 synthesizer (Argonaut Technologies Ltd) were added PS-carbodiimide **16** ($1.26 \text{ mmol} \cdot \text{g}^{-1}$; 595 mg, 0.75 mmol) and CH_2Cl_2 (5.0 mL). The resin was washed/swollen for 15 min. The solvent was filtered and the process repeated twice. The resin was suspended again in CH_2Cl_2 (5.0 mL). Then, the corresponding amines (0.25 mmol) were added to each tube, followed by 1,3-bis(*tert*-butoxycarbonyl)thiourea (103 mg, 0.37 mg). The mixtures were shaken at rt under N_2 atmosphere for 16 h. Then, PS-trisamine **17** ($4.2 \text{ mmol} \cdot \text{g}^{-1}$; 120 mg, 0.50 mmol) and CH_2Cl_2 (1.0 mL) were added to each mixture. The shaking was continued for 16 h at rt. The polymers were removed by filtration and washed with CH_2Cl_2 ($2 \times 6 \text{ mL}$), and the resulting solns were evaporated under reduced pressure. The yields were determined by mass recovery, and the purity of each protected guanidine was calculated by LC-MS-UV and ^1H NMR analyses. Crude protected guanidines were further treated with a 25% soln of TFA in CH_2Cl_2 (5.0 mL) at rt for 6 h. Evaporation of the solvent gave the corresponding deprotected guanidines. Yields and purities were calculated by LC-MS-UV and ^1H NMR analyses.

1-(Alkoxy carbonyl)guanidines 20 (R^1 = Alkyl) from (Alkoxy carbonyl)thioureas 19 (R^1 = Alkyl); General Procedure:^[7,56]

Alkyl Isothiocyanatoformates 18 (R^1 = Alkyl):

A sat. soln of KSCN (40 g) in boiling EtOH (300 mL) was added to Et₂O (1.5 L), forming a fine, white powder. The solid was collected by filtration and washed with Et₂O (300 mL), before being dried in vacuo over P₂O₅. Finely powdered KSCN was isolated; yield: 33 g (82%). The alkyl chloroformate (20 mmol) was slowly added to a stirred suspension of the freshly powdered KSCN (10 g, 110 mmol) in 20% toluene/MeCN (250 mL). After 2 d of stirring, no chloroformate was detectable by TLC (silica, CH₂Cl₂/hexanes 1:5). The mixture was filtered through Celite, and the solid was washed with toluene (2 × 50 mL). The solvent was removed in vacuo with mild heating, before isolating the product by distillation or chromatography (silica gel).

(Alkoxy carbonyl)thioureas 19 (R^1 = Alkyl):

A soln of the alkyl isothiocyanatoformate **18** (R^1 = alkyl; 1.0 mmol) in CH₂Cl₂ (50 mL) was cooled to 0 °C before adding the desired alkylamine (1.0 mmol). The ice bath was removed, and the soln was stirred for 4 h under N₂. The soln was washed with 1% HCl, H₂O, and brine, and dried (Na₂SO₄). The solvent was removed under reduced pressure, yielding a white solid. As an alternative to extractive workup, the mixture could be transferred into pentane (50 mL). The white solid that formed was collected by filtration and dried in vacuo.

1-(Alkoxy carbonyl)guanidines 20 (R^1 = Alkyl):

An (alkoxy carbonyl)thiourea **19** (R^1 = alkyl; 1.0 mmol), the desired alkylamine (1.5 mmol), and iPr₂NEt (1.0 mmol) were added to anhyd CH₂Cl₂ (10 mL) and cooled to 0 °C. Then, N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide (EDCI; 1.5–2.0 mmol) was added, and the soln was stirred under N₂. After 1 h, the ice bath was removed and the soln was stirred for an additional 10 h at rt. In cases where TLC indicated unreacted starting material, addition of more amine and EDCI resulted in increased yields. The mixture was washed with 1% HCl, H₂O, and brine, and dried (Na₂SO₄). The residue that remained after removal of solvent under reduced pressure was purified by chromatography (silica gel).

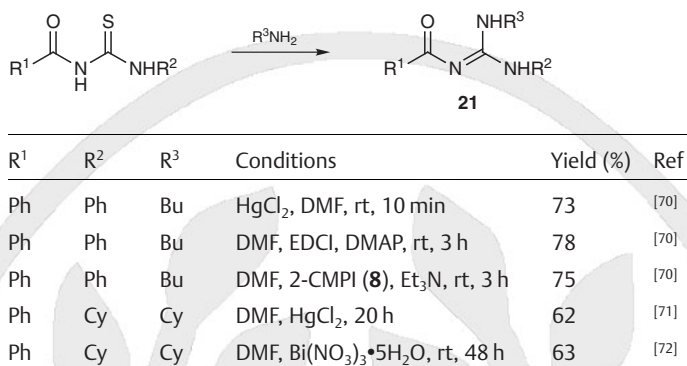
3-Benzyl-1-(ethoxycarbonyl)thiourea (19, R^1 = Et; R^2 = Bn; R^3 = H); Typical Procedure:^[57]

BnNH₂ (2.3 g, 21.6 mmol) was added to ethyl isothiocyanatoformate (**18**, R^1 = Et; 1.8 g, 13.7 mmol) dissolved in CH₂Cl₂ (10 mL). Gas evolution occurred and a yellow solid formed immediately. The product was purified by flash chromatography (silica gel, CH₂Cl₂/hexanes 2:3).

18.13.1.1.2.1

**Variation 1:
Reaction of Amines with Acylthioureas**

Procedures for the synthesis of acylguanidines **21** are summarized in Scheme 11, and include the use of various catalysts, such as mercury(II) chloride,^[70,71] N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide (EDCI),^[70] 2-chloro-1-methylpyridinium iodide (2-CMPI **8**, Mukaiyama's reagent),^[70] and bismuth(III) nitrate pentahydrate.^[72] The yields of such reactions are moderate to good. An example of the use of acylthioureas in the synthesis of natural products is the synthesis of the potent antibiotic agents TAN A–D, active against methicillin-resistant strains of *Staphylococcus aureus*.^[73]

Scheme 11 Synthesis of Acylguanidines from Acylthioureas and Primary Amines^[70–72]

2-Benzoyl-1-butyl-3-phenylguanidine (21, R¹ = R² = Ph; R³ = Bu) Using Mercury(II) Chloride as Catalyst; Typical Procedure:^[70]

CAUTION: Mercury(II) chloride is a poison by ingestion and is toxic by skin contact. When heated to decomposition it emits toxic fumes of mercury.

To a soln of BzNH₂ (29 mg, 0.24 mmol) in DMF (0.5 mL) was added 95% NaH (7.2 mg, 0.31 mmol). After stirring for 5 min, PhNCS (24 μL, 0.20 mmol) was added via a syringe. The mixture was stirred at 60 °C for 30 min, until completion (TLC). To the above mixture was added BuNH₂ (24 μL, 0.24 mmol) and HgCl₂ (65 mg, 0.24 mmol). After stirring at rt for 10 min, the mixture was diluted with EtOAc (10 mL) and filtered through a pad of Celite, and the filtrate was concentrated. Purification of the residue on a column (silica gel) gave the product; yield: 43.6 mg (73%).

2-Benzoyl-1-butyl-3-phenylguanidine (21, R¹ = R² = Ph; R³ = Bu) Using *N*-[3-(Dimethylamino)propyl]-*N*'-ethylcarbodiimide (EDCI) as Catalyst; Typical Procedure:^[70]

To a soln of BzNH₂ (29 mg, 0.24 mmol) in DMF (0.5 mL) was added 95% NaH (7.2 mg, 0.31 mmol). After stirring for 5 min, PhNCS (24 μL, 0.20 mmol) was added via a syringe. The mixture was stirred at 60 °C for 30 min, until completion (TLC). To the mixture was added BuNH₂ (24 μL, 0.24 mmol), *N*-[3-(dimethylamino)propyl]-*N*'-ethylcarbodiimide (EDCI; 46 mg, 0.24 mmol), and a catalytic amount of DMAP. After stirring at rt for 3 h, the mixture was quenched with H₂O and extracted with EtOAc (3 × 5 mL). The organic phase was washed with sat. brine and dried (MgSO₄). The solvent was removed to give a crude product, which was purified on a column (silica gel, 5–10% MeOH/EtOAc); yield: 46.5 mg (78%).

2-Benzoyl-1-butyl-3-phenylguanidine (21, R¹ = R² = Ph; R³ = Bu) Using 2-Chloro-1-methylpyridinium Iodide (8**) as Catalyst; Typical Procedure:^[70]**

To a soln of BzNH₂ (29 mg, 0.24 mmol) in DMF (0.5 mL) was added 95% NaH (7.2 mg, 0.31 mmol). After stirring for 5 min, PhNCS (24 μL, 0.20 mmol) was added via a syringe. The mixture was stirred at 60 °C for 30 min, until completion (TLC). To the mixture was added BuNH₂ (24 μL, 0.24 mmol), 2-chloro-1-methylpyridinium iodide (**8**; 61.3 mg, 0.24 mmol), and Et₃N (33 μL, 0.24 mmol). After stirring at rt for 3 h, the mixture was quenched with H₂O and extracted with EtOAc (3 × 5 mL). The organic phase was washed with sat. brine, dried (MgSO₄), and filtered. The solvent was removed to give the crude product. Purification of the crude product on a column (silica gel, 5–10% MeOH/EtOAc) provided the product; yield: 45.1 mg (75%).

2-Benzoyl-1,3-dicyclohexylguanidine (21, R¹ = Ph; R² = R³ = Cy) Using Mercury(II) Chloride as Catalyst; Typical Procedure:^[71]

CAUTION: Mercury(II) chloride is a poison by ingestion and is toxic by skin contact. When heated to decomposition it emits toxic fumes of mercury.

To a soln of the thiourea (1 mmol) in DMF (5 mL) was added the amine (1 mmol), Et₃N (2 mmol), and HgCl₂ (1 mmol) with vigorous magnetic stirring and ice-bath cooling. The suspension became black after a few min and was left to react for 20 h at rt. After this time, EtOAc (10 mL) was added, the suspension was filtered through a pad of Celite, and the pad was washed with CH₂Cl₂ (10 mL). The filtrate was concentrated and the residue (~5 mL) was dissolved in CH₂Cl₂ (15 mL), extracted with H₂O (3 × 15 mL), and dried (MgSO₄). After filtration, the solvent was evaporated and the crude residue recrystallized (Et₂O/petroleum ether); yield: 62%.

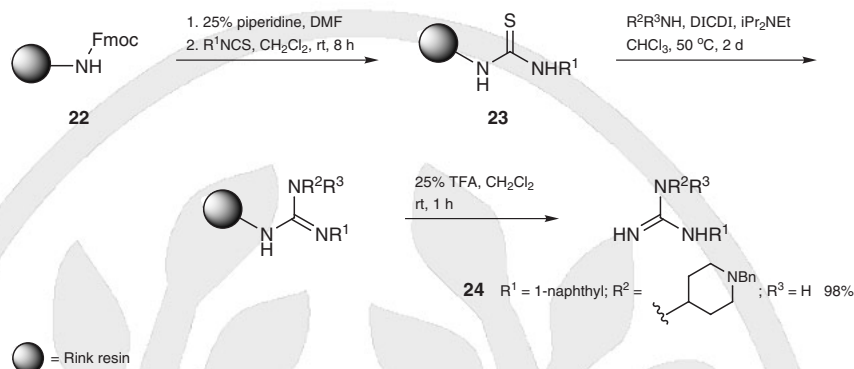
Acylguanidines 21 Using Bismuth(III) Nitrate Pentahydrate as Catalyst; General Procedure:^[72]

To a soln of the thiourea (0.5 mmol) in DMF (3 mL) was added the amine (1 mmol), Et₃N (2 mmol), and Bi(NO₃)₃·5H₂O (0.5 mmol) with vigorous magnetic stirring and ice-bath cooling. The suspension became black after a few min and was left stirring at the indicated temperature, until completion (TLC). When thiourea was consumed, CH₂Cl₂ (10 mL) was added and the suspension was filtered through a pad of Celite. The filtrate was concentrated and the residue (~3 mL) was dissolved in CH₂Cl₂ (15 mL), extracted with H₂O (4 × 15 mL), and dried (MgSO₄). After filtration, the solvent was evaporated and the crude residue was recrystallized (Et₂O/petroleum ether).

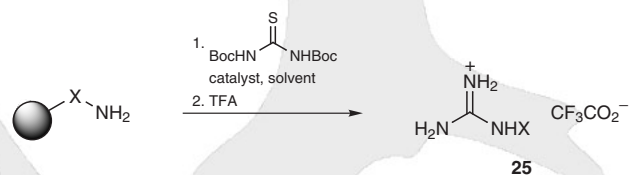
18.13.1.1.2.2

**Variation 2:
Solid-Phase Reaction of Amines with Thioureas**

The solid-phase synthesis of guanidines has been reviewed in detail,^[5] and therefore will not be extensively discussed herein. Two main approaches have been envisioned, namely the use of a solid-phase bonded amidine source, such as thiourea derivatives or 2-alkylisothiureas, or the use of a solid-phase bonded amine which is reacted with an amidine source. The solid-phase synthesis of guanidines with resin-bound thioureas has been extensively developed. The first of these examples (Scheme 12) involves the synthesis of various resin-bound thioureas **23** from a Rink amide polystyrene resin **22** and substituted isothiocyanates. The resin-bound thioureas are reacted with a series of secondary amines in the presence of diisopropylcarbodiimide (DICDI) as a coupling reagent. The guanidine is removed from the resin in trifluoroacetic acid/dichloromethane, giving the free guanidine in good to excellent yields.^[74]

Scheme 12 Solid-Phase Synthesis of Guanidines from Rink Amide Polystyrene Resin Bound Thioureas and Secondary Amines^[74]

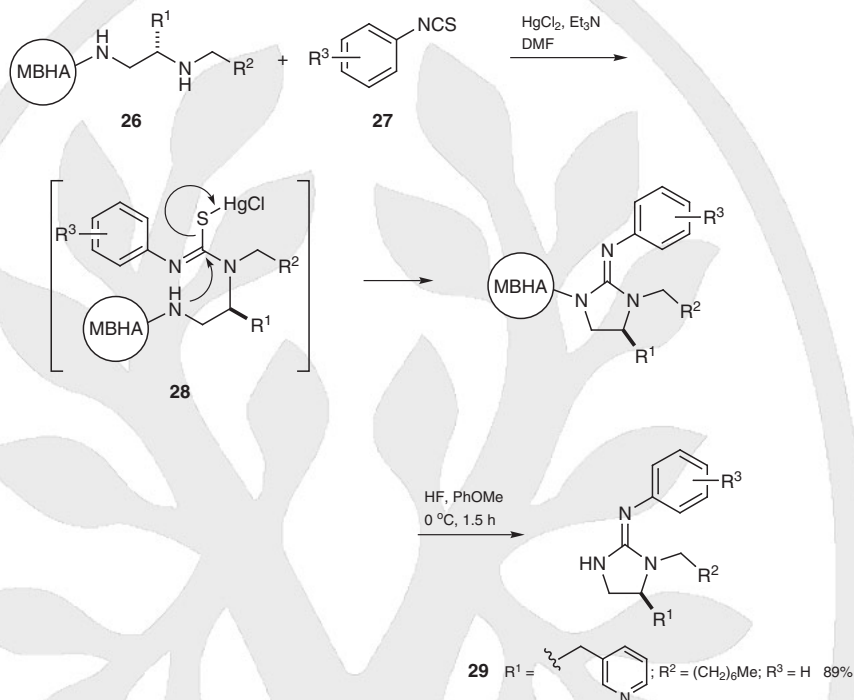
A T2* diazonium resin was used in the synthesis of various 1,2,3-trisubstituted guanidines in the presence of silver nitrate or mercury oxide as catalyst,^[75] with yields from moderate to quantitative. Solid-phase synthesis of guanidines from a Wang resin bonded (alkoxycarbonyl)thiourea has also been developed, but no experimental details or yields of individual guanidines are provided.^[76] A carboxypolystyrene resin was employed in the synthesis of different 1,1,3-trisubstituted guanidines using *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (EDCI) and Hünig's base (*i*Pr₂NEt) as coupling reagents.^[77] The overall yields of resin-free guanidines after five reaction steps are very good, but no experimental details are provided. The thiourea resin bound approach has been used toward the synthesis of superpotent sweeteners, although the true guanylating reagent is a carbodiimide and not the thiourea itself.^[34] A related approach is used in the synthesis of larger aromatic bis(guanidines),^[41] and in the solid-phase synthesis of *N,N'*-disubstituted 4-guanidinobenzoic acids.^[37] The solid-phase synthesis of guanidines from resin-bound amines has also been widely employed. An early example of such an approach evaluated the reaction of both Wang- and Rink-bound amines with 1,3-bis(*tert*-butoxycarbonyl)thiourea under various conditions, followed by cleavage by trifluoroacetic acid (Scheme 13).^[78] In this case, the yields of formation of guanidines **25** are very good to excellent.

Scheme 13 Solid-Phase Synthesis of Guanidines from Wang or Rink Resin Bound Amines and 1,3-Bis(*tert*-butoxycarbonyl)thiourea^[78]

A series of three different resin-bound aromatic amines give the 1,3-bis(*tert*-butoxycarbonyl)-protected guanidines in respectable yields, but no specific experimental details are provided.^[79] A more elaborated variation of the same approach involved the synthesis of 1,5-disubstituted 2-aryliminoimidazolidines from methylbenzhydrylamine (MBHA) resin bound *N*¹,1-disubstituted diamines **26** and aryl-substituted isothiocyanates **27** in the presence of mercury(II) chloride, to afford the products **29** after resin cleavage with hydrofluoric acid (Scheme 14).^[80] The same synthesis was tentatively performed with thio-carbonyldiimidazole, followed by sulfur methylation by iodomethane before reaction with a group of primary amines. However, only poor yields (>20%) are obtained. The isothiocyanate–mercury(II) chloride reaction presumably proceeds through intermediate

28, with almost no racemization.^[80] Several applications of solid-phase synthesis of guanidines based on thioureas are known.^[5]

Scheme 14 Solid-Phase Synthesis of 1,5-Disubstituted 2-Aryliminoimidazolidines from Methylbenzhydrylamine Resin Bound *N*¹,1-Disubstituted Diamines and Aryl-Substituted Isothiocyanates^[80]



Solid-Phase Synthesis of Trisubstituted Guanidines 24 from Resin-Bound Thioureas 23 and Secondary Amines; General Procedure:^[74]

The commercial Rink amide polystyrene resin (0.3 g; $0.7\text{ mmol}\cdot\text{g}^{-1}$; Advanced ChemTech) was treated with 25% piperidine/DMF (4 mL) at rt for 1 h, filtered, and washed successively with DMF (3 \times), CH_2Cl_2 (3 \times), MeOH (3 \times), and CH_2Cl_2 (3 \times). To a slurry of the deprotected resin in CH_2Cl_2 (4 mL) was added a substituted isothiocyanate (5 equiv), and the mixture was agitated at rt for 8 h. The resin was filtered and washed in the same way as above. The resin was then treated with a secondary amine (5 equiv), DICDI (5 equiv), and $i\text{Pr}_2\text{NEt}$ (5 equiv) in CHCl_3 (4 mL) at 50°C for 2 d, and then filtered and washed in the same way as above. The resin was cleaved with 25% TFA/ CH_2Cl_2 (4 mL) at rt for 1 h, filtered, and washed with CH_2Cl_2 and MeOH. The filtrate was evaporated to dryness to give the desired products.

4-(Carboxybenzyl)guanidinium Trifluoroacetate (25, $\text{X} = 4\text{-HO}_2\text{CC}_6\text{H}_4\text{CH}_2$):^[78]

To a mixture of Wang resin (10 g, 6 mmol), Fmoc 4-aminomethylbenzoate (17.92 g, 48 mmol), DICDI (6.06 g, 48 mmol), BtOH (6.49 g, 48 mmol) in CH_2Cl_2 (80 mL), and DMF (20 mL) was added $i\text{Pr}_2\text{NEt}$ (2.32 g, 18 mmol). The mixture was agitated for 64 h, collected on a glass frit and rinsed with the wash solvents (100 mL each). Drying in a N_2 atmosphere gave Wang Fmoc 4-aminomethylbenzoate ester ($0.36\text{ meq}\cdot\text{g}^{-1}$ by cleavage). To a mixture of Fmoc 4-aminomethylbenzoate ester resin (70 mg, 25 μmol) and 1,3-bis(*tert*-butoxycarbonyl)thiourea (14 mg, 50 μmol) was added DICDI (6 mg, 50 μmol) in 1,2-dichloroethane (8 mL). After stirring for 9 d, the resin was washed with 10 mL of each rinse solvent. Drying, cleavage, and purification gave the product; yield: 6.7 mg (87%).

1,5-Disubstituted 2-Aryliminoimidazolidines 29; General Procedure:^[80]

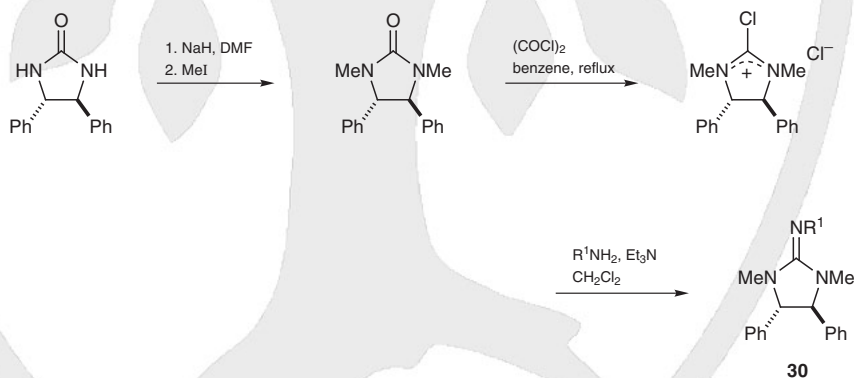
CAUTION: Hydrogen fluoride fumes are severely irritating and extremely destructive to the respiratory system.

The resin-bound diamine **26** was reacted with the aryl isothiocyanate (**27**; 5 equiv, 0.1 M) in the presence of HgCl_2 (5 equiv, 0.1 M) and Et_3N (5 equiv, 0.1 M) in anhyd DMF at rt overnight to afford the corresponding resin-bound guanidines. Following washes with DMF (3 \times), MeOH (3 \times), and CH_2Cl_2 (3 \times), the resin was cleaved by anhyd HF in the presence of PhOMe at 0 °C for 1.5 h. The product was extracted with 95% aq AcOH and lyophilized. Following purification by reversed-phase HPLC, the identities of the product aryliminoimidazolidines were confirmed by LC-MS, ^1H NMR, and ^{13}C NMR.

18.13.1.1.3**Method 3:****Reaction of Amines with 2-Chloro-4,5-dihydro-1H-imidazol-3-ium Chlorides**

The synthesis of guanidines from amines and 2-chloro-4,5-dihydro-1H-imidazol-3-ium chlorides is somewhat related to the classic synthesis of 2-amino-substituted pyrimidines based on the aromatic nucleophilic displacement of chloride by amines.^[81] The present method has been employed by a single research group to generate optically active 2-amino-4,5-dihydro-1H-imidazol-3-ium salts (five-membered 4,5-disubstituted cyclic guanidines). The approach consists of a three-step reaction sequence, starting from a chiral 4,5-disubstituted imidazolidin-2-one, which is dialkylated on nitrogens and then converted into the corresponding 2-chloro-4,5-dihydro-1H-imidazol-3-ium chloride, which is finally reacted with a primary amine to give the desired cyclic guanidine **30** (Scheme 15).^[82,83] The yields for the conversion of the 2-chloro-4,5-dihydro-1H-imidazol-3-ium chlorides into the corresponding cyclic guanidines are very good to excellent.

Scheme 15 Synthesis of Chiral Guanidines from Amines and Chiral 2-Chloro-4,5-dihydro-1H-imidazol-3-ium Chlorides^[82,83]



R ¹	Conditions	Yield (%) of 30	Ref
	CH ₂ Cl ₂ , rt	95	[82]
	CH ₂ Cl ₂ , rt	74	[82]
4-pyridyl	MeCN, 3 h	64	[83]
	MeCN, 0.3 h	84	[83]

(4*S*,5*S*)-1,3-Dimethyl-4,5-diphenylimidazolidin-2-imines **30; General Procedure:**^[82]

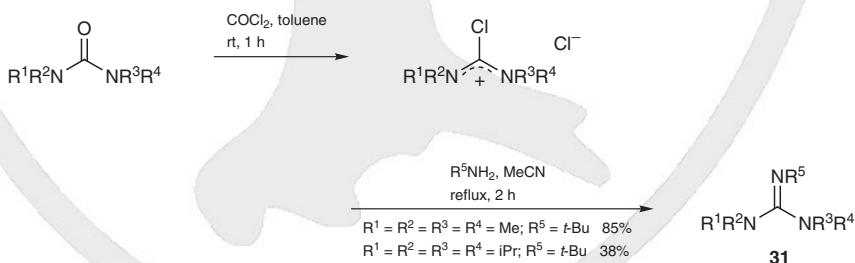
To a soln of a primary amine (8.94 mmol) and Et₃N (1.81 g, 17.9 mmol) in CH₂Cl₂ (50 mL) was added dropwise a soln of (4*S*,5*S*)-2-chloro-1,3-dimethyl-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium chloride (8.94 mmol) in CH₂Cl₂ (40 mL) at rt. The mixture was stirred at rt for 20 min, transferred to a dil HCl soln, and extracted with CH₂Cl₂ (2 × 100 mL). The organic soln was evaporated to dryness. The residue was dissolved in H₂O and washed with toluene (2 × 100 mL). The aqueous soln was made alkaline with dil aq NaOH and extracted with toluene. The toluene soln was dried (Na₂SO₄) and evaporated to dryness to yield pure guanidines. In some cases further purification was needed.

18.13.1.1.4

Method 4:**Reaction of Amines with Chloroformimidamides**

This method is closely related to that in Section 18.13.1.1.3, and a single report found in the literature illustrates its versatility, providing pentasubstituted guanidines **31** in moderate to good yields,^[84] even with bulky amines such as *tert*-butylamine (Scheme 16).

Scheme 16 Synthesis of Pentasubstituted Guanidines from Primary Amines and [Amino(chloro)methylene]ammonium Chlorides^[84]



2-*tert*-Butyl-1,1,3,3-tetramethylguanidine (31**, R¹ = R² = R³ = R⁴ = Me; R⁵ = *t*-Bu);**

Typical Procedure:^[84]

CAUTION: Phosgene is a severe respiratory irritant and very toxic by inhalation.

To a stirred soln of phosgene (8.29 g, 0.084 mol) in dry toluene (25 mL) at 0 °C was added dropwise a dried and distilled soln of tetramethylurea (5.00 g, 0.043 mol) in dry benzene (20 mL) (**CAUTION:** carcinogen). The mixture was left at rt for 1 h and then the solvents and

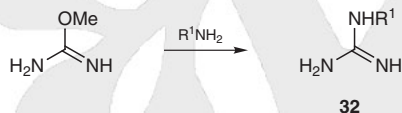
excess phosgene were evaporated. The crystalline hygroscopic residue was dissolved in MeCN (10 mL) and to this soln, cooled to 0 °C, was added dropwise with stirring, *t*-BuNH₂ (15 mL, 0.143 mol). The mixture was refluxed for 2 h and cooled, and the solvents were evaporated. The residue was triturated with Et₂O (4 × 50 mL) and mixed cautiously with 25% aq NaOH (40 mL). The product was extracted with Et₂O (2 × 125 mL) and the solvent was evaporated. The soln was filtered and evaporated to give a light yellow oil. Distillation under reduced pressure gave 2-*tert*-butyl-1,1,3,3-tetramethylguanidine as a liquid, which was stored under N₂; yield: 6.25 g (85%).

18.13.1.1.5

Method 5:**Reaction of Primary Amines with O-Methylisoureas**

This method has been of special interest in the synthesis of guanidine-bearing natural products.^[9,12] The method has also been of interest in preparing nucleotide mimetics and peptide mimetics. In a first example, a nucleotide-linked aminobutylphosphoramidate was converted into the corresponding guanidine, but no yield or an experimental procedure was given.^[85] In a second example, the synthesis of a modified arginine in di- and tripeptides [e.g., **32**, NHR¹ = Orn(α-CF₃)-Gly-Asp-NH(CH₂)₂Ph] was achieved in a good yield (Scheme 17).^[86] During the synthesis of naturally derived crambines (crambescins) and ptilomycin A, different authors used 2-methylisourea sulfate in order to introduce a masked guanidine function on the carbon skeleton; subsequent transformation to the guanidine group is achieved by treatment with ammonium hydroxide in methanol and anhydrous ammonia.^[87–90]

Scheme 17 Synthesis of Monosubstituted Guanidines from Primary Amines and O-Methylisourea^[85,86]



R ¹	Conditions	Yield (%)	Ref
(CH ₂) ₄ NHPO(OR ²) ₂ ^a	H ₂ O, 15% aq NH ₃ , 65 °C, 45 min	– ^b	[85]
	2 M NaOH, 75 °C, 1 h	75	[86]

^a R² = 2-deoxyribose (mixture of α- and β-epimers).

^b Yield not reported.

Modified Arginine in a Tripeptide; H-Arg(α-CF₃)-Gly-Asp-NH(CH₂)₂Ph·HBr

[**32**, NHR¹ = Orn(α-CF₃)-Gly-Asp-NH(CH₂)₂Ph]; **Typical Procedure:**^[86]

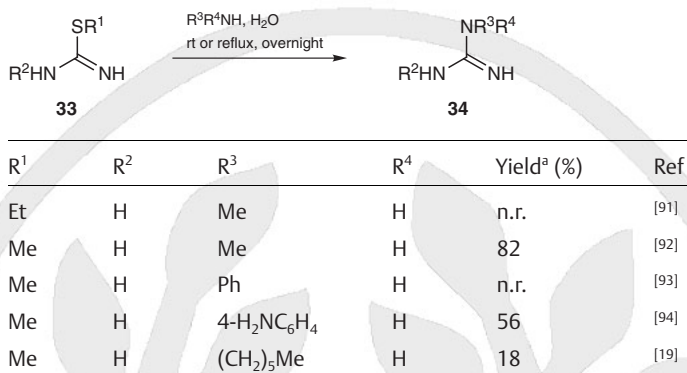
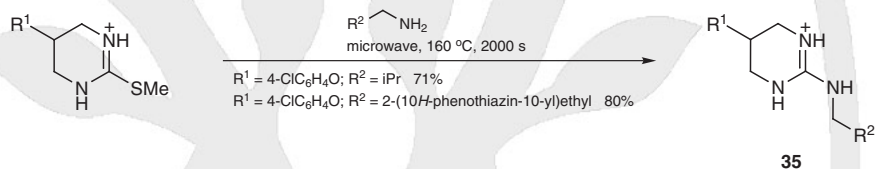
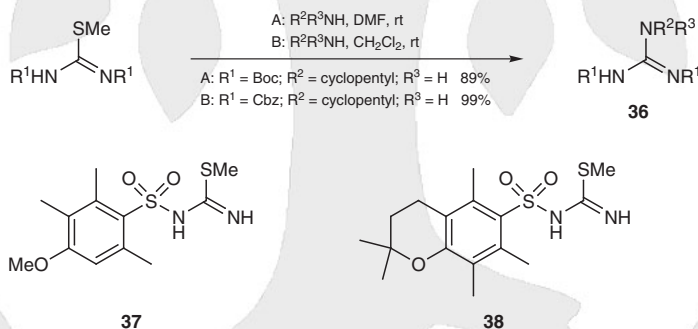
The unpurified tripeptide H-Orn(α-CF₃)-Gly-Asp-NH(CH₂)₂Ph (720 mg, 1.024 mmol) was dissolved in H₂O (99 mL) and 2-methylisourea sulfate (1.763 g, 10.24 mmol) was added, followed by 2 M NaOH (11.8 mL). Maintenance of pH 10 during the reaction was essential. The mixture was heated at 75 °C for 1 h with stirring. After 1 h, the reaction was complete. The product was recovered as a TFA salt (purity >99%); yield: 75%. In order to convert the TFA salt into the HBr salt, the product (100 mg) was dissolved in 0.1 M HBr (2.77 mL), concentrated to a small volume under reduced pressure at a temperature of about 30 °C, di-

luted with H₂O (5 mL), and taken to dryness. The residue was redissolved in H₂O and taken to dryness again, and the same operation repeated several times. At the end, the products were dissolved in H₂O (5 mL) and lyophilized to obtain the pure tripeptide HBr salt; yield: 85 mg.

18.13.1.1.6

Method 6:**Reaction of Amines with 2-Methylisothioureas**

The synthesis of guanidines from primary and secondary amines and alkylisothioureas (also known as alkylpseudothioureas) has been known since the 1920s. Early examples of this method are shown in Scheme 18. While reaction yields with 2-ethylisothiourea have not been provided,^[91] reaction with 2-methylisothiourea (**33**, R¹ = Me; R² = H) gives good yields in the presence of methylamine or dimethylamine, but moderate to fair yields with larger amines.^[19,92–94] The reaction yields are improved within a microwave-assisted system, where cyclic guanidines such as **35** are obtained from cyclic 2-methylisothioureas (Scheme 19) in moderate to good yields.^[22] By far the commonest use, of widest application in synthesis, is the preparation of protected guanidines, since the unprotected derivatives are strongly basic. Different protecting groups have been introduced in 2-methylisothiourea as a precursor of protected guanidines. The preparation of mono- or bis(*tert*-butoxycarbonyl)guanidines **36** (R¹ = Boc), or bis(benzyloxycarbonyl)guanidines **36** (R¹ = Cbz), is more often found (Scheme 20). Both protecting groups provide the corresponding protected guanidines in good to excellent yields, except in the case of bulky amines (e.g., *tert*-butylamine).^[95] The conversion of 1,3-bis(benzyloxycarbonyl)-protected 2-methylisothiourea carboxylic acids into their respective guanidine counterparts, using chlorotrimethylsilane as a coupling reagent, gives the products with very good to excellent yields.^[96] Alternatively, 1-fluoro-2,4-dinitrobenzene (Sanger's reagent) is also used in the preparation of 3-arylbis(*tert*-butoxycarbonyl)-1-methylguanidines, with yields ranging from very poor in the case of electron-withdrawing aromatic substituents to very good in the case of electron-donating aromatic substituents.^[97] The efficacy of the reaction of amines with protected 2-methylisothiourea is improved by the use of 2-bromobenzyloxycarbonyl and 2-chlorobenzyloxycarbonyl protecting groups rather than benzyloxycarbonyl, although no yields or procedures for these reactions are provided.^[95] Interesting examples of the use of benzyloxycarbonyl-protected 2-methylisothioureas in the synthesis of guanidines are known. These include the synthesis of (aminocarbonyl)guanidines starting from mono- and bis(benzyloxycarbonyl)-protected 2-methylisothioureas.^[98] Another example is the synthesis of 1,2,5-trisubstituted 4,5-dihydroimidazoles from diamines using 1,3-bis(methoxycarbonyl)-2-methylisothiourea as a masked guanidine, in very satisfactory yields.^[99] Additionally, 1-[(4-methoxy-2,3,6-trimethylbenzene)sulfonyl] (Mtr) and 1-[(2,2,5,7,8-pentamethyl-3,4-dihydro-2H-1-benzopyran-6-yl)sulfonyl] (Pmc) protected 2-methylisothioureas (**37** and **38**, respectively) have been proposed as alternative reagents for the synthesis of guanidines, from various amines under conditions that provide the corresponding protected guanidines in yields varying from poor to very good.^[100] The use of protected and unprotected 2-methylisothioureas in the synthesis of guanidines is of wide application. It includes the synthesis of guanidines on multivalent soluble supports,^[101] synthesis of nitroguanidines as potent insecticides,^[102] the synthesis of guanidine-bearing sugar mimetics,^[103–106] synthesis of modified arginines and peptide mimetics,^[107–109] of a fluorescent probe within a superpotent sweetening guanidine,^[110] of selective nonpeptidic thrombin inhibitors,^[111] inhibitors of influenza neuraminidase,^[112] and many others.^[40,113–117]

Scheme 18 Synthesis of Mono- and 1,1-Disubstituted Guanidines from Primary or Secondary Amines and Alkylisothiureas^[19,91–94]^a n.r. = not reported.**Scheme 19** Microwave-Assisted Synthesis of 5-Phenoxy-2-(alkylamino)-1,4,5,6-tetrahydropyridinium Trifluoroacetates^[22]**Scheme 20** Synthesis of Bis(*tert*-butoxycarbonyl)- or Bis(benzyloxycarbonyl)-Protected Guanidines from Bis(*tert*-butoxycarbonyl)- or Bis(benzyloxycarbonyl)-Protected Methylisothiurea^[95]**Methylguanidine (34, R² = R⁴ = H; R³ = Me); Typical Procedure:**^[91]

The hydrobromide salt of 2-ethylisothiurea (**33**, R¹ = Et; R² = H) was dissolved in an excess of a 33% soln of MeNH₂ and allowed to stand overnight. The excess of amine and EtSH was then evaporated and the soln, after filtering from a slight turbidity, was divided into two parts. One part was precipitated with picric acid; the picrate formed needles which melted sharply at 200 °C. The remaining soln was precipitated with aq 5-methyl-4-nitro-2-(4-nitrophenyl)-2,4-dihydro-3*H*-pyrazol-3-one (picrolonic acid). The salt formed a compact, not bulky, yellow precipitate which when recrystallized (H₂O) formed minute, diamond-shaped tables or blocks. The product was obtained as a picrolonic acid salt. It decomposed with effervescence at 291 °C.

Alternative Synthesis of Methylguanidine (34, $R^2 = R^4 = H$; $R^3 = Me$); Typical Procedure:^[92]

To a suspension of 2-methylisothiourea sulfate (**33**, $R^1 = Me$; $R^2 = H$; 700 g) in cold H_2O (700 mL) was added, all at once, 33% aq $MeNH_2$ (525 g). The vessel was immediately fitted with a reflux condenser, from the upper end of which tubes led the evolved gas through a wash bottle containing 10% aq HCl (250 mL; to remove any entrained $MeNH_2$), then into 25% $NaOH$ soln (700 mL) cooled by running H_2O . When the mixture in the flask was shaken and gently warmed, a vigorous reaction set in at about 30 °C; $MeSH$ was evolved at a steady rate without application of heat. When the reaction slackened, the mixture was heated until finally it boiled. It was then concentrated under reduced pressure until the weight was ca. 1000 g. The resulting syrup was chilled to –5 °C, whereupon it set to a mass of crystals. $MeOH$ (300 mL) was then added and the crystals were collected by suction and washed with cold $MeOH$ in which the product, obtained as a sulfuric acid salt, was practically insoluble; yield: 500 g (82%).

5-(4-Chlorophenoxy)-2-(isobutylamino)-3,4,5,6-tetrahydropyrimidin-1-ium Trifluoroacetate (35, $R^1 = 4-ClC_6H_4O$; $R^2 = iPr$); Typical Procedure:^[22]

To a soln of 5-(4-chlorophenoxy)-2-(methylsulfanyl)-3,4,5,6-tetrahydropyrimidin-1-ium trifluoroacetate (37 mg, 0.10 mmol) in $MeCN$ (0.6 mL) was added $iBuNH_2$ (8 mg, 0.11 mmol) and the mixture was heated for 800 s at 160 °C in a microwave. The mixture was diluted with $MeCN$ (0.3 mL) and THF (0.9 mL) and the excess of 5-(4-chlorophenoxy)-2-(methylsulfanyl)-3,4,5,6-tetrahydropyrimidin-1-ium trifluoroacetate was scavenged with Wang resin (0.25 mmol). After the mixture was heated for an additional 1000 s at 150 °C in the microwave, $MeNCO$ on resin (0.30 mmol) was added to remove the unreacted amine. The resins were filtered off and washed with CH_2Cl_2 (2 mL) and $MeOH$ (2 × 2 mL), and the organic layer was concentrated in vacuo to give the product as a yellow oil; yield: 20 mg (71%).

Bis(*tert*-butoxycarbonyl)- or Bis(benzyloxycarbonyl)-Protected Guanidines 36 ($R^1 = Boc, Cbz$); General Procedure:^[95]

To a soln of either 1,3-bis(*tert*-butoxycarbonyl)-2-methylisothiourea or 1,3-bis(benzyloxycarbonyl)-2-methylisothiourea (0.5 mmol) in DMF or CH_2Cl_2 (2 mL) was added the amine (1 mmol), and optionally $DMAP$ (0.05 mmol), and the mixture was stirred at rt until completion (TLC). The solvent was evaporated, the residue dissolved in $EtOAc$ (50 mL), and the organic phase was successively washed with 10% aq citric acid (3 × 10 mL), sat. aq $NaHCO_3$ (3 × 10 mL), and H_2O (3 × 10 mL). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to dryness to give the corresponding protected guanidine.

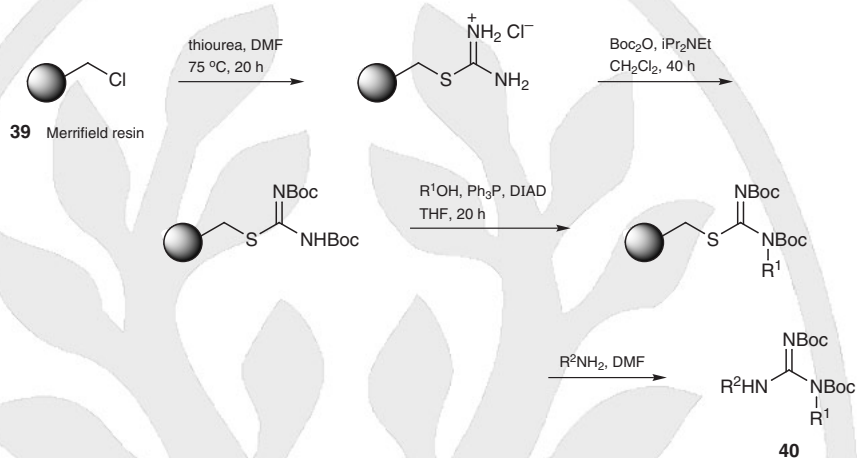
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Variation 1:**Solid-Phase Synthesis of Amines with Methylisothioureas**

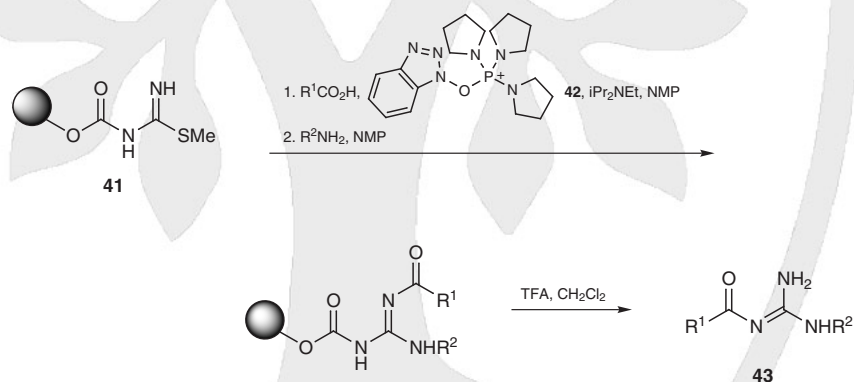
As in the solid-phase synthesis of guanidines from thioureas, the solid-phase synthesis from isothioureas also has been explored and found some applications. An early example of solid-phase synthesis of guanidines makes use of a Merrifield resin (**39**), which is derivatized with thiourea, bis(*tert*-butoxycarbonyl)-protected, *N*-alkylated under Mitsunobu conditions, and reacted with different amines in order to give the corresponding bis(*tert*-butoxycarbonyl)-protected guanidines **40** in very good yields (Scheme 21).^[118] Another example is the solid-phase synthesis of substituted arylguanidines from *N*-aryl-substituted 2-methylisothioureas in very good yields.^[119] Two additional examples report the solid-phase synthesis of acylguanidines. The first one involves the use of Wang resin bound 1-carboxy-2-methylisothiourea **41**, which is *N*-acylated in the presence of 7-azabenzotriazol-1-yloxy(tripyrrolidin-1-yl)phosphonium hexafluorophosphate (PyAOP, **42**) as a coupling reagent, reacted with different primary amines in 1-methylpyrrolidin-2-one, and the resin removed by trifluoroacetic acid to give products **43**. Although no yields of such

reactions are provided, the purity of products indicates a clean reaction sequence (Scheme 22).^[120] The second example includes a somewhat extended investigation on the solid-phase synthesis of 1-acyl-3-alkyl-2-ureidoguanidines, employing both Wang and Rink resins. Resin cleavage by trifluoroacetic acid gives a variety of differently substituted guanidines, in general with excellent overall yields.^[121]

Scheme 21 Solid-Phase Synthesis of Bis(*tert*-butoxycarbonyl)-Protected Guanidines^[118]



Scheme 22 Solid-Phase Synthesis of 3-Substituted 1-Acylguanidines^[120]



R ¹	R ²	HPLC Purity of 43 (%)	Ref
iBu	Bn	>95	[120]
2,6-Cl ₂ C ₆ H ₃ CH ₂	Pr	>95	[120]

1,2-Bis(*tert*-butoxycarbonyl)-1-(2-phenoxyethyl)guanidine [40, R¹ = (CH₂)₂OPh; R² = H] and 3-Benzyl-1,2-bis(*tert*-butoxycarbonyl)-1-(2-phenoxyethyl)guanidine [40, R¹ = (CH₂)₂OPh; R² = Bn]; Typical Procedure:^[118]

A mixture of Merrifield resin (**39**; 2.5 g, 2.35 mmol; Cl load of 0.94 mol·g⁻¹) and thiourea (0.94 g, 11.8 mmol) in DMF (25 mL) was heated at 75 °C for 16 h. The resin-bound isothiourethane was washed successively with DME (4 × 50 mL), THF (3 × 50 mL), MeOH (3 × 50 mL), and CH₂Cl₂ (3 × 50 mL). The resin-bound isothiourethane was dried under high vacuum for

10 h. Subsequently, the resin-bound isothioureia and Boc_2O (3.0 g, 14.0 mmol) were slurried in CH_2Cl_2 (50 mL) and treated with iPr_2NEt (4.1 mL, 24 mmol) over 5 min, and were subsequently gently shaken for 40 h. The resin-bound bis(*tert*-butoxycarbonyl)isothioureia was washed using the sequence of solvents described above and dried under high vacuum for 10 h. A 250-mg sample of resin-bound bis(*tert*-butoxycarbonyl)isothioureia in dry THF (4 mL) was treated with sat. NH_3 in MeOH (0.5 mL) and shaken for 12 h to liberate bis(*tert*-butoxycarbonyl)guanidine (45 mg, 92% based on starting Merrifield resin) as the only product, thus establishing the resin load of bis(*tert*-butoxycarbonyl)isothioureia to be $0.7 \text{ mmol} \cdot \text{g}^{-1}$. To a mixture of resin-bound bis(*tert*-butoxycarbonyl)isothioureia (250 mg, 0.175 mmol), Ph_3P (175 mg, 0.875 mmol), and 2-phenoxyethanol (110 μL , 0.875 mmol) in dry THF (3 mL) was added diisopropyl azodicarboxylate (DIAD; 175 μL , 0.85 mmol). The mixture was gently shaken for 14 h, and the resin was washed as described above and air dried. To a portion (100 mg) of the resin in dry DMF (3 mL) was added a sat. soln of NH_3 in MeOH (300 μL , excess). The mixture was shaken for 15 h. The cleaved material was isolated and the resin rinsed with THF ($2 \times 1 \text{ mL}$). The solvent was removed in vacuo to give 1,2-bis(*tert*-butoxycarbonyl)-1-(2-phenoxyethyl)guanidine; yield: 24 mg (100%, assumed loading of $0.7 \text{ mmol} \cdot \text{g}^{-1}$) with HPLC purity >98%. A second batch of the resin-bound phenoxyethylisothioureia (100 mg) was suspended in DMF (2 mL) and was treated with BnNH_2 (3 equiv) at 50°C for 16 h. The resin was filtered and rinsed with THF ($2 \times 1 \text{ mL}$) and the solvent was removed in vacuo. The product was dissolved in CH_2Cl_2 (3 mL) and the contaminating excess amine was scavenged using a fourfold excess of isocyanate resin at 30°C for 12 h to give 3-benzyl-1,2-bis(*tert*-butoxycarbonyl)-1-(2-phenoxyethyl)guanidine; yield: 27 mg (90%).

Solid-Phase Synthesis of 3-Substituted 1-Acylguanidines 43; General Procedure:^[120]

A mixture of 4-nitrophenylcarbonate resin (2.5 g, $1.1 \text{ mmol} \cdot \text{g}^{-1}$, 2.75 mmol), *S*-methylisothiuronium sulfate (1.9 g, 6.88 mmol), and Cs_2CO_3 (9 g, 28 mmol) was suspended in dry DMF (70 mL). The mixture was shaken vigorously for 48 h at rt. The resin was washed successively with 10% $\text{H}_2\text{O}/\text{DMF}$ ($3 \times 50 \text{ mL}$), DMF ($3 \times 30 \text{ mL}$), THF ($3 \times 30 \text{ mL}$), and CH_2Cl_2 ($3 \times 30 \text{ mL}$). The 1-carboxy-2-methylisothioureia resin **41** was dried under high vacuum for 10 h. A mixture of the 1-carboxy-2-methylisothioureia resin **41** (0.1 mmol), a carboxylic acid derivative (0.3 mmol), and PyAOP (**42**; 160 mg, 0.3 mmol) was slurried in NMP (2 mL), treated dropwise with iPr_2NEt (175 mL, 1 mmol), and gently shaken for 60 h, although the reactions in most instances were complete within 24–48 h. The resin was washed using the sequence of solvents described above and dried under high vacuum. A sample of the acylated resin (0.05 mmol) in dry NMP (1 mL) was treated with the amine (0.25 mmol) and shaken at rt for 48 h [for amine hydrochlorides, iPr_2NEt (1 mmol) was added to the mixture]. The resin-bound product was washed thoroughly with DMF ($3 \times 2 \text{ mL}$), THF ($4 \times 2 \text{ mL}$), and CH_2Cl_2 ($4 \times 2 \text{ mL}$), suspended in 25% TFA/ CH_2Cl_2 (1 mL), and shaken for 1.5 h. The filtrate was collected and concentrated in vacuo. The purity of the isolated product was established by HPLC using UV (220 nm) and ELS detectors.

18.13.1.1.7

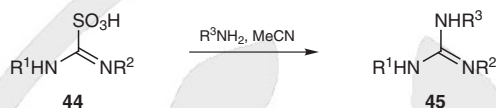
Method 7:

Reaction of Primary Amines with Alkylamino(imino)methanesulfonic Acids

Alkylamino(imino)methanesulfonic acids **44** have proven to be suitable reagents for the generation of guanidines **45** from amines, since it has been demonstrated that even bulky amines react with these amidine sources in very good yields (Scheme 23).^[122,123] Two systematic investigations demonstrated that α -guanidino acids can be obtained from α -amino acids in low to moderate or good yields with the same amidine source.^[124,125] Various guanidines are obtained from amines and 1,3-diaryl-substituted thioureas which have been oxidized in situ to either the corresponding sulfinic or sulfonic acid derivatives, in the presence of benzyltriethylammonium permanganate (BTEAP), tetrabutylammoni-

um permanganate (TBAP), or hexadecyltrimethylammonium permanganate (CTMAP), in moderate yields.^[126] Amino(imino)methanesulfonic acid is used in a total synthesis of the marine-algae-derived cyclopropyl amino acid carnosadine.^[127]

Scheme 23 Synthesis of 1,2,3-Trisubstituted Guanidines from N,N'-Disubstituted Amino(imino)methanesulfonic Acids^[122,123]



1,2,3-Trisubstituted Guanidines 45 from N,N'-Disubstituted Amino(imino)methanesulfonic Acids; General Procedure:^[122]

The substituted amino(imino)methanesulfonic acid **44** (0.01 mol) was added to the amine (0.013 mol) in MeCN (5 mL) at rt. In some cases an exotherm was observed. In some cases, it was necessary to warm the mixture to reflux to ensure complete reaction. Upon completion (TLC), the reaction was worked up by adjusting the pH to the range of 12–14 with 3 M NaOH. In some cases, the desired guanidine formed as a solid precipitate and was then isolated by filtration. Otherwise, the mixture was extracted rapidly with CH₂Cl₂, dried (Na₂SO₄), and concentrated. The desired guanidine was obtained in a purity ranging from 80–95%. The guanidine could be further purified by recrystallization (hexane) by or formation of an appropriate salt.

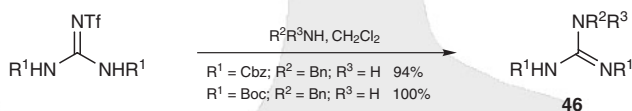
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Method 8:

Reaction of Primary Amines with (Trifluoromethylsulfonyl)guanidines

Commercially available N-activated N-(trifluoromethylsulfonyl)guanidines are useful reagents for the conversion of amines into protected guanidines. A systematic study with 12 amines demonstrated an efficient interconversion into their respective protected guanidines **46** with excellent yields (Scheme 24).^[128,129] (Trifluoromethylsulfonyl)guanidines are useful in solid-phase synthesis of guanidines,^[79,130] as well in the synthesis of guanidinoglycosides, inhibitors of HIV-1 replication in HeLa cells.^[131]

Scheme 24 Synthesis of 1,3-Bis(*tert*-butoxycarbonyl)- or 1,3-Bis(benzyloxycarbonyl)-Protected Guanidines from the Corresponding Protected (Trifluoromethylsulfonyl)guanidines^[128,129]



1,3-Bis(*tert*-butoxycarbonyl)- or 1,3-Bis(benzyloxycarbonyl)-Protected Guanidines 46 from the Corresponding Protected (Trifluoromethylsulfonyl)guanidines;

General Procedure:^[128,129]

In a typical reaction, the amine (0.5 mmol) was added neat to a soln of 1,3-bis(*tert*-butoxycarbonyl)-2-(trifluoromethylsulfonyl)guanidine or 1,3-bis(benzyloxycarbonyl)-2-(trifluoromethylsulfonyl)guanidine (0.45 mmol) and Et₃N (0.5 mmol) in CH₂Cl₂ (2 mL, filtered over neutral alumina) or CHCl₃, and the mixture was allowed to stir at rt until the guanidine reactant was consumed (TLC). After the reaction was complete, the mixture was diluted with CH₂Cl₂ or CHCl₃ (3 mL) and washed with 2 M NaHSO₄, sat. NaHCO₃, and brine. The organic extract was then dried (Na₂SO₄) and filtered, and the solvent was removed under

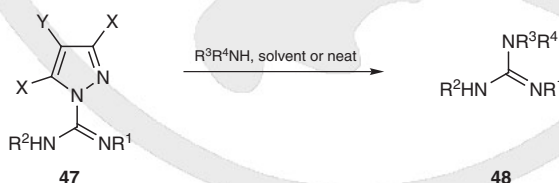
reduced pressure. The crude products were further purified by flash column chromatography to afford material suitable for elemental analysis or reversed-phase analytical HPLC.

18.13.1.1.9

Method 9:**Reaction of Primary Amines with 1*H*-Pyrazole-1-carboximidamides**

The synthesis of guanidines **48** from 1*H*-pyrazole-1-carboximidamides has been known for more than 50 years. The yields of such reactions are moderate to good, independent of the nature of the amine (Scheme 25).^[132–134] Analogously, 1,3-bis(*tert*-butoxycarbonyl)- or 1,3-bis(benzyloxycarbonyl)-protected guanidines **49** have been prepared in excellent yields (Scheme 26).^[135,136] A comparative study on the reactivity of bis(*tert*-butoxycarbonyl)-protected 1*H*-pyrazole-1-carboximidamide **47** ($R^1 = R^2 = \text{Boc}$; $X = Y = \text{H}$) and its corresponding 4-nitro derivative **47** ($R^1 = R^2 = \text{Boc}$; $X = \text{H}$; $Y = \text{NO}_2$) demonstrated the superior reaction rates and yields of the nitro reagent, even with unreactive amines (Scheme 25).^[137] Another superior reagent for the synthesis of guanidines is *N*-(*tert*-butoxycarbonyl)-*N'*-tosyl-1*H*-pyrazole-1-carboximidamide (**47**, $R^1 = \text{Boc}$; $R^2 = \text{Ts}$; $X = Y = \text{H}$), which significantly accelerates the reaction rates and provides products in excellent yields.^[138] The protecting groups are easily removed by hydrolysis with trifluoroacetic acid or by hydrogenolysis. Reagents for the solid-phase synthesis of guanidines using resin-bound 1*H*-pyrazole-1-carboximidamide have also been developed, giving the corresponding guanidines in moderate to very good yields.^[139–141] An *N*-*tert*-butoxycarbonyl-protected 1*H*-pyrazole-1-carboximidamide linker on TentaGel-NH₂ derivatized resin reacts with both primary and secondary amines in very good yields.^[139] In a second example, the amidine source for guanidine formation with amines is prepared from a Wang-based carbamate linked directly to 1*H*-pyrazole-1-carboximidamide, which is subsequently acylated and reacted with different amines, giving, after resin cleavage, the corresponding acylguanidines in moderate to good yields.^[140] A third example compares the effectiveness of formation of guanidines **52** from new amidine-transfer reagents, 4-benzyl-3,5-dimethyl-1*H*-pyrazole-1-carboximidamide (**50**) and Merrifield resin bound 3,5-dimethyl-1*H*-pyrazole-1-carboximidamide **51** (Scheme 27).^[141] Applications of the synthesis of guanidines from 1*H*-pyrazole-1-carboximidamides include the preparation of sugar mimetics as a potential influenza virus hemagglutinin inhibitor,^[142] the synthesis of catalysts for the transesterification of 2-hydroxypropyl 4-nitrophenyl phosphate,^[143] the solid-phase synthesis of an unnatural dioxopiperazine catalyst of enantioselective Strecker reactions,^[144] the synthesis of RGD analogues,^[86] synthesis of carbohydrate-based cRGDFV analogues,^[145] the design and synthesis of thrombin-receptor-derived nonpeptide mimetics,^[146] as well as in the synthesis of many naturally derived guanidines.^[9–12]

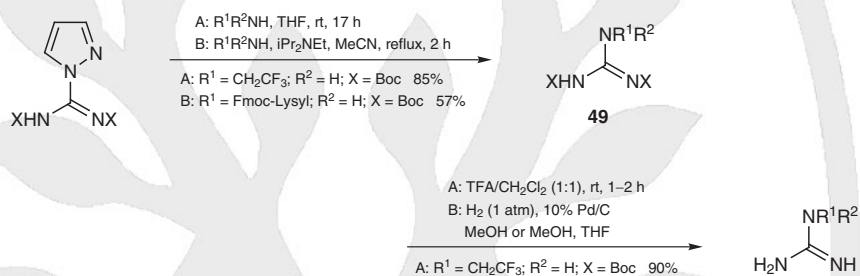
Scheme 25 Synthesis of Guanidines from 1*H*-Pyrazole-1-carboximidamides and Primary or Secondary Amines^[132–134,138]



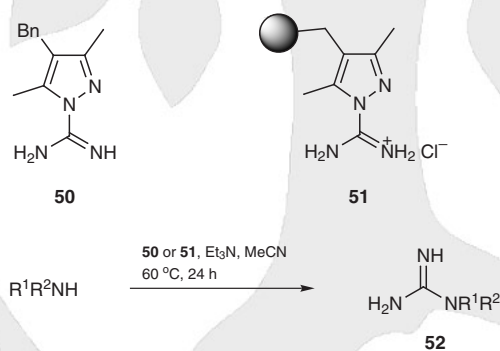
X	Y	R ¹	R ²	R ³	R ⁴	Conditions	Yield (%)	Ref
Me	H	H	H	Ph	H	neat, reflux 2 h	79	[132]
Me	H	H	H	Cy	H	– ^a	85	[133]
H	H	H	H	CH ₂ CO ₂ H	H	1.0 M Na ₂ CO ₃ , rt, 3 h	77	[134]
H	H	Boc	Boc	Bn	H	DMF	80	[134]
H	NO ₂	Boc	Boc	Bn	H	DMF	94	[134]
H	H	Boc	Ts	CH ₂ CO ₂ Me	H	DMF, 5 h	100	[138]
H	H	Boc	Ts	4-O ₂ NC ₆ H ₄	H	DMF, 24 h	0	[138]

^a Not reported.

Scheme 26 Synthesis of 1,3-Bis(*tert*-butoxycarbonyl)- or 1,3-Bis(benzyloxycarbonyl)-Protected Guanidines from *N,N'*-Bis(*tert*-butoxycarbonyl)- or *N,N'*-Bis(benzyloxycarbonyl)-Protected 1*H*-Pyrazole-1-carboximidamides and Primary or Secondary Amines^[135,136]



Scheme 27 Synthesis of Guanidines from 4-Benzyl-3,5-dimethyl-1*H*-pyrazole-1-carboximidamide or from Merrifield Resin Bound 3,5-Dimethyl-1*H*-pyrazole-1-carboximidamide^[141]



R ¹	R ²	Amidine Reagent	Yield (%)	Ref
Cy	H	50	96	[141]
Cy	H	51	69	[141]
	(CH ₂) ₅	50	92	[141]
	(CH ₂) ₅	51	82	[141]

2-Guanidinoacetic Acid (48, $R^1 = R^2 = R^4 = H$; $R^3 = CH_2CO_2H$); Typical Procedure:^[134]

A mixture of glycine (0.15 g, 2.0 mmol), 1*H*-pyrazole-1-carboximidamide hydrochloride (0.293 g, 2.0 mmol), and 1.0 M Na_2CO_3 (2.0 mL) was stirred for 3 h at rt. The white solid product which separated was collected and washed with several small portions of MeOH/ H_2O (1:1). The product was dried to constant weight in vacuo; yield: 178 mg (77%).

Guanidines 48 by Reaction of Amines with *N,N'*-Bis(*tert*-butoxycarbonyl)-4-nitro-1*H*-pyrazole-1-carboximidamide; General Procedure:^[134]

A 0.2 M soln of the amine in anhyd DMF was treated with *N,N'*-bis(*tert*-butoxycarbonyl)-4-nitro-1*H*-pyrazole-1-carboximidamide (1.2 equiv) and stirred at 25 °C until reaction was judged complete (TLC). Upon completion, the solvent was evaporated, and the residue was redissolved in Et₂O and washed with H₂O. The organic layer was dried (MgSO₄), the solvent was evaporated, and the product was purified by flash chromatography.

Guanidines 48 by Reaction of Amines with *N*-(*tert*-Butoxycarbonyl)-*N'*-tosyl-1*H*-pyrazole-1-carboximidamide; General Procedure:^[138]

A mixture of *N*-(*tert*-butoxycarbonyl)-*N'*-tosyl-1*H*-pyrazole-1-carboximidamide (21.8 mg, 0.06 mmol) and the amine (0.055 mmol) in THF (0.5 mL) was stirred at rt for 5 min. H₂O and EtOAc were added, and the organic layer was washed with 0.5 M citric acid, H₂O, and brine, and dried (Na₂SO₄). After removal of solvent in vacuo, the residue was purified by chromatography (silica gel, EtOAc/hexane 3:1).

1,3-Bis(*tert*-butoxycarbonyl)- or 1,3-Bis(benzyloxycarbonyl)-Protected Guanidines 49 from the Corresponding Protected 1*H*-Pyrazole-1-carboximidamides and Primary or Secondary Amines; General Procedure:^[135]

To *N,N'*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboximidamide hydrochloride or *N,N'*-bis(benzyloxycarbonyl)-1*H*-pyrazole-1-carboximidamide hydrochloride (1.0 mmol) was added the amine (1.1 mmol) followed by dry THF (0.3–0.4 mL) and the resulting mixture was stirred at rt. At the end of the reaction, the medium was diluted with hexanes and transferred to a short silica gel (15 g) column and the products separated from unreacted reagents by a stepwise gradient elution from 0 to 30% EtOAc in hexanes. Crystalline products were obtained after evaporation of the solvents.

Alternative Synthesis of 1,3-Bis(*tert*-butoxycarbonyl)guanidines 49; General Procedure:^[136]

To a stirred soln of *N,N'*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboximidamide hydrochloride (1.55 g, 5 mmol), and *i*Pr₂NEt (1.05 mL, 6 mmol) in MeCN/ H_2O (95:5, 25 mL) was added the appropriate amino acid (5 mmol) and the mixture was stirred at rt or reflux for 2–20 h, depending on the amino acid. After the reaction was complete (TLC, CH₂Cl₂/MeOH 9:1), the solvent was removed under reduced pressure and the residue dissolved in EtOAc (50 mL). The organic phase was washed with 5% HCl (2 × 25 mL) and brine, and dried (MgSO₄). The solvent was removed under reduced pressure to yield the product, which was purified either by crystallization and/or by column chromatography.

Piperidine-1-carboximidamide [52, $R^1, R^2 = (CH_2)_5$]; Typical Procedure:^[141]

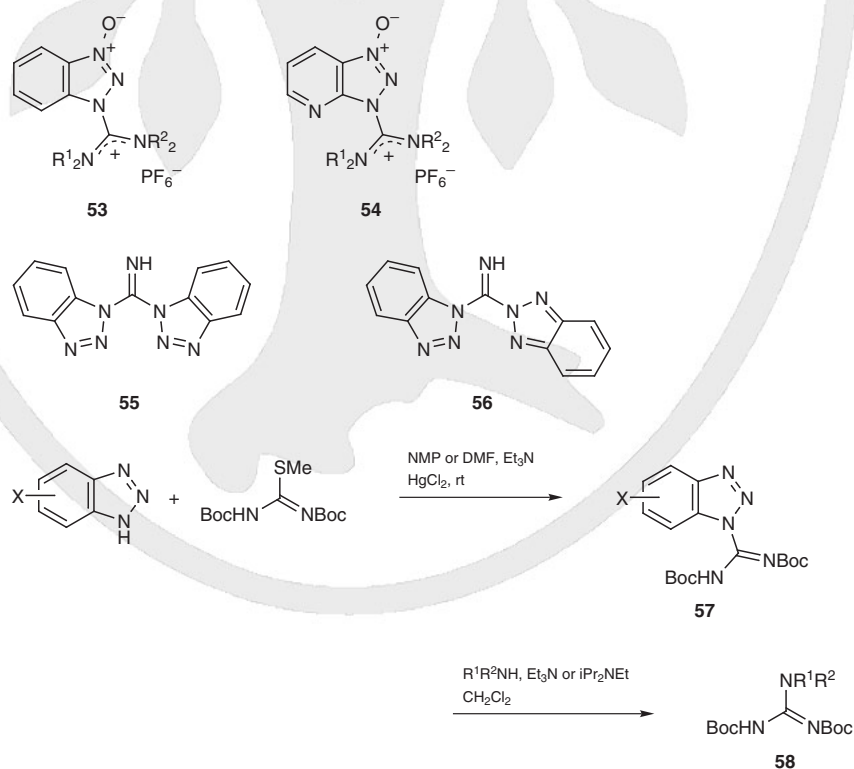
The resin-bound amidine **51** (870 mg), piperidine (29.7 μ L, 0.3 mmol), and Et₃N (208 μ L, 1.5 mmol) in dry THF (4 mL) were stirred at 60 °C for 24 h. After completion of the reaction (TLC) the mixture was filtered, the resin on the filter was washed with THF (2 × 2 mL) and MeOH (3 × 4 mL), and the combined filtrates were evaporated in vacuo. The residue was taken up in H₂O (5 mL) and passed through a column of Amberlite IRA-400 (hydroxide-form, 10 mL), eluting with H₂O. The eluate was cooled to –30 °C and lyophilized affording the product as a light green adhesive solid; yield: 31 mg (82%).

18.13.1.1.9.1

Variation 1:**Reaction of Amines with Di-1*H*-benzotriazol-1-ylmethanimines and with Di-1*H*-imidazol-1-ylmethanimine**

Di-1*H*-benzotriazol-1-ylmethanimines and di-1*H*-imidazol-1-ylmethanimine have been introduced as new reagents for generating guanidines from amines.^[147–151] Amino(1*H*-benzotriazol-1-yl)methaniminium salts **53** and their 7-aza analogues **54** were originally designed for the solid-phase synthesis of modified peptides, introducing a guanidine group on a lysine residue.^[147] The benzotriazolylmethanimine reagent is obtained by a stepwise sequence from an *N,N*-disubstituted carbamic chloride. Although no yields or experimental details have been provided for such reactions, the purity of the products are excellent, suggesting the method is a very good alternative for guanidine synthesis.^[147] Simpler reagents for the synthesis of guanidines, di-1*H*-benzotriazol-1-ylmethanimine (**55**) and 1*H*-benzotriazol-1-yl-(2*H*-benzotriazol-2-yl)methanimine (**56**), are obtained from 1*H*-benzotriazole and cyanogen bromide.^[148] Sequential reaction of **56** with two amines gives substituted guanidines in moderate to good yields.^[148] A variation on the same theme is the preparation of bis(*tert*-butoxycarbonyl)-protected guanidines **58** from two different *N,N'*-bis(*tert*-butoxycarbonyl)-protected 1*H*-benzotriazole-1-carboximidamides **57** (X = 5-Cl, 6-NO₂) in moderate to good yields (Scheme 28).^[149] Subsequently, an array of polysubstituted guanidines and acylguanidines has been synthesized by this method.^[150] Di-1*H*-imidazol-1-ylmethanimine is a somewhat similar reagent for the synthesis of guanidines, prepared from imidazole and cyanogen bromide.^[151] Di-1*H*-imidazol-1-ylmethanimine reacts sequentially with two amines, giving guanidines in moderate to good yields, depending on the nucleophilicity of the second amine in the displacement of the remaining imidazole group.^[151]

Scheme 28 Synthesis of Guanidines from *N,N'*-Bis(*tert*-butoxycarbonyl)-Protected 1*H*-Benzotriazole-1-carboximidamides^[146,149]



X	R ¹	R ²	Reaction Time (h)	Yield (%) of 58	Ref
H	Ph	H	1	60	[149]
H	Ph	H	2	90	[149]
5-Cl	Ph	H	1	70	[146]

***N,N'*-Bis(*tert*-butoxycarbonyl)-1*H*-benzotriazole-1-carboximidamide (57, X = H), *N,N'*-Bis(*tert*-butoxycarbonyl)-5-chloro-1*H*-benzotriazole-1-carboximidamide (57, X = 5-Cl), and *N,N'*-Bis(*tert*-butoxycarbonyl)-6-nitro-1*H*-benzotriazole-1-carboximidamide (57, X = 6-NO₂);**^[149]

CAUTION: Mercury(II) chloride is a poison by ingestion and is toxic by skin contact. When heated to decomposition it emits toxic fumes of mercury.

To a stirred soln of 1*H*-benzotriazole, 5-chloro-1*H*-benzotriazole, or 6-nitro-1*H*-benzotriazole (3 mmol), 1,3-bis(*tert*-butoxycarbonyl)thiourea (3 mmol), and Et₃N (9.9 mmol) in dry DMF or NMP (6 mL) at 0 °C was added HgCl₂ (3.3 mmol). After 12 h at rt, the mixture was concentrated under reduced pressure, diluted with EtOAc (100 mL), and filtered through a Celite pad. The filtrate was washed with H₂O (20 mL), 5% aq Na₂CO₃ (20 mL), H₂O (20 mL), and brine (20 mL), and dried (Na₂SO₄). The solvent was removed, and the products were isolated as follows: *N,N'*-bis(*tert*-butoxycarbonyl)-1*H*-benzotriazole-1-carboximidamide: by crystallization (*t*-BuOMe/hexane); yield: 67%; mp 143–144 °C. Reaction with 5-chloro-1*H*-benzotriazole gave a mixture of the 5- and 6-chloro derivatives which were separated by flash chromatography (EtOAc/hexane 3:1) and recrystallized (*t*-BuOMe/hexane) to give *N,N'*-bis(*tert*-butoxycarbonyl)-5-chloro-1*H*-benzotriazole-1-carboximidamide; yield: 50%; mp 170–175 °C; and *N,N'*-bis(*tert*-butoxycarbonyl)-6-chloro-1*H*-benzotriazole-1-carboximidamide; yield: 9%; mp 129–132 °C. *N,N'*-bis(*tert*-butoxycarbonyl)-6-nitro-1*H*-benzotriazole-1-carboximidamide was purified by recrystallization (*t*-BuOMe/hexane); yield: 50%; mp 126–128 °C.

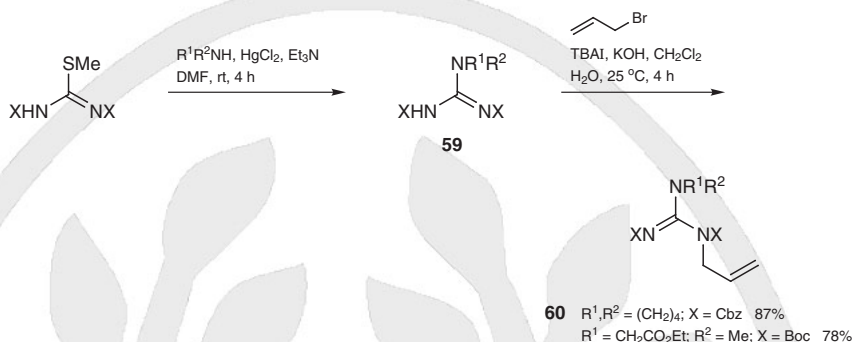
1,3-Bis(*tert*-butoxycarbonyl)-2-phenylguanidine (58, R¹ = Ph; R² = H); Typical Procedure:^[146] A 0.2 M soln of the reagent **57** (X = H, 5-Cl or 6-NO₂) (1 equiv) was reacted with PhNH₂ (1.2 equiv) in CH₂Cl₂ in the presence of Et₃N (1 equiv) or iPr₂NEt for 1 or 2 h at 20 °C, and the mixture was worked up by known procedures.

18.13.1.1.10

Method 10:**Reaction of Guanidines with Alkyl and Aryl Halides**

The synthesis of guanidines from alkyl halides is simply a variation of the Gabriel synthesis of amines. A major problem using guanidine as a nucleophile is the formation of poly-substituted guanidine derivatives, as one might expect. Therefore, mono- or, more frequently, bis-protected guanidines are more effectively employed in such reactions, also known as guanidinylation of alkyl halides.^[8] One such example is the synthesis of 1,3-bis(*tert*-butoxycarbonyl)-protected benzylguanidines, under standard conditions, with yields ranging from moderate to good.^[152] Reaction of 6-chloro-9*H*-purine derivatives with guanidine gives 2-(9*H*-purin-6-yl)guanidines in the presence of 1,4-diazabicyclo[2.2.2]octane in reasonable yields.^[153] Alkylation of 1,3-bis(*tert*-butoxycarbonyl)- or 1,3-bis(benzyloxycarbonyl)-protected 2,2-disubstituted guanidines **59** have been performed under phase-transfer conditions, with a large excess of the alkylation reagent, giving excellent yields of products such as **60** (Scheme 29).^[8] The scope of the reaction was further expanded, demonstrating its versatility for the synthesis of polysubstituted guanidines.^[150] The reaction of a substituted guanidine with an α-bromo ketone is used in a total synthesis of cylindrospermopsin.^[30]

Scheme 29 Phase-Transfer Synthesis of 1,3-Disubstituted or 1,1,3-Trisubstituted 2,3-Bis(*tert*-butoxycarbonyl)-Protected Guanidines from 1-Substituted or 1,1-Disubstituted 2,3-Bis(*tert*-butoxycarbonyl)guanidines^[8]



Phase-Transfer Synthesis of 1,3-Disubstituted or 1,1,3-Trisubstituted 2,3-Bis(*tert*-butoxycarbonyl)-Protected Guanidines 60 ($X = Boc$) from 1-Substituted or 1,1-Disubstituted 2,3-Bis(*tert*-butoxycarbonyl)guanidines; General Procedure:^[8]

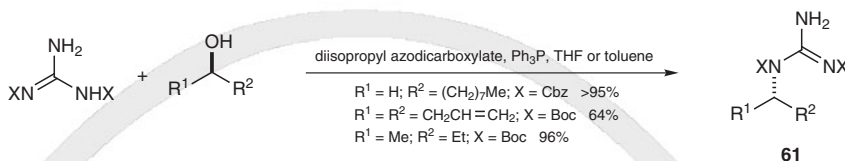
A biphasic soln of a 1,3-diprotected guanidine **59** ($X = Boc$; 0.50 mmol), TBAI (18 mg, 0.05 mmol), and KOH (56 mg, 1.0 mmol) in CH_2Cl_2/H_2O (1:1, 5 mL) was treated with the alkyl halide (0.60–1.0 mmol). The mixture was stirred at 25–50 °C (depending on electrophile) for 2–4 h, and then the mixture was transferred into H_2O (25 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The product was purified by flash chromatography through a short column of silica gel.

18.13.1.1.11

Method 11:

Reaction of Guanidines with Alcohols or Activated Alcohols

The reaction of guanidine or guanidine derivatives with alcohols or activated alcohols (in particular 4-toluenesulfonates and methanesulfonates) has been known since the 1960s. Two examples illustrate pioneering applications of this method. In the first case, a substituted guanidine is formed in situ by reaction of aniline with a cyanamide pyranosil derivative. The substituted guanidine reacts directly with a vicinally attached methanesulfonate, in good yield.^[154] In the second example, guanidine hydrochloride is reacted with (2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)methyl 4-toluenesulfonate in the presence of sodium hydride to give [(2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)methyl]guanidine also in good yield.^[155] Bis(*tert*-butoxycarbonyl)-protected or bis(benzyloxycarbonyl)-protected guanidines react with chiral alcohols via a Mitsunobu protocol to give the corresponding optically active guanidines **61** as single enantiomers in excellent yields (Scheme 30).^[156] Different guanidino amino acids have also been synthesized by a similar Mitsunobu protocol, in yields ranging from moderate to excellent.^[128] Applications of the preparation of guanidines using alcohols, frequently using Mitsunobu conditions, include the synthesis of dianhydrohexitol integrin antagonists,^[157] as well as in the synthesis of different alkaloids^[9–12] such as batzelladine D,^[158] batzelladine A,^[159,160] in the synthesis of ptilomycalin A analogues,^[161] and in the synthesis of (2*S*,3*R*)-capreomycinidine.^[162]

Scheme 30 Synthesis of Bis(*tert*-butoxycarbonyl)-Protected or Bis(benzyloxycarbonyl)-Protected Chiral Guanidines from Chiral Alcohols via a Mitsunobu Protocol^[156]**(S)-1,3-Bis(*tert*-butoxycarbonyl)-2-*sec*-butylguanidine (61, R¹ = Me; R² = Et; X = Boc);****Typical Procedure:**^[156]

To a soln of 1,3-bis(*tert*-butoxycarbonyl)guanidine (259 mg, 1.0 mmol) and Ph₃P (200 mg, 0.75 mmol) in dry toluene (5 mL) under argon was added via syringe (*R*)-*s*-BuOH (0.046 mL, 0.5 mmol). The mixture was cooled to 0 °C and diisopropyl azodicarboxylate (0.150 mL, 0.75 mmol) was added dropwise over 15 min. The mixture was stirred at rt for 5 h. H₂O (5 drops) was added, and the solvent was evaporated in vacuo. The crude mixture was subjected to chromatography (silica gel, 10% EtOAc/hexanes) to give the product; yield: 151 mg (96%).

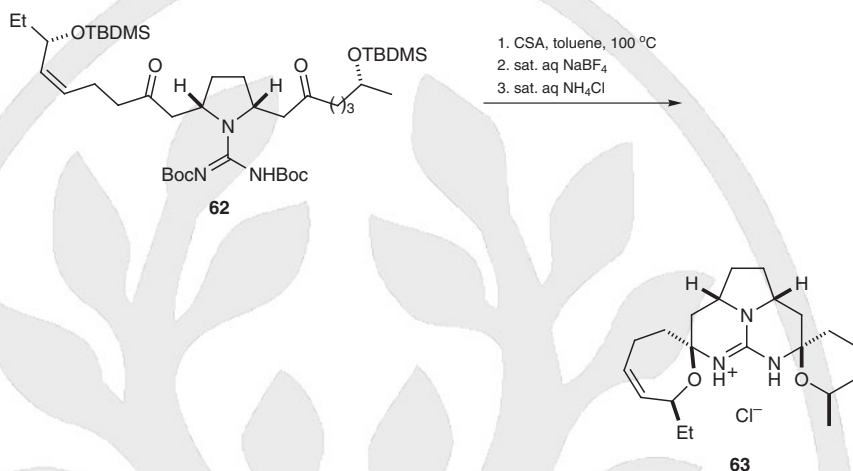
18.13.1.1.12

Method 12:**Addition of Guanidine to Aldehydes, Ketones, and Esters To Give Cyclic Guanidinium Salts**

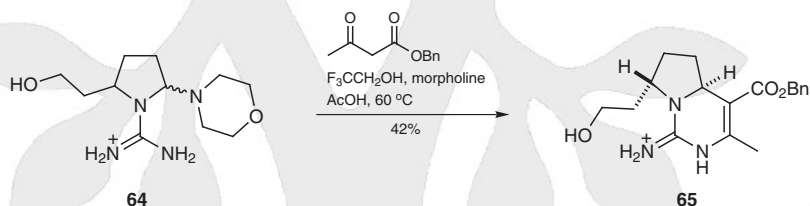
The reaction of guanidines with simple ketones was unknown until the early 1980s, when Snider first reported the synthesis of (±)-ptilocalin with the addition of guanidine to an α,β-unsaturated ketone as the last synthetic step.^[163,164] In precedent, the reactions between monosubstituted guanidines with β-diketones to give substituted pyrimidin-2-amines,^[165–169] and of guanidine with dimethyl 3-oxopentanedioate to give methyl 2-(2-amino-6-hydroxypyrimidin-4-yl)acetate, were known.^[170,171] The addition reaction of a guanidine to a saturated ketone was firstly reported as the last step in the synthesis of (–)-ptilocalin.^[172] In developing a synthesis of ptilomycalin A,^[69] 3-phenyl-1,2,4a,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidin-1-amine hydrochloride was prepared from *N,N'*-bis(*tert*-butoxycarbonyl)-protected 2-(2-oxo-2-phenylethyl)pyrrolidine-1-carboximidamide in quantitative yield. In the last step of a synthesis of crambescidin 359 (**63**),^[173] the bis(*tert*-butoxycarbonyl)-protected guanidino diketone **62** is reacted with camphorsulfonic acid, to give the desired natural product after counterion exchange (Scheme 31). In an additional example of this method, a 1,3-bis(*tert*-butoxycarbonyl)-protected guanidine methyl ketal, as a masked aldehyde, is used as a precursor in the synthesis of 8,11-dideoxytetrodotoxin and 4,9-anhydro-8,11-dideoxytetrodotoxin.^[174] A very similar approach is used within the synthesis of 11-deoxytetrodotoxin and anhydroepi-11-deoxytetrodotoxin,^[45] and in the synthesis of tetrodotoxin.^[175] Guanidines also react with β-diester to give cyclic guanidines.^[176] A very interesting variation of this latter reaction, developed as an alternative of the tethered Biginelli condensation, is the condensation of a 1,1-disubstituted guanidine with a β-oxo ester.^[177] It has been found that when a 2-morpholinopyrrolidine-derived guanidinium **64** reacts with benzyl 3-oxobutanoate under Knoevenagel conditions, the only stereoisomer of the product **65** obtained is *trans* (Scheme 32).^[178] However, the stereochemistry of this reaction can be reversed using a 4-methoxy-2,3,6-trimethylbenzenesulfonyl-protected guanidine, giving predominately the *cis*-isomer.^[178] Overman's group explored the tethered Biginelli reaction between substituted guanidines and β-oxo esters in the preparation of a variety of polycyclic guanidines.^[179–184] Complex polycyclic guanidine alkaloids such as ptilomycalin A, crambescidin 657, neofolitispates 2, crambescidin 800,^[180] 13,14,15-isocrambescidin 800, 13,14,15-isocrambescidin 657,^[181] (–)-dehydrobatzelladine C,^[182] as well as a variety of batzelladine analogues,^[183,184] have

been synthesized by the tethered Biginelli condensation between 1,1-disubstituted guanidines and β -oxo esters.^[177]

Scheme 31 Synthesis of Crambesidin 359 from a Bis(*tert*-butoxycarbonyl)-Protected Guanidine^[173]



Scheme 32 Synthesis of a *trans*-Bicyclic Guanidinium via a Tethered Biginelli Condensation Using Knoevenagel Conditions^[178]



Crambesidin 359 (63):^[173]

To a soln of the diketone **62** (9.8 mg, 0.0116 mmol) in toluene (2 mL) was added *D*-CSA (2.7 mg, 0.0116 mmol), and the resulting mixture was heated at 110 °C for 20 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography to give crambesidin 359 as a camphorsulfonate; yield (3 steps): 3 mg (44%). To the soln of the camphorsulfonate (3 mg) in CH_2Cl_2 (3 mL) was added sat. NaBF_4 (3 mL), and the mixture was vigorously stirred at rt for 2 h. The resulting mixture was extracted with CHCl_3 (5 \times), and the organic layer was dried (MgSO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, CHCl_3 , then $\text{CHCl}_3/\text{MeOH}$) to give (–)-crambesidin 359 as the HBF_4 salt (2.3 mg). To a soln of the HBF_4 salt in CHCl_3 (3 mL) was added sat. NH_4Cl (3 mL), and the mixture was stirred for overnight at rt. The resulting mixture was extracted with CHCl_3 (5 \times), and the organic layer was dried (MgSO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, CHCl_3 , then $\text{CHCl}_3/\text{MeOH}$) to give (–)-crambesidin 359 as the HCl salt; yield: 2 mg.

Benzyl (4*aS*,7*S*)-7-(2-Hydroxyethyl)-1-imino-3-methyl-1,2,4*a*,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylate Hydroformate (65):^[178]

A soln of crude aminal **64** (0.60 mmol), benzyl 3-oxobutanoate (0.16 mL, 0.90 mmol), morpholinium acetate (140 mg, 0.90 mmol), and 2,2,2-trifluoroethanol (0.6 mL) was maintained at 60 °C for 2 d. After being cooled to rt, the mixture was partitioned between Et_2O

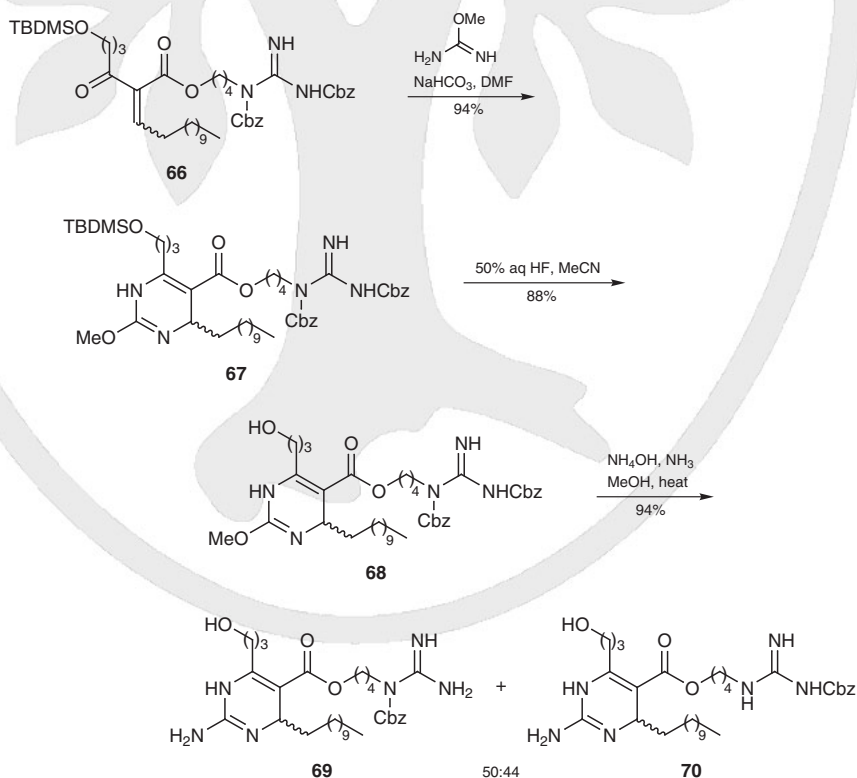
(20 mL) and 50% aq NH_4Cl (5 mL). The layers were separated, the organic layer was dried (MgSO_4) and filtered, and the filtrate was concentrated. The crude product was purified (silica gel, $\text{CHCl}_3/\text{iPrOH}/\text{HCO}_2\text{H}$ 1:0:0 to 10:1:0 to 100:10:1) to yield the desired product as a colorless oil; yield: 0.95 g (42%).

18.13.1.1.13

Method 13:**Addition of 2-Methylisoureas to Aldehydes and Ketones**

The use of 2-methylisourea in the synthesis of cyclic guanidines was first introduced by Snider, during the synthesis of polycyclic guanidine alkaloids isolated from the sponge *Crambe crambe*. Previously, this approach was known for the synthesis of 1,4-dihydropyrimidines.^[185] While the reaction of β -oxo α,β' -unsaturated ester **66** with guanidine free base gives a tetrahydropyrimidine derivative, reaction with 2-methylisourea provides the corresponding protected urea **67** in 94% yield. Hydrolysis of the silyl ether protecting group gives **68**, which is converted into a mixture of the mono(benzyloxycarbonyl)-protected bis-guanidines **69** and **70** using ammonia and ammonium acetate in *tert*-butyl alcohol, followed by treatment with aqueous sodium carbonate in methanol (Scheme 33). Further reaction steps give the major crambescine C homologue.^[88] The same approach is used in the synthesis of the central pentacyclic core of ptilomycalin A by the same authors.^[89] Essentially the same approach is employed in the synthesis of a tricyclic model of ptilomycalin A,^[173] in the total synthesis of crambescins A, B and C2,^[69] and in the synthesis of the tricyclic central core of batzelladines A, B, and batzelladine E.^[186–188] Interesting variations of this method have been reported, in the synthesis of a tricyclic model of batzelladine A,^[189] and in the synthesis of epicylindropermopsin.^[190–192]

Scheme 33 Synthesis of Bis-guanidines from a β -Oxo α,β' -Unsaturated Ester via a Methylisourea^[88]



4-[[[(Benzyloxy)carbonyl][[(benzyloxy)carbonyl]amino}(imino)methyl]amino]butyl 6-[3-*tert*-Butyl(dimethyl)siloxy]propyl]-2-methoxy-4-undecyl-1,4-dihydropyrimidine-5-carboxylate (67):^[88]

A suspension of **66** (580 mg, 0.72 mmol), 2-methylisourea sulfate (560 mg, 2.3 mmol), and NaHCO₃ (400 mg, 4.8 mmol) in DMF (6 mL) was stirred at 55 °C for 3 h, treated with H₂O (10 mL), and extracted with hexane/EtOAc (2:1, 3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na₂SO₄). Removal of the solvent under reduced pressure followed by flash chromatography (silica gel, hexane/EtOAc 9:1) gave a colorless oil; yield: 0.58 g (94%).

4-[[Amino(imino)methyl][[(benzyloxy)carbonyl]amino]butyl 2-Amino-6-(3-hydroxypropyl)-4-undecyl-1,4-dihydropyrimidine-5-carboxylate (69) Hydrochloride and 4-[[[(Benzyloxy)carbonyl]amino}(imino)methyl]amino]butyl 2-Amino-6-(3-hydroxypropyl)-4-undecyl-1,4-dihydropyrimidine-5-carboxylate (70) Hydrochloride:^[88]

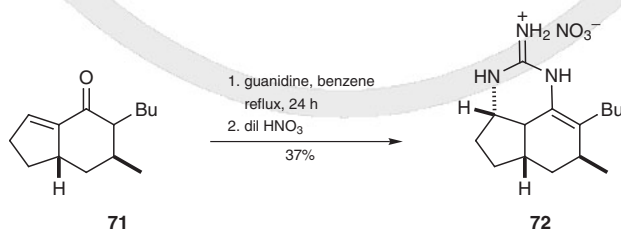
A soln of **68** (148 mg, 0.20 mmol) and NH₄OAc (40 mg, 0.5 mmol) in *t*-BuOH (20 mL) was saturated with NH₃ at 10 °C for 5 min and heated in a sealed tube at 60 °C for 3 d. The solvent was removed under reduced pressure, the residue was dissolved in CHCl₃ (20 mL), and the residual solid was separated by filtration. Removal of the solvent under reduced pressure gave a light yellow oil. A soln of the oil and Na₂CO₃ (20 mg) in MeOH/H₂O (2:1, 10 mL) was stirred at rt for 12 h to convert any spirocyclic compound into **69** and **70**. MeOH was removed under reduced pressure and the mixture was treated with brine (10 mL) and extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried (Na₂SO₄). Removal of the solvent under reduced pressure followed by flash chromatography (silica gel, CH₂Cl₂/MeOH 92:8) gave **69**; yield: 56 mg (44%). Further elution (CH₂Cl₂/MeOH 85:15) gave **70**; yield: 63 mg (50%).

18.13.1.1.14

Method 14:**Addition of Guanidine to α,β -Unsaturated Aldehydes, Ketones, and Esters**

The first report dealing with the addition of guanidine to an α,β -unsaturated carbonyl compound to give a cyclic guanidinium salt was Snider and Faith's synthesis of racemic ptilocaulin (**72**), simply by addition of guanidine free base to (6*S*,7*aS*)-5-butyl-6-methyl-1,2,5,6,7,7*a*-hexahydroinden-4-one (**71**) under equilibrating conditions as the last reaction step, since the natural product is the thermodynamically most stable isomer (Scheme 34).^[164] Basically the same procedure is used in other approaches to the total synthesis of the same compound.^[193,194] A similar approach was subsequently employed to the synthesis of various polycyclic guanidines. For example, reaction of guanidine free base with methyl acrylate, followed by treatment with concentrated hydrochloric acid, gives 3,4,6,7-tetrahydro-1*H*-pyrimido[1,2-*a*]pyrimidine-2,8-dione.^[195] Murphy's group used this approach toward the synthesis of various polycyclic guanidines,^[172,195–201] and more recently in the synthesis of crambescidin 359.^[202]

Scheme 34 Synthesis of (–)-Ptilocaulin from (6*S*,7*aS*)-5-Butyl-6-methyl-1,2,5,6,7,7*a*-hexahydroinden-4-one^[164]



(3a*S*,5a*S*,7*S*,8*bR*)-8-Butyl-7-methyl-3,3a,4,5,5a,6,7,8*b*-octahydrocyclopenta[*de*]quinazolin-2(1*H*)-iminium Nitrate (Ptilocaulin Nitrate, 72):^[164]

A 0.69 M soln of guanidine in MeOH (0.35 mL) was transferred to a flask fitted with a Dean–Stark trap and septum. After removal of the excess solvent under reduced pressure, the flask was charged with N₂ and (6*S*,7a*S*)-5-butyl-6-methyl-1,2,5,6,7,7a-hexahydro-4*H*-inden-4-one (**71**; 0.032 g, 0.156 mmol) in dry benzene (20 mL) (**CAUTION: carcinogen**) was added by syringe. The mixture was refluxed, with stirring, under a N₂ atmosphere. The success of the reaction was dependent upon the rigorous exclusion of air, for the unprotonated form of the product is readily oxidized. When the theoretical volume of H₂O had been collected (25 h), the mixture was allowed to cool and then quenched with 1% HNO₃ (2.2 mL, 0.240 mmol). The layers were separated and the aqueous layer was extracted with CHCl₃ (2 × 20 mL). The combined organic layers were dried (MgSO₄) and evaporated to give a crude product. Chromatography (silica gel, CHCl₃/MeOH 83:17) gave pure ptilocaulin nitrate; yield: 0.018 g (37%).

References

- [1] Pauling, L., *The Nature of Chemical Bond*, Cornell University Press: Ithaca, (1960); p 286.
- [2] Jones, J. H., *J. Pept. Sci.*, (2002) **8**, 285.
- [3] Shen, Z. X.; Wang, Y. L.; Zhang, Y. W., *Chin. J. Org. Chem.*, (2002) **22**, 388.
- [4] Ishikawa, T.; Isobe, T., *Chem.-Eur. J.*, (2002) **8**, 553.
- [5] Manimala, J. C.; Anslyn, E. V., *Eur. J. Org. Chem.*, (2002), 3909.
- [6] Nagasawa, K.; Hashimoto, Y., *Chem. Rec.*, (2003) **3**, 201.
- [7] Orner, B. P.; Hamilton, A. D., *J. Incl. Phen. Macrocycl. Chem.*, (2001) **41**, 141.
- [8] Powell, D. A.; Ramsden, P. D.; Batey, R. A., *J. Org. Chem.*, (2003) **68**, 2300.
- [9] Berlinck, R.G. S., *Nat. Prod. Rep.*, (2002) **19**, 617.
- [10] Berlinck, R.G. S., *Nat. Prod. Rep.*, (1999) **16**, 339.
- [11] Berlinck, R.G. S., *Nat. Prod. Rep.*, (1996) **13**, 377.
- [12] Berlinck, R.G. S., *Prog. Chem. Org. Nat. Prod.*, (1995) **66**, 119.
- [13] Torokne, A.; Palovics, A.; Bankine, M., *Environ. Toxicol. Chem.*, (2001) **16**, 512.
- [14] Codd, G. A.; Bell, S. G.; Kaya, K.; Ward, C. J.; Beattie, K. A.; Metcalf, J. S., *Eur. J. Phycol.*, (1999) **34**, 405.
- [15] Falconer, I. R., *Environ. Toxicol. Chem.*, (1999) **14**, 5.
- [16] Jerome, F.; Kharchafi, G.; Adam, I.; Barrault, J., *Green Chem.*, (2004) **6**, 72.
- [17] Blanc, A. C.; Macquarrie, D. J.; Valle, S.; Renard, G.; Quinn, C. R.; Brunel, D., *Green Chem.*, (2000) **2**, 283.
- [18] Juyal, P.; Anand, O. N., *Fuel*, (2003) **82**, 97.
- [19] Braun, C. E., *J. Chem. Soc.*, (1933), 1280.
- [20] Snider, B. B.; Ahn, Y.; O'Hare, S. M., *Org. Lett.*, (2001) **3**, 4217.
- [21] Lundquist, J. T.; Orwig, K. S.; Dix, T. A., *J. Org. Chem.*, (1999) **64**, 9265.
- [22] Sandin, H.; Swanstein, M.-L.; Wellner, E., *J. Org. Chem.*, (2004) **69**, 1571.
- [23] Ma, D.; Cheng, K., *Tetrahedron: Asymmetry*, (1999) **10**, 713.
- [24] Ishikawa, F.; Kosasayama, A.; Nakamura, S.; Konno, T., *Chem. Pharm. Bull.*, (1978) **26**, 3658.
- [25] Acharya, A. N.; Ostresh, J. M.; Houghten, R. A., *Tetrahedron*, (2001) **57**, 9911.
- [26] Reddy, N. L.; Hu, L. Y.; Cotter, R. E.; Fischer, J. B.; Wong, W. J.; McBurney, R. N.; Weber, E.; Holmes, D. L.; Wong, S. T.; Prasad, R.; Keana, J. F. W., *J. Med. Chem.*, (1994) **37**, 260.
- [27] Reddy, N. L.; Fan, W.; Magar, S. S.; Perlman, M. E.; Yost, E.; Zhang, L.; Berlove, D.; Fischer, J. B.; Burke-Howie, K.; Wolcott, T.; Durant, G. J., *J. Med. Chem.*, (1998) **41**, 3298.
- [28] Kusumoto, S.; Tsuji, S.; Shiba, T., *Tetrahedron Lett.*, (1974), 1417.
- [29] Shiba, T.; Ukita, T.; Mizuno, K.; Teshima, T.; Wakamiya, T., *Tetrahedron Lett.*, (1977), 2681.
- [30] Xie, C.; Runnegar, M. T. C.; Snider, B. B., *J. Am. Chem. Soc.*, (2000) **122**, 5017.
- [31] Molina, P.; Alajarin, M.; Sánchez-Andrada, P., *Tetrahedron Lett.*, (1995) **36**, 9405.
- [32] Molina, P.; Alajarin, M.; Sánchez-Andrada, P.; Sanz-Aparicio, J.; Martínez-Ripoli, M., *J. Org. Chem.*, (1998) **63**, 2922.
- [33] Chinchilla, R.; Nájera, C.; Sánchez-Agulló, P., *Tetrahedron: Asymmetry*, (1994) **5**, 1393.
- [34] Chen, J.; Pattarawarapan, M.; Zhang, A. J.; Burgess, K., *J. Comb. Chem.*, (2000) **2**, 276.
- [35] Saito, T.; Tsuda, K., *Tetrahedron Lett.*, (1996) **37**, 9071.
- [36] Gelbard, G.; Vielfaure-Joly, F., *Tetrahedron Lett.*, (1998) **39**, 2743.
- [37] Kilburn, J. P.; Lau, J.; Jones, R. C. F., *Tetrahedron*, (2002) **58**, 1739.
- [38] Noguchi, M.; Okada, H.; Watanabe, M.; Okuda, K.; Nakamura, O., *Tetrahedron*, (1996) **52**, 6581.
- [39] Drewry, D. H.; Gerritz, S. W.; Linn, J. A., *Tetrahedron Lett.*, (1997) **38**, 3377.
- [40] Barvian, M. R.; Hollis Showalter, H. D. H.; Doherty, A. M., *Tetrahedron Lett.*, (1997) **38**, 6799.
- [41] Schneider, S. E.; Bishop, P. A.; Salazar, M. A.; Bishop, O. A.; Anslyn, E. V., *Tetrahedron*, (1998) **54**, 15063.
- [42] Wang, F.; Hauske, J. R., *Tetrahedron Lett.*, (1997) **38**, 8651.
- [43] Yamamoto, N.; Isobe, M., *Chem. Lett.*, (1994), 2299.
- [44] Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M., *Pure Appl. Chem.*, (2003) **75**, 251.
- [45] Nishikawa, T.; Asai, M.; Isobe, M., *J. Am. Chem. Soc.*, (2002) **124**, 7847.
- [46] Chan, G. W.; Mong, S.; Hemling, M. E.; Freyer, A. J.; Offen, P. H.; DeBrosse, C. W.; Sarau, H. M.; Westley, J. W., *J. Nat. Prod.*, (1993) **56**, 116.
- [47] Levallet, C.; Lerpiniere, J.; Ko, S. Y., *Tetrahedron*, (1997) **53**, 5291.
- [48] Ramadas, K.; Janarthanan, N.; Pritha, R., *Synlett*, (1997), 1053.

- [49] Ramadas, K.; Srinivasan, N., *Tetrahedron Lett.*, (1995) **36**, 2841.
- [50] Ramadas, K., *Tetrahedron Lett.*, (1996) **37**, 5161.
- [51] Kim, K. S.; Qian, L., *Tetrahedron Lett.*, (1993) **34**, 7677.
- [52] Yong, Y. F.; Kowalski, J. A.; Lipton, M. A., *J. Org. Chem.*, (1997) **62**, 1540.
- [53] Guisado, O.; Martínez, S.; Pastor, J., *Tetrahedron Lett.*, (2002) **43**, 7105.
- [54] Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z., *Tetrahedron Lett.*, (1992) **33**, 5933.
- [55] Li, J.; Zhang, G.; Zhang, Z.; Fan, E., *J. Org. Chem.*, (2003) **68**, 1611.
- [56] Linton, B. R.; Carr, A. J.; Orner, B. P.; Hamilton, A. D., *J. Org. Chem.*, (2000) **65**, 1566.
- [57] Manimala, J. C.; Anslyn, E. V., *Tetrahedron Lett.*, (2002) **43**, 565.
- [58] Linkletter, B. A.; Bruice, T. C., *Bioorg. Med. Chem. Lett.*, (1998) **8**, 1285.
- [59] Reddy, P. M.; Bruice, T. C., *J. Am. Chem. Soc.*, (2004) **126**, 3736.
- [60] Challa, H.; Bruice, T. C., *Bioorg. Med. Chem.*, (2004) **12**, 1475.
- [61] Albert, J. S.; Peczu, M. W.; Hamilton, A. D., *Bioorg. Med. Chem.*, (1997) **5**, 1455.
- [62] Isobe, T.; Fukuda, K.; Tokunaga, T.; Seki, H.; Yamaguchi, K.; Ishikawa, T., *J. Org. Chem.*, (2000) **65**, 7774.
- [63] Isobe, T.; Fukuda, K.; Yamaguchi, K.; Seki, H.; Tokunaga, T.; Ishikawa, T., *J. Org. Chem.*, (2000) **65**, 7779.
- [64] Katsura, Y.; Nishino, S.; Tomishi, T.; Sakane, K.; Matsumoto, Y.; Ishikawa, H.; Takasugi, H., *Bioorg. Med. Chem. Lett.*, (1998) **8**, 1307.
- [65] Davis, A. P.; Lawless, L. J., *Chem. Commun. (Cambridge)*, (1999), 9.
- [66] Knieps, S.; Dove, S.; Michel, M. C.; Rottmeier, K.; Werner, W.; Bernhardt, G.; Buschauer, A., *Pharm. Pharmacol. Lett.*, (1996) **6**, 27.
- [67] Jeong, J.-H.; Murray, B. W.; Takayama, S.; Wong, C.-H., *J. Am. Chem. Soc.*, (1996) **118**, 4227.
- [68] Fotsch, C. H.; Wong, C.-H., *Tetrahedron Lett.*, (1994) **35**, 3481.
- [69] Louwrier, S.; Tuynman, A.; Hiemstra, H., *Tetrahedron*, (1996) **52**, 2629.
- [70] Zhang, J.; Shi, Y.; Stein, P.; Atwal, K.; Li, C., *Tetrahedron Lett.*, (2002) **43**, 57.
- [71] Cunha, S.; Costa, M. B.; Napolitano, H. B.; Lariucci, C.; Vencato, I., *Tetrahedron*, (2001) **57**, 1671.
- [72] Cunha, S.; Lima, B. R.; Souza, A. R., *Tetrahedron Lett.*, (2002) **43**, 49.
- [73] Yuan, C.; Williams, R. M., *J. Am. Chem. Soc.*, (1997) **119**, 11777.
- [74] Li, M.; Wilson, L. J.; Portlock, D. E., *Tetrahedron Lett.*, (2001) **42**, 2273.
- [75] Dahmen, S.; Brase, S., *Org. Lett.*, (2000) **2**, 3563.
- [76] Josey, J. A.; Tarlton, C. A.; Payne, C. E., *Tetrahedron Lett.*, (1998) **39**, 5899.
- [77] Wilson, L. J.; Klopfenstein, S. R.; Li, M., *Tetrahedron Lett.*, (1999) **40**, 3999.
- [78] Robinson, S.; Roskamp, E. J., *Tetrahedron*, (1997) **53**, 6697.
- [79] Ho, K. C.; Sun, C. M., *Bioorg. Med. Chem. Lett.*, (1999) **9**, 1517.
- [80] Yu, Y.; Ostresh, J. M.; Houghten, R. A., *J. Org. Chem.*, (2002) **67**, 3138.
- [81] Gilchrist, T. L., *Heterocyclic Chemistry*, 2nd ed., Longman Scientific and Technical: Harlow, UK, (1992); pp 250–252.
- [82] Isobe, T.; Fukuda, K.; Ishikawa, T., *Tetrahedron: Asymmetry*, (1998) **9**, 1729.
- [83] Isobe, T.; Fukuda, K.; Ishikawa, T., *J. Org. Chem.*, (2000) **65**, 7770.
- [84] Barton, D. H. R.; Elliott, J. D.; Géro, S. D., *J. Chem. Soc., Perkin Trans. 1*, (1982), 2085.
- [85] Michel, T.; Debart, F.; Vasseur, J.-J., *Tetrahedron Lett.*, (2003) **44**, 6579.
- [86] Dal Pozzo, A.; Muzi, L.; Moroni, M.; Rondanin, R.; de Catiglione, R.; Bravo, P.; Zanda, M., *Tetrahedron*, (1998) **54**, 6019.
- [87] Snider, B. B.; Shi, Z., *J. Org. Chem.*, (1992) **57**, 2526.
- [88] Snider, B. B.; Shi, Z., *J. Org. Chem.*, (1993) **58**, 3828.
- [89] Snider, B. B.; Shi, Z., *J. Am. Chem. Soc.*, (1994) **116**, 549.
- [90] Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A., *J. Am. Chem. Soc.*, (1995) **117**, 2657.
- [91] Wheeler, H. L.; Jamieson, G. S., *J. Biol. Chem.*, (1907) **4**, 111.
- [92] Phillips, R.; Clarke, H. T., *J. Am. Chem. Soc.*, (1923) **45**, 1755.
- [93] Smith, G. B. L., *J. Am. Chem. Soc.*, (1929) **51**, 476.
- [94] Braun, C. E., *J. Am. Chem. Soc.*, (1932), **54**, 1511.
- [95] Gers, T.; Kunc, D.; Markowski, P.; Izdebski, J., *Synthesis*, (2004), 37.
- [96] Lal, B.; Gangopadhyay, A. K., *Tetrahedron Lett.*, (1996) **37**, 2483.
- [97] Lammin, S. G.; Pedgrift, B. L.; Ratcliffe, A. J., *Tetrahedron Lett.*, (1996) **37**, 6815.
- [98] Yuan, C.; Williams, R. M., *Tetrahedron Lett.*, (1996) **37**, 1945.
- [99] Naim, S. S.; Sharma, S., *Synthesis*, (1992), 664.
- [100] Kent, D. R.; Cody, W. L.; Doherty, A. M., *Tetrahedron Lett.*, (1996) **37**, 8711.

- [101] Chang, J.; Oyelaran, O.; Esser, C. K.; Kath, G. S.; King, G. W.; Uhrig, B. G.; Konteatis, Z.; Kim, R. M.; Chapman, K. T., *Tetrahedron Lett.*, (1999) **40**, 4477.
- [102] Maienfisch, P.; Huerlimann, H.; Haettenschwiler, J., *Tetrahedron Lett.*, (2000) **41**, 7187.
- [103] Chan, A. W. Y.; Ganem, B., *Tetrahedron Lett.*, (1995) **36**, 811.
- [104] Gravier-Pelletier, C.; Bourissou, D.; Le Merrer, Y.; Depezay, J.-C., *Synlett*, (1996), 275.
- [105] Lin, P. S.; Heng, S. C. H.; Sim, M. M., *Synthesis*, (2003), 255.
- [106] Wang, M.; Xu, Z.; Tu, P.; Yu, X.; Xiao, S.; Yang, M., *Bioorg. Med. Chem. Lett.*, (2004) **14**, 2585.
- [107] Feldman, P. L., *Tetrahedron Lett.*, (1991) **32**, 875.
- [108] Adang, A. E. P.; Lucas, H.; de Man, A. P. A.; Engh, R. A.; Grootenhuis, P. D. J., *Bioorg. Med. Chem. Lett.*, (1998) **8**, 3603.
- [109] Moroni, M.; Kokschi, B.; Osipov, S. N.; Crucianelli, M.; Frigerio, M.; Bravo, P.; Burger, K., *J. Org. Chem.*, (2001) **66**, 130.
- [110] Feng, Y.; Burgess, K.; Pledger, D.; Cairns, N.; Linthicum, D. S., *Bioorg. Med. Chem. Lett.*, (1998) **8**, 881.
- [111] Weber, I. R.; Neidlein, R.; von der Saal, W.; Grams, F.; Leinert, H.; Strein, K.; Engh, R. A.; Kucznierz, R., *Bioorg. Med. Chem. Lett.*, (1998) **8**, 1613.
- [112] Brouillette, W. J.; Atigadda, V. R.; Luo, M.; Air, G. M.; Babu, Y. S.; Bantia, S., *Bioorg. Med. Chem. Lett.*, (1999) **9**, 1901.
- [113] Bonnat, M.; Bradley, M.; Kilburn, J. D., *Tetrahedron Lett.*, (1996) **37**, 5409.
- [114] Calis, U.; Finch, J. R.; Soltis, E. E.; Digenis, G. A., *Pharm. Res.*, (1994) **11**, 1211.
- [115] Knieps, S.; Michel, M. C.; Buschauer, A., *Bioorg. Med. Chem. Lett.*, (1995) **5**, 2065.
- [116] Garrett, G. S.; McPhail, S. J.; Tornheim, K.; Correa, P. E.; McIver, J. M., *Bioorg. Med. Chem. Lett.*, (1999) **9**, 301.
- [117] Padmanabhan, S.; Lavin, R. C.; Thakker, P. M.; Guo, J.; Zhang, L.; Moore, D.; Perlman, M. E.; Kirk, C.; Daly, D.; Burke-Howie, K. J.; Wolcott, T.; Chari, S.; Berlove, D.; Fischer, J. B.; Holt, W. F.; Durant, G. J.; McBurney, R. N., *Bioorg. Med. Chem. Lett.*, (2001) **11**, 3151.
- [118] Dodd, D. S.; Wallace, O. B., *Tetrahedron Lett.*, (1998) **39**, 5701.
- [119] Kearney, P. C.; Fernandez, M.; Flygare, J. A., *Tetrahedron Lett.*, (1998) **39**, 2663.
- [120] Dodd, D. S.; Zhao, Y., *Tetrahedron Lett.*, (2001) **42**, 1259.
- [121] Lin, P.; Ganesan, A., *Tetrahedron Lett.*, (1998) **39**, 9789.
- [122] Maryanoff, C. A.; Stanzione, R. C.; Plampin, J. N.; Mills, J. E., *J. Org. Chem.*, (1986) **51**, 1882.
- [123] Kim, K.; Lin, Y.-T.; Mosher, H. S., *Tetrahedron Lett.*, (1988) **29**, 3183.
- [124] Miller, A. E.; Bischoff, J. J., *Synthesis*, (1986), 777.
- [125] Jursic, B. S.; Neumann, D.; McPherson, A., *Synthesis*, (2000), 1656.
- [126] Srinivasan, N.; Ramadas, K., *Tetrahedron Lett.*, (2001) **42**, 343.
- [127] Aitken, D. J.; Royer, J.; Husson, J. P., *J. Org. Chem.*, (1990) **55**, 2814.
- [128] Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M., *J. Org. Chem.*, (1998) **63**, 3804.
- [129] Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M., *J. Org. Chem.*, (1998) **63**, 8432.
- [130] Zapf, C. W.; Creighton, C. J.; Tomioka, M.; Goodman, M., *Org. Lett.*, (2001) **3**, 1133.
- [131] Baker, T. J.; Luedtke, N. W.; Tor, Y.; Goodman, M., *J. Org. Chem.*, (2000) **65**, 9054.
- [132] Scott, F. L.; O'Donovan, D. G.; Reilly, J., *J. Am. Chem. Soc.*, (1953) **75**, 4053.
- [133] Bannard, R. A. B.; Casselman, A. A.; Cockburn, W. F.; Brown, G. M., *Can. J. Chem.*, (1958) **36**, 1541.
- [134] Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R., *J. Org. Chem.*, (1992) **57**, 2497.
- [135] Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R., *Tetrahedron Lett.*, (1993) **34**, 3389.
- [136] Drake, B.; Patek, M.; Lebl, M., *Synthesis*, (1994), 579.
- [137] Yong, Y. F.; Kowalski, J. A.; Thoen, J. C.; Lipton, M. A., *Tetrahedron Lett.*, (1999) **40**, 53.
- [138] Zhang, Y.; Kennan, A. J., *Org. Lett.*, (2001) **3**, 2341.
- [139] Pátek, M.; Smrčina, N.; Nakanishi, E.; Izawa, H., *J. Comb. Chem.*, (2000) **2**, 370.
- [140] Ghosh, A. K.; Hol, W. G. J.; Fan, E., *J. Org. Chem.*, (2001) **66**, 2161.
- [141] Dräger, G.; Solodenko, W.; Messinger, J.; Schön, U.; Kirschning, A., *Tetrahedron Lett.*, (2002) **43**, 1401.
- [142] Ciccotosto, S.; von Itzstein, M., *Tetrahedron Lett.*, (1995) **36**, 5405.
- [143] Oost, T.; Filippazzi, A.; Kalesse, M., *Liebigs Ann./Recl.*, (1997), 1005.
- [144] Kowalski, J.; Lipton, M. A., *Tetrahedron Lett.*, (1996) **37**, 5839.
- [145] Nicolaou, K. C.; Trujillo, J. I.; Chibale, K., *Tetrahedron*, (1997) **53**, 8751.
- [146] Alexopoulos, K.; Fatseas, P.; Melissari, E.; Vlahakos, D.; Smith, J.; Mavroumoustakos, T.; Saifeddine, M.; Moore, G.; Hollenberg, M.; Matsoukas, J., *Bioorg. Med. Chem.*, (1999) **7**, 1033.

- [147] Del Fresno, M.; El-Faham, A.; Carpino, L. A.; Royo, M.; Albericio, F., *Org. Lett.*, (2000) **2**, 3539.
- [148] Katritzky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V., *J. Org. Chem.*, (2000) **65**, 8080.
- [149] Muisol, H.-J.; Moroder, L., *Org. Lett.*, (2001) **3**, 3859.
- [150] Katritzky, A. R.; Rogovoy, B. V.; Cai, X.; Kirichenko, N.; Kovalenko, K. V., *J. Org. Chem.*, (2004) **69**, 309.
- [151] Wu, Y.-Q.; Hamilton, S. K.; Wilkinson, D. E.; Hamilton, G. S., *J. Org. Chem.*, (2002) **67**, 7553.
- [152] Vaidyanathan, G.; Zalutsky, M. R., *J. Org. Chem.*, (1997) **62**, 4867.
- [153] Cesnek, M.; Holy, A.; Masojdkova, M., *Tetrahedron*, (2002) **58**, 2985.
- [154] Baker, B. R.; Neilson, T., *J. Org. Chem.*, (1964) **29**, 1063.
- [155] Monro, A. M., *Chem. Ind. (London)*, (1964), 1806.
- [156] Dodd, D. S.; Kozikowski, A. P., *Tetrahedron Lett.*, (1994) **35**, 977.
- [157] Osterkamp, F.; Wehlan, H.; Koert, U.; Wiesner, M.; Raddatz, P.; Goodman, S. L., *Tetrahedron*, (1999) **55**, 10713.
- [158] Ishiwata, T.; Hino, T.; Koshino, H.; Hashimoto, Y.; Nakata, T.; Nagasawa, K., *Org. Lett.*, (2002) **4**, 2921.
- [159] Nagasawa, K.; Ishiwata, T.; Hashimoto, Y.; Nakata, T., *Tetrahedron Lett.*, (2002) **43**, 6383.
- [160] Shimokawa, J.; Shirai, K.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K., *Angew. Chem.*, (2004) **116**, 1585; *Angew. Chem. Int. Ed.*, (2004) **43**, 1559.
- [161] Georgieva, A.; Hirai, M.; Hashimoto, Y.; Nakata, T.; Ohizuli, Y.; Nagasawa, K., *Synthesis*, (2003), 1427.
- [162] DeMong, D. E.; Williams, R. M., *J. Am. Chem. Soc.*, (2003) **125**, 8561.
- [163] Snider, B. B.; Faith, W. C., *Tetrahedron Lett.*, (1983) **24**, 861.
- [164] Snider, B. B.; Faith, W. C., *J. Am. Chem. Soc.*, (1984) **106**, 1443.
- [165] Leclercq, P. A.; Smith, L. C.; Disiderio, D. M., Jr., *Biochem. Biophys. Res. Commun.*, (1971) **45**, 937.
- [166] Gilbert, H. F., III; O'Leary, M. H., *Biochem.*, (1975) **14**, 5194.
- [167] Beyermann, K.; Wissner, H., *Z. Anal. Chem.*, (1969) **245**, 376.
- [168] Shimada, K.; Fujii, Y.; Nambana, T., *Chem. Pharm. Bull.*, (1973) **21**, 2183.
- [169] Vetter-Diechtl, H.; Vetter, W.; Richter, W.; Biemann, K., *Experientia*, (1968) **24A**, 340.
- [170] Bycroft, B. W.; Cameron, D.; Croft, L. R.; Johnson, A. W., *Chem. Commun.*, (1968), 1301.
- [171] Bycroft, B. W.; Cameron, D.; Johnson, A. W., *J. Chem. Soc. C*, (1971), 3040.
- [172] Walts, A. E.; Roush, W. R., *Tetrahedron*, (1985) **41**, 3463.
- [173] Nagasawa, K.; Georgieva, A.; Koshino, H.; Nakata, T.; Kita, T.; Hashimoto, Y., *Org. Lett.*, (2002) **4**, 177.
- [174] Nishikawa, T.; Urabe, D.; Yoshida, K.; Iwabuchi, T.; Asai, M.; Isobe, M., *Org. Lett.*, (2002) **4**, 2679.
- [175] Ohyabu, N.; Nishikawa, T.; Isobe, M., *J. Am. Chem. Soc.*, (2003) **125**, 8798.
- [176] Esser, F.; Pook, K.-H.; Carpy, A., *Synthesis*, (1990), 72.
- [177] Aron, Z. D.; Overman, L. E., *Chem. Commun. (Cambridge)*, (2004), 253.
- [178] McDonald, A. I.; Overman, L. E., *J. Org. Chem.*, (1999), **64**, 1520.
- [179] Overman, L. E.; Wolfe, J. P., *J. Org. Chem.* (2001) **66**, 3167.
- [180] Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A., *J. Am. Chem. Soc.*, (2000) **122**, 4893.
- [181] Coffey, D. S.; Overman, L. E.; Stappenbeck, F., *J. Am. Chem. Soc.*, (2000) **122**, 4904.
- [182] Collins, S. K.; McDonald, A. I.; Overman, L. E.; Rhee, Y. H., *Org. Lett.*, (2004) **6**, 1253.
- [183] Cohen, F.; Collins, S. K.; Overman, L. E., *Org. Lett.*, (2003) **5**, 4485.
- [184] Aron, Z. D.; Pietraszkiewicz, H.; Overman, L. E.; Valeriote, F.; Cuevas, C., *Bioorg. Med. Chem. Lett.*, (2004) **14**, 3445.
- [185] Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J., *J. Org. Chem.*, (1989) **54**, 5898.
- [186] Snider, B. B.; Shi, Z., *Tetrahedron Lett.*, (1993) **34**, 2099.
- [187] Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J., *Tetrahedron Lett.*, (1996) **37**, 6977.
- [188] Snider, B. B.; Chen, J., *Tetrahedron Lett.*, (1998) **39**, 5697.
- [189] Rama Rao, A. V.; Gurjar, M. K.; Vasudevan, J., *J. Chem. Soc., Chem. Commun.*, (1995), 1369.
- [190] Heintzelman, G. R.; Fang, W. K.; Keen, S. P.; Wallace, G. A.; Weinreb, S. M., *J. Am. Chem. Soc.*, (2002) **124**, 3939.
- [191] Looper, R. E.; Williams, R. M., *Angew. Chem.*, (2004) **116**, 2990; *Angew. Chem. Int. Ed.*, (2004) **43**, 2930.
- [192] White, J. D.; Hansen, J. D., *J. Am. Chem. Soc.*, (2002) **124**, 4950.
- [193] Uyehara, T.; Furuta, T.; Kabawawa, Y.; Yamada, J.; Kato, T.; Yamamoto, Y., *J. Org. Chem.*, (1988) **53**, 3669.

- [194] Hassner, A.; Murthy, K. S. K., *Tetrahedron Lett.*, (1986) **27**, 1407.
- [195] Murphy, P. J.; Williams, H. L.; Hursthouse, M. B.; Malik, K. M. A., *J. Chem. Soc., Chem. Commun.*, (1994), 119.
- [196] Murphy, P. J.; Williams, H. L., *J. Chem. Soc., Chem. Commun.*, (1994), 819.
- [197] Murphy, P. J.; Williams, H. L.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A., *Tetrahedron*, (1996) **52**, 8315.
- [198] Black, G. P.; Murphy, P. J.; Walshe, N. D. A.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A., *Tetrahedron Lett.*, (1996) **37**, 6943.
- [199] Black, G. P.; Murphy, P. J.; Thornhill, A. J.; Walshe, N. D. A.; Zanetti, C., *Tetrahedron*, (1999) **55**, 6547.
- [200] Black, G. P.; Coles, S. J.; Hizi, A.; Howard-Jones, A. G.; Hursthouse, M. B.; McGown, A. T.; Loya, S.; Moore, C. G.; Murphy, P. J.; Smith, N. K.; Walshe, N. D. A., *Tetrahedron Lett.*, (2001) **42**, 3377.
- [201] Allingham, M. T.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. W. R., *Tetrahedron Lett.*, (2003) **44**, 8677.
- [202] Moore, C. G.; Murphy, P. J.; Williams, H. L.; McGown, A. T.; Smith, N. K., *Tetrahedron Lett.*, (2003) **44**, 251.

Product Class 14: Phosphorus Analogues of Guanidine

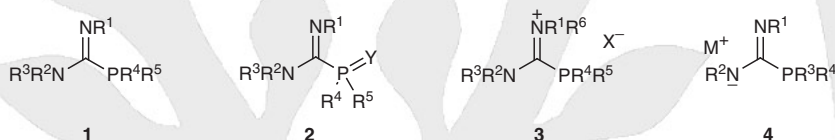
T. L. Gilchrist

18.14.1

Product Subclass 1: Imines with One Nitrogen and One Phosphorus Substituent

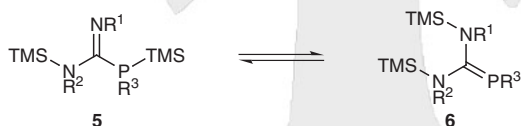
Members of this subclass are often referred to in the literature as phosphaguanidines. The subclass includes both structures **1** with a phosphorus(III) substituent and structures **2** (Y = O, S) with a phosphorus(V) substituent. Examples of phosphaguanidinium salts **3**^[1,2] and of phosphaguanidate salts **4**^[3] have also been described (Scheme 1).

Scheme 1 Phosphaguanidines and Their Salts^[1–3]



The generic name “phosphaguanidine” can cause confusion because it has also been applied to other structures in Section 18.14, particularly to structures with a formal C=P(III) bond and two nitrogen substituents. Indeed, there can be an easy equilibration between the two types of structure, as is the case with the trimethylsilyl-substituted compounds **5** and **6** (Scheme 2).^[4] Structures such as **6** are described in Section 18.14.3 and the term “phosphaguanidine” is restricted here to members of Product Subclass 18.14.1.

Scheme 2 Isomerization of Trimethylsilyl-Substituted Phosphaguanidines^[4]



18.14.1.1

Synthesis of Product Subclass 1

The most general, and most widely used, method of synthesis for members of this subclass is the addition of phosphorus compounds to carbodiimides (Section 18.14.1.1.4). The other methods are restricted either to a few examples or to a limited range of structural variations.

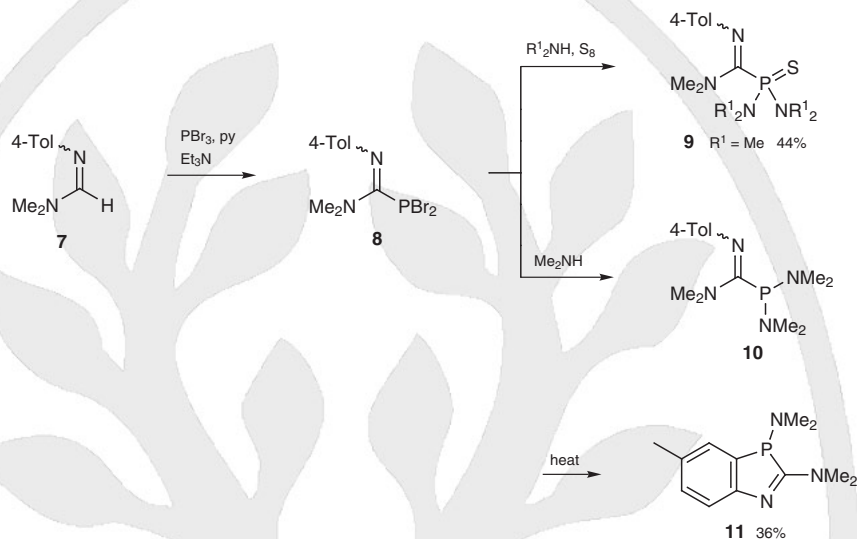
18.14.1.1.1

Method 1: Substitution of Hydrogen on Imines

The reaction of phosphorus tribromide with *N,N*-dimethyl-*N'*-(4-tolyl)formamidine (**7**) in the presence of pyridine and triethylamine leads to the formation of the phosphaguanidine **8**. This is not isolated, but is converted into the phosphaguanidines **9** (R¹ = Me, Et) by reaction with dimethylamine or diethylamine and sulfur (Scheme 3).^[5] If the sulfur is

omitted from the second stage of the procedure the phosphaguanidine **10** is formed, but its isolation is complicated by cyclization to the benzazaphosphole **11** on distillation under reduced pressure.^[6]

Scheme 3 Synthesis of a Phosphaguanidine from Substitution of Hydrogen in *N,N*-Dimethyl-*N'*-(4-tolyl)formamidine^[5]



(*N,N*-Dimethyl-*N'*-4-tolylformamidino)thiophosphonic Bis(dimethylamide) (**9**, $\text{R}^1 = \text{Me}$);

Typical Procedure:^[5]

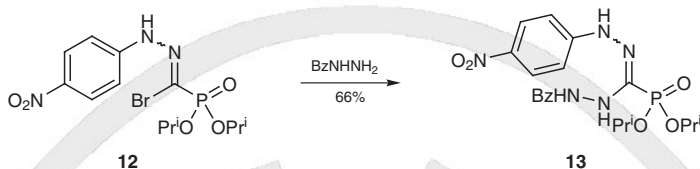
A soln of PBr_3 (13.5 g, 0.05 mol) in dry pyridine (20 mL) was added dropwise at 0°C to a mixture of the formamidine **7** (8.1 g, 0.05 mol), pyridine (50 mL), and Et_3N (7.1 g, 0.07 mol). After 24 h, Me_2NH (11.2 g, 0.25 mol) was added, followed, after a further 1 h, by S_8 (1.6 g, 0.05 mol). The mixture was stirred at rt for 8 h, diluted with benzene (50 mL) (**CAUTION: carcinogen**), and filtered. The filtrate was evaporated and the residue recrystallized; yield: 5.2 g (44%); mp $106\text{--}107^\circ\text{C}$ (hexane).

18.14.1.1.2

Method 2:

Displacement of a Halogen from Phosphorus-Substituted Imidoyl Halides by Nitrogen

The displacement of chlorine or bromine from phosphorus-substituted imidoyl halides by nitrogen nucleophiles occurs very readily. The reaction has been used mostly for the displacement of halogens from α -chlorooximes and α -chlorohydrazone. An example of the reaction, in which the nucleophile is a monosubstituted hydrazine and gives the phosphorylated amidrazone **13** from the bromohydrazone **12**, is shown in Scheme 4,^[7] but there are many closely related examples which utilize other hydrazines,^[8] primary^[9–12] and secondary amines,^[13,14] and azide ions^[15] as the nucleophiles. Occasionally, a related reaction involving the displacement of a methylsulfanyl group by a nitrogen nucleophile has also been used to synthesize phosphaguanidines.^[9,16,17]

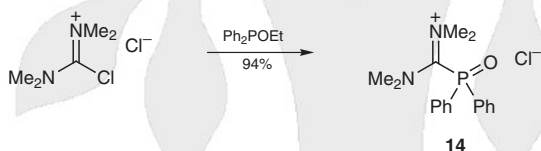
Scheme 4 Synthesis of a Phosphaguanidine by Displacement of a Halogen from a Phosphorus-Substituted Imidoyl Halide^[7]**Diisopropyl ((2-Benzoylhydrazino)[(4-nitrophenyl)hydrazono]methyl)phosphonate (13); Typical Procedure:**^[7]

To a soln of the bromohydrazone **12** (4.9 g, 0.013 mol) in iPrOH (15 mL), a hot soln of benzylhydrazine (1.7 g, 0.0125 mol) in iPrOH (20 mL) was added. The mixture was left at 20–25 °C for 2 d. The yellow crystals were collected by filtration, washed with H₂O, and recrystallized (iPrOH/H₂O 2:1, then MeCN); yield: 3.7 g (66%); mp 177–178 °C (dec) (MeCN).

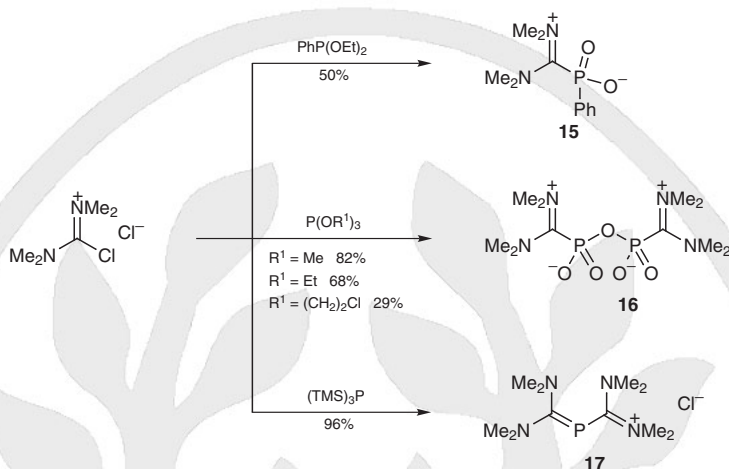
18.14.1.1.3

Method 3:**Displacement of Chlorine from a Chloroformamidinium Salt by Phosphorus**

This method provides a route to phosphaguanidinium salts but the final product is highly dependent upon the nature of the phosphorus nucleophile. A simple example of the method is shown in Scheme 5.^[1] The reaction of tetramethylchloroformamidinium chloride with ethyl diphenylphosphinite leads to the formation of the formamidinium chloride **14** by displacement of chlorine followed by a Michaelis–Arbuzov elimination of chloroethane.

Scheme 5 Synthesis of a Phosphaguanidinium Salt by Displacement of Chlorine from a Chloroformamidinium Salt^[1]

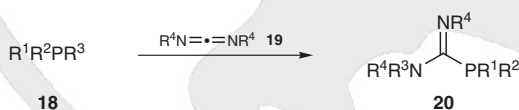
With other phosphorus(III) nucleophiles the initial displacement reaction is followed by further reactions that vary with the reagent. Three examples are shown in Scheme 6. Diethyl phenylphosphinite leads to a stable zwitterionic inner salt **15** and trialkyl phosphites give a phosphonic anhydride **16**.^[1] Tris(trimethylsilyl)phosphine produces the salt **17** after the loss of all three trimethylsilyl groups [see also *Science of Synthesis*, Vol. 22 (Three Carbon–Heteroatom Bonds: Thio-, Seleno-, and Tellurocarboxylic Acids and Derivatives; Imidic Acids and Derivatives; Ortho Acid Derivatives)].^[2] Some related reactions of chloroformamidines^[18] and other chloroformamidinium salts^[19] with phosphorus(III) compounds give analogous products.

Scheme 6 Disparate Phosphaguanidine Products Resulting from Displacement by Phosphorus(III) Compounds^[1,2]***N,N,N',N'*-Tetramethyl(diphenylphosphinyl)formamidine Chloride (14):^[1]**

Ethyl diphenylphosphinite (6.9 g, 0.03 mol) was added dropwise to a stirred mixture of chloro-*N,N,N',N'*-tetramethylformamidine chloride (5.1 g, 0.03 mol) and MeCN (20 g) under N_2 . All of the formamidine chloride dissolved during the course of the addition; then another solid separated. The mixture was stirred at rt overnight and then the salt was collected by filtration; yield: 9.6 g (94%); mp 137.5–138.5 °C (MeCN).

18.14.1.1.4**Method 4:****Addition of Phosphorus Compounds to Carbodiimides****18.14.1.1.4.1****Variation 1:****Addition of Phosphines**

Phosphines **18**, in which one or more of the substituents is a hydrogen or a trimethylsilyl group, can give phosphaguanidines **20** by addition to carbodiimides **19** (Scheme 7). A range of phosphaguanidines has been produced by this method. Phosphines of the type $\text{R}^1\text{P}(\text{TMS})_2$ undergo this reaction, but the final products are phosphalkenes formed by the migration of a trimethylsilyl group from phosphorus to nitrogen.^[4]

Scheme 7 Phosphaguanidines from Addition of Phosphines to Carbodiimides^[20–23]

R^1	R^2	R^3	R^4	Conditions	Yield (%)	Ref
Ph	H	TMS	Ph	rt, 1 d	80	[20]
Ph	Ph	TMS	Ph	80 °C, 1 h	53	[20]
Ph	Ph	H	4-Tol	60 °C, 4 h	quant	[21]
Ph	Ph	H	iPr	BuLi, 0 °C, then rt	71	[22]
Ph	$(\text{CH}_2)_2\text{SH}$	H	Cy	78 °C, 1 h	67	[23]

***N,N'*-Diisopropyl-*P,P*-diphenylphosphaguanidine (20, $R^1 = R^2 = \text{Ph}$; $R^3 = \text{H}$; $R^4 = \text{iPr}$):**^[22]

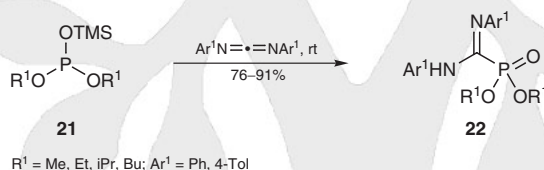
A 2.5 M soln of BuLi in hexane (2.4 mL, 6.00 mmol) was added dropwise to an ice-cooled soln of Ph_2PH (**18**, $R^1 = R^2 = \text{Ph}$; $R^3 = \text{H}$; 1.0 g, 5.37 mmol) in THF (50 mL). The resultant orange-red soln of Ph_2PLi was stirred for 0.5 h at 0 °C and then a soln of diisopropylcarbodiimide (**19**, $R^4 = \text{iPr}$; 0.92 mL, 5.90 mmol) in THF (20 mL) was added dropwise. The mixture was allowed to warm to rt and stirred overnight. Dry triethylammonium chloride (0.81 g, 5.90 mmol) was added as a slurry in THF to the clear yellow soln and the mixture was stirred for 1 h to produce a colorless soln. The volatile components were removed under reduced pressure and the product was extracted with hexane (2 × 50 mL). The extracts were concentrated and stored at –30 °C to give the phosphaguanidine as colorless needles; yield: 1.19 g (71%).

18.14.1.1.4.2

Variation 2:**Addition of Phosphites and Related Compounds**

These reactions of carbodiimides have been reported with dialkyl trimethylsilyl phosphites,^[24,25] sodium salts of dialkyl phosphites,^[26] phosphoramidites, $(\text{R}^1\text{O})_2\text{PNHAr}^1$,^[27] and the magnesium salt of bis(diethylamino)phosphinous acid, $(\text{Et}_2\text{N})_2\text{POH}$.^[28] The reaction between diarylcarbodiimides and dialkyl trimethylsilyl phosphites **21** is typical and gives the phosphaguanidines **22**, as illustrated in Scheme 8. This reaction is reported to fail with dicyclohexylcarbodiimide and with bis(trimethylsilyl)carbodiimide,^[24] but a wider range of carbodiimides react with the sodium salts of dialkyl phosphites.^[26]

Scheme 8 Phosphaguanidines from the Addition of Dialkyl Trimethylsilyl Phosphites to Diarylcarbodiimides^[24,25]

**Diethyl 4-Tolylamino(4-tolylimino)methylphosphonate (22, $R^1 = \text{Et}$; $\text{Ar}^1 = 4\text{-Tol}$):**^[24]

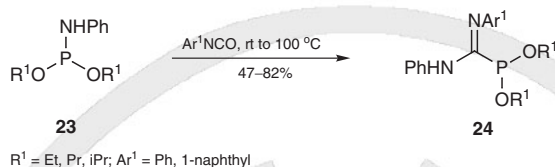
TMSCl (0.35 mL, 2.78 mmol) was added to a stirred soln of diethyl phosphite (0.35 g, 2.53 mmol) and Et_3N (0.39 mL, 2.78 mmol) in CH_2Cl_2 at 0 °C under argon. [The formation of diethyl trimethylsilyl phosphite can be monitored from the ^{31}P NMR spectrum by the signal at δ 128.4 (D_3PO_4 , $\delta = 0$) in CD_2Cl_2 .] Bis(4-tolyl)carbodiimide (2.53 mmol) was added after 15 min and the soln was brought to rt. The mixture was poured into H_2O (50 mL) and the product extracted with CH_2Cl_2 (2 × 75 mL). It was isolated by column chromatography (silica gel); yield: 0.68 g (76%); mp 88 °C.

18.14.1.1.5

Method 5:**Addition to Isocyanates**

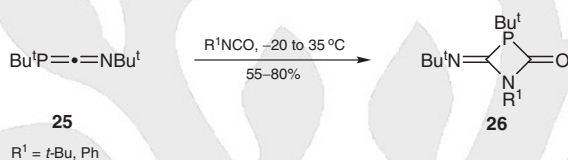
Aryl isocyanates react exothermically with *N*-phenylphosphoramidites **23** to give phosphaguanidines **24** (Scheme 9).^[29,30] An analogous addition to trichloroacetyl isocyanate has also been described.^[31]

Scheme 9 Phosphaguanidines from the Addition of *N*-Phenylphosphoramidites to Aryl Isocyanates^[29,30]



Two cyclic phosphaguanidines **26** have been synthesized by the addition of di-*tert*-butylcarboimidophosphine **25** to *tert*-butyl isocyanate or to phenyl isocyanate (Scheme 10).^[32,33] There is also an example of a 1,3-dipolar cycloaddition of a phosphorus-substituted nitrilimine to an isocyanate to give a cyclic phosphaguanidine.^[34]

Scheme 10 Phosphaguanidines from the Addition of Di-*tert*-butylcarboimidophosphine to Isocyanates^[32,33]



Diethyl Anilino(phenylimino)methylphosphonite (24, R¹ = Et; Ar¹ = Ph);
Typical Procedure:^[29]

CAUTION: Phenyl isocyanate is a skin, eye, and respiratory tract irritant. Chronic exposure can cause sensitization of the respiratory tract.

Diethyl *N*-phenylphosphoramidite (**23**, R¹ = Et; 4.26 g, 0.02 mol) and PhNCO (2.38 g, 0.02 mol) were mixed at rt. An exothermic reaction took place and the mixture solidified. Recrystallization of the solid gave the product as colorless plates; yield: 5.2 g (78%); mp 109–111 °C (toluene/pentane).

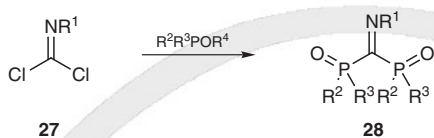
18.14.2 Product Subclass 2: Imines with Two Phosphorus Substituents

18.14.2.1 Synthesis of Product Subclass 2

This is a small subclass and the only method of synthesis that has any generality is the double displacement of chlorine from carbonimidic dichlorides by phosphorus(III) compounds.

18.14.2.1.1 Method 1: Displacement of Chlorine from Carbonimidic Dichlorides by Phosphorus

Carbonimidic dichlorides **27** react with phosphite esters to give iminophosphonic acid derivatives of type **28** (Scheme 11). Arylcarbonimidic dichlorides also react with phenylbis(trimethylsilyl)phosphine, but the nature of the products depends upon the reaction conditions.^[35–38] These reactions are described in Section 18.14.4.1.1.

Scheme 11 Iminophosphonic Acid Derivatives from Carbonimidic Dichlorides and Phosphorus(III) Compounds^[39–45]

R ¹	R ²	R ³	R ⁴	Conditions	Yield (%)	Ref
CO ₂ Et	OEt	OEt	Et	rt to 90 °C	60 ^a	[39]
C ₅ Cl ₄ N ^b	OEt	OEt	Et	heat	93	[40]
Ph	OEt	OEt	Et	80–100 °C	84	[41]
4-ClC ₆ H ₄	OEt	OEt	Et	80 °C	75	[42]
P(O)(OEt) ₂	OEt	OEt	Et	0–40 °C	41	[43]
SO ₂ Ph	OMe	OMe	Me	0–60 °C	95	[44]
Ph	NEt ₂	NEt ₂	Et	0–40 °C	71	[45]
Ph	Ph	Ph	Me	rt to 40 °C	75	[41]

^a This compound has also been synthesized (81%) from Cl₃CNCO, P(OEt)₃, and EtOH.^[46]

^b C₅Cl₄N = 2,3,5,6-tetrachloro-4-pyridyl.

N-[Bis(dimethoxyphosphinyl)methylene]benzenesulfonamide (28, R¹ = SO₂Ph; R² = R³ = OMe); Typical Procedure:^[44]

CAUTION: Trimethyl phosphite is flammable and has a powerful, obnoxious odor. It induces headaches, is a severe skin and eye irritant, and is corrosive and irritating to the respiratory tract.

P(OMe)₃ (R⁴ = Me; 7.4 g, 60 mmol) was added to a cooled and stirred soln of phenylsulfonyl-carbonimidic dichloride (27, R¹ = SO₂Ph; 7.1 g, 30 mmol) in dry benzene (30 mL) (**CAUTION:** carcinogen). The mixture was stirred for 1.5 h at rt and then heated for a further 1 h at 60 °C. The soln was cooled and the solvent was removed to leave a viscous colorless oil; yield: 10.8 g (95%); bp 110–112 °C/0.001 Torr.

18.14.3

Product Subclass 3: Alkylidenephosphines with Two Nitrogen Substituents

Substances that contain the C=PR¹ functional group are commonly known as phosphalkenes. Their chemistry has been reviewed several times^[47–50] and a review on phosphalkenes with inverse electron density is particularly relevant to this and later subclasses in Section 18.14.^[51] Most of the members of these subclasses have been reported since 1980.

18.14.3.1

Synthesis of Product Subclass 3

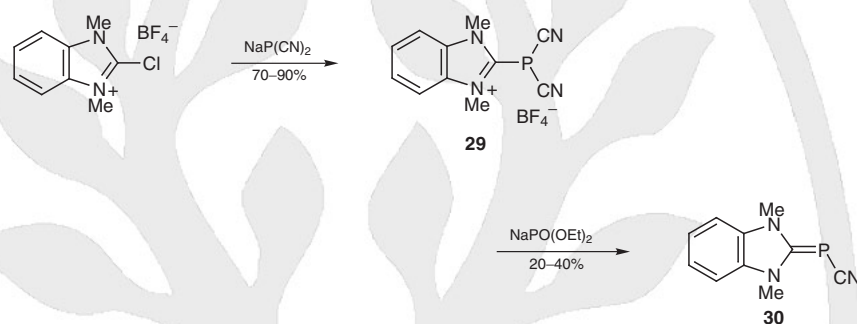
There is no completely general method for the synthesis of members of this subclass. A method that has been used for several bis(dialkylamino)phosphalkenes is the reaction of salts of phosphines with tetramethylisouronium and -isothiouronium salts (Section 18.14.3.1.3). Several members of the subclass have been prepared from P-(trimethylsilyl)-phosphalkenes by substitution of the trimethylsilyl group (Section 18.14.3.1.5).

18.14.3.1.1

Method 1:**Elimination of Cyanide from Dicyanophosphines**

This method is specific to the phosphalkene **30** and to one related example [see *Science of Synthesis*, Vol. 22 (Three Carbon—Heteroatom Bonds: Thio-, Seleno-, and Tellurocarboxylic Acids and Derivatives; Imidic Acids and Derivatives; Ortho Acid Derivatives)]. By analogy with the reactions described in Section 18.14.1.1.3, reaction of sodium dicyanophosphide with 2-chloro-1,3-dimethylbenzimidazolium tetrafluoroborate gives the benzimidazolium salt **29** in high yield. When this is treated with the sodium salt of diethyl phosphite, the yellow crystalline phosphalkene **30** is isolated (Scheme 12).^[52]

Scheme 12 Synthesis of a Phosphalkene from a Benzimidazolium Salt and Sodium Dicyanophosphide^[52]

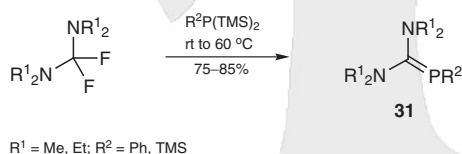


18.14.3.1.2

Method 2:**Addition of Phosphines to Bis(dialkylamino)difluoromethanes**

Bis(dialkylamino)difluoromethanes react with tris(trimethylsilyl)phosphine or with phenylbis(trimethylsilyl)phosphine at room temperature or on gentle warming to give phosphalkenes **31** in high yields (Scheme 13).^[53]

Scheme 13 Phosphalkenes from Diaminodifluoromethanes and Phosphines^[53,54]

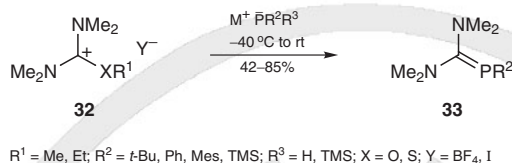
**Phosphalkenes 31 ($\text{R}^2 = \text{TMS}$); General Procedure:**^[54]

To tris(trimethylsilyl)phosphine (0.05 mol) at 30–35 °C under argon the diaminodifluoromethane (0.05 mol) was added in portions. The mixture was cooled if fluorotrimethylsilane was liberated vigorously. The products were isolated by distillation at 0.05 Torr; yield: 75–85%.

18.14.3.1.3

Method 3:**Addition of Phosphines to Tetramethylisouronium and Tetramethylisothiuronium Salts**

This method is outlined in Scheme 14. The sodium or lithium salt of a mono- or disubstituted phosphine reacts with an *O*-alkyltetramethylisouronium tetrafluoroborate **32** ($\text{X} = \text{O}; \text{Y} = \text{BF}_4$)^[55–57] or with an *S*-alkyltetramethylisothiuronium iodide **32** ($\text{X} = \text{S}; \text{Y} = \text{I}$)^[58,59] to give a bis(dimethylamino)phosphalkene **33**.

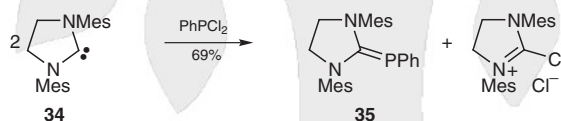
Scheme 14 Phosphaalkenes from Tetramethylisouronium and Tetramethylisothiouronium Salts and Phosphines^[55–59]**[Bis(dimethylamino)methylene]-*tert*-butylphosphine (33, R² = *t*-Bu); Typical Procedure:**^[59]

A soln of LiP(*t*-Bu)TMS [prepared from *t*-BuPH(TMS) (3.84 g, 28.6 mmol) and 1.6 M BuLi (17.9 mL, 28.6 mmol) in DME (30 mL)] was added dropwise to a slurry of [(Me₂N)₂CSMe]I (7.85 g, 28.6 mmol) in DME (40 mL). The mixture was stirred overnight and then concentrated to dryness. Pentane (30 mL) was added to the residue and the mixture was stirred for 10 min and then filtered. The filter cake was washed with pentane until the washings were colorless. The yellow filtrate and the combined washings were concentrated to leave an orange oil which was purified by distillation. The product was obtained as a yellow oil; yield: 3.92 g (71%); bp 39–42 °C/0.03 Torr.

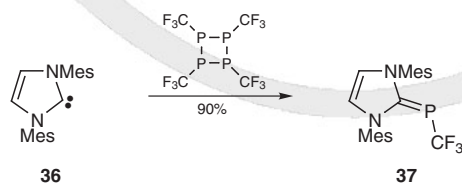
18.14.3.1.4

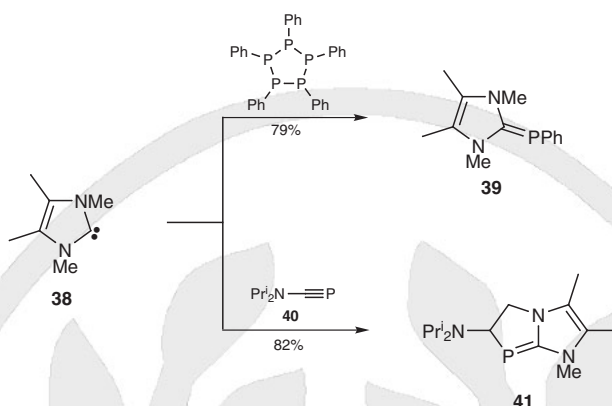
Method 4:**Addition of Phosphines to Bis(dialkylamino)carbenes**

Stable nucleophilic carbenes combine with reagents that can act as sources of the fragments PR¹ (R¹ = Ph or CF₃) to give phosphaalkenes. The most straightforward preparation of this type is represented in Scheme 15, in which 1,3-dimesitylimidazolin-2-ylidene (**34**) and dichloro(phenyl)phosphine combine in a 2:1 ratio to produce the phosphaalkene **35**.^[60] The side product, 2-chloro-1,3-dimesitylimidazolium chloride, is easily removed.

Scheme 15 Phosphaalkenes from 1,3-Dimesitylimidazolin-2-ylidene and Dichloro(phenyl)phosphine^[60]

Alternatively, cyclic oligomers, (PCF₃)₄^[60] and (PPh)₅^[61] have been used as the source of phosphorus fragments in combination with unsaturated nucleophilic carbenes such as **36** and **38** to give compounds **37** and **39**, respectively (Scheme 16). A further example is provided by the reaction of the carbene **38** with a phosphaalkyne **40** to produce the cyclic phosphaalkene **41**.^[62] This curious reaction requires an insertion into one of the methyl groups of the carbene.

Scheme 16 Phosphaalkenes from Other Nucleophilic Carbenes^[60–62]



1,3-Dimesityl-2-(phenylphosphinidene)imidazolidine (35):^[60]

A soln of PhPCl_2 (45 mg, 0.25 mmol) in toluene (5 mL) was added to a soln of 1,3-dimesityl-imidazolin-2-ylidene (153 mg, 0.50 mmol) in THF (20 mL) at 23 °C under N_2 . A colorless solid precipitated immediately. After 1 h the precipitate was removed by filtration and the filtrate was concentrated to leave a light yellow solid, which was purified by crystallization; yield: 72 mg (69%); mp 99–101 °C (hexane).

18.14.3.1.5

Method 5: Exchange of Substituents on Phosphorus

P-(Trimethylsilyl)phosphaalkenes **42** are available by the methods outlined in Sections 18.14.3.1.2 and 18.14.3.1.3. The trimethylsilyl group can be displaced by a variety of electrophiles and this provides a useful method for the synthesis of other *P*-substituted phosphaalkenes **43**. The method is illustrated in Scheme 17. Besides simple electrophilic substitution with the loss of chlorotrimethylsilane, the reactions also include desilylation^[63] and addition across the *P*–Si bond (with electrophilic cumulenes).^[64,65] The phosphorus atom of the resulting phosphaalkenes can be further substituted by acids or by alkylating agents to give isolable salts.^[66] The phosphaalkenes $(\text{R}^1_2\text{N})_2\text{C}=\text{PH}$ ($\text{R}^1 = \text{Me}, \text{Et}$) have been oxidatively dimerized to the corresponding 2,3-diphosphabutadienes by reaction with a mercury(II) amide.^[67]

Scheme 17 Phosphaalkenes from Substitution of a *P*-Trimethylsilyl Group^[63–65,68–74]



R^1	Reagent	Conditions	R^2 in 43	Yield (%)	Ref
Me	TESOH	–78 °C to rt	H	75	[63]
Et	$i\text{Pr}_2\text{NPCl}_2$	0 °C	$\text{P}(\text{Cl})\text{N-}i\text{Pr}_2$	94	[68,69]
Et	Ph_3SnCl	40 °C	SnPh_3	quant	[70]
Me	$t\text{-Bu}_2\text{PCl}$	48 °C	$\text{P}(t\text{-Bu})_2$	80	[71]
Me	$(\text{TMS})_2\text{C}=\text{PCl}$	–78 °C to rt	$\text{P}=\text{C}(\text{TMS})_2$	95	[72]
Me	$\text{Ar}^1\text{N}=\text{PCl}^a$	0 °C to rt	$\text{P}=\text{NAr}^1$	91	[73]
Me	BzCl	–30 °C	Bz	77	[65]
Me	CS_2	–50 °C	$\text{C}(\text{S})\text{STMS}$	86	[65]
Me	PhNCS	–30 °C	$\text{C}(\text{S})\text{N}(\text{TMS})\text{Ph}$	72	[65]

^a $\text{Ar}^1 = 2,4,6\text{-}t\text{-Bu}_3\text{C}_6\text{H}_2$

Benzoyl[bis(dimethylamino)methylene]phosphine (43, $R^1 = \text{Me}$; $R^2 = \text{Bz}$):^[65]

A soln of BzCl (0.19 g, 1.32 mmol) in pentane (10 mL) was added dropwise to a chilled (-30°C) soln of the phosphalkene **42** ($R^1 = \text{Me}$; 0.27 g, 1.32 mmol) in pentane (40 mL). A yellow precipitate separated. The chilled slurry was filtered and the solid was washed with cold (-30°C) pentane (50 mL). After drying the solid under reduced pressure the product was obtained as a yellow powder; yield: 0.24 g (77%).

18.14.4 Product Subclass 4:
Alkylidenephosphines with One Nitrogen and One Phosphorus Substituent

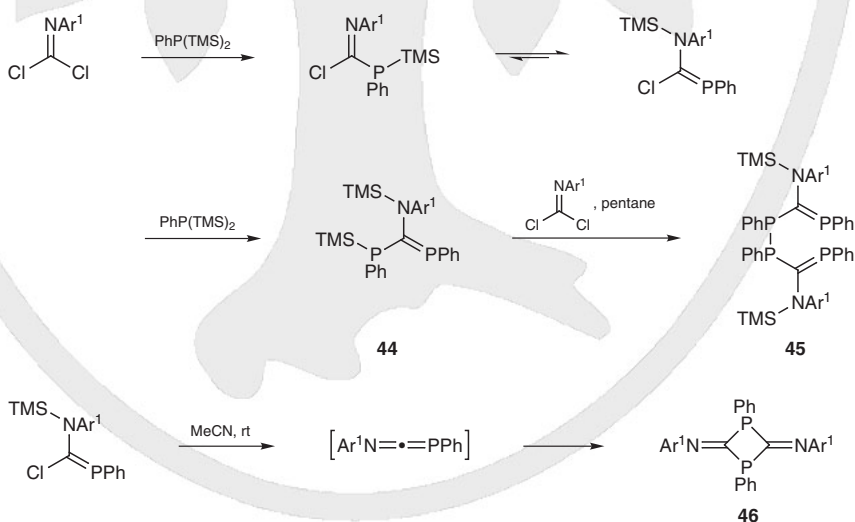
18.14.4.1 Synthesis of Product Subclass 4

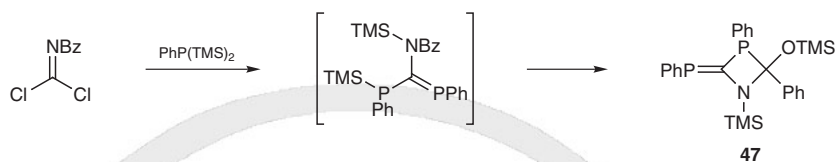
This class consists of a small number of compounds with few common structural features. There are thus no general methods for their synthesis. The available methods are summarized briefly.

18.14.4.1.1 Method 1:
Substitution of Carbonimidic Dichlorides Using
Bis(trimethylsilyl)phosphines

The reaction of phenylbis(trimethylsilyl)phosphine with arylcarbonimidic dichlorides leads to the formation of products that result from migration of a trimethylsilyl group from phosphorus to nitrogen (Scheme 18).^[35,36,38] In toluene, at or below room temperature, the major products are the phosphalkenes **44**,^[38] but in pentane at room temperature further reaction can lead to the isolation of 1,3,4,6-tetraphosphahexadienes **45**.^[36] Reaction of the species in acetonitrile at room temperature has also allowed diphosphetanes **46** to be isolated.^[36] With benzoylcarbonimidic dichloride, a further silyl migration to oxygen leads to a 1,3-azaphosphetidine **47**.^[37]

Scheme 18 Products from the Reactions of Carbonimidic Dichlorides with Phenylbis(trimethylsilyl)phosphine^[35,36,38]





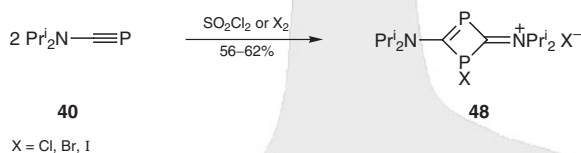
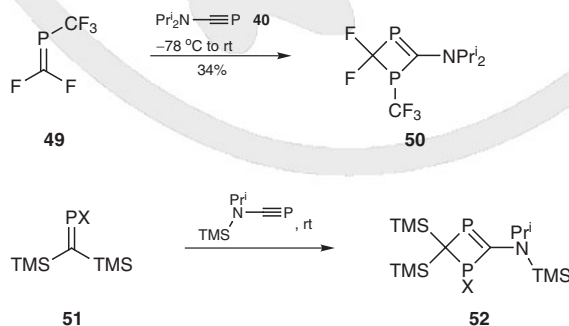
2-[(2-Chlorophenyl)(trimethylsilyl)amino]-1,3-diphenyl-3-(trimethylsilyl)-1,3-diphosphapropene (44, Ar¹ = 2-ClC₆H₄):^[38]

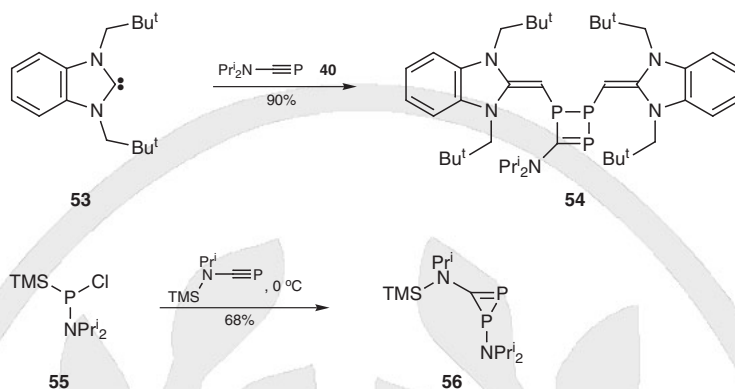
A soln of (2-chlorophenyl)carbonyldichloride (7.80 g, 37.5 mmol) in toluene (50 mL) was added slowly over 12 h to a stirred soln of phenylbis(trimethylsilyl)phosphine (12.70 g, 50 mmol) in toluene (100 mL) at 0 °C. The mixture was stirred at 0 °C for a further 24 h and then the solvent was concentrated at rt under reduced pressure. A small amount (0.2–1.5 g) of a diphosphetane side product **46** (Ar¹ = 2-ClC₆H₄) was precipitated by the addition of pentane (20 mL) and the mixture was filtered. The desired product slowly crystallized from the filtrate. It was collected by filtration and washed with a little cold pentane; yield: 9.0 g (48%); mp 85 °C (dec, pentane).

18.14.4.1.2

Method 2:**Addition Reactions of Alkylidynephosphines**

These disparate preparations have the common feature that they use *C*-aminophosphaalkynes **40** (and related structures) as one of the reagents. The reaction of phosphoalkyne **40**^[75] with either sulfur, selenium, or a halogen causes dimerization to give diphosphetenium salts (Scheme 19). The cations **48** are delocalized species but they can be represented in one resonance form as members of this subclass. Other examples of similar reactions are shown in Scheme 20. The difluorophosphaalkene **49** combines with the phosphoalkyne **40** to give the 1,2-dihydro-1,3-diphosphete **50**;^[76] a related reaction of the phosphoalkenes **51** (X = Cl, Br) gives the diphosphetes **52**.^[77] The triphosphete **54** has been isolated from reaction of the stabilized carbene **53** with the phosphoalkyne **40**. This is a multistep process involving both additions and rearrangements, but the phosphoalkene is isolated in high yield.^[78] A diphosphacyclopropene **56** is formed from the same phosphoalkyne and the chlorophosphine **55**.^[79]

Scheme 19 Phosphaalkenes from a Phosphoalkyne and Halogens^[75]**Scheme 20** Alkylidenephosphines from Addition to Alkylidynephosphines^[76–79]

**Diphosphetenium Salts 48; Typical Procedure:**^[75]

CAUTION: Sulfuryl chloride can react explosively with alkalis and is an irritant.

CAUTION: Bromine is a severe irritant of the eyes, mucous membranes, lungs, and skin. Liquid bromine causes severe and painful burns on contact with eyes and skin.

To a soln of SO_2Cl_2 , Br_2 , or I_2 (0.5 mmol) in CH_2Cl_2 , prepared in an ampoule with break seals and an NMR tube, the phosphalkyne **40** (145 mg, 1.0 mmol) was added by vacuum condensation at -196°C . The mixture was stirred during a warming-up period of ca. 1 h to reach rt. NMR measurements indicated complete consumption of the phosphalkyne and formation of the diphosphetenium salts. In the case of the *P*-chloro compound, some by-products (e.g., PCl_3) were detected by ^{31}P NMR. After concentration of the solvent and recrystallization (toluene or MeCN) the *P*-bromo compound **48** ($\text{X} = \text{Br}$) was obtained as a pale yellow powder; yield: 124.8 mg (56%); or the *P*-iodo compound **48** ($\text{X} = \text{I}$) as a pale yellow powder; yield: 167.3 mg (62%); both are air and moisture sensitive.

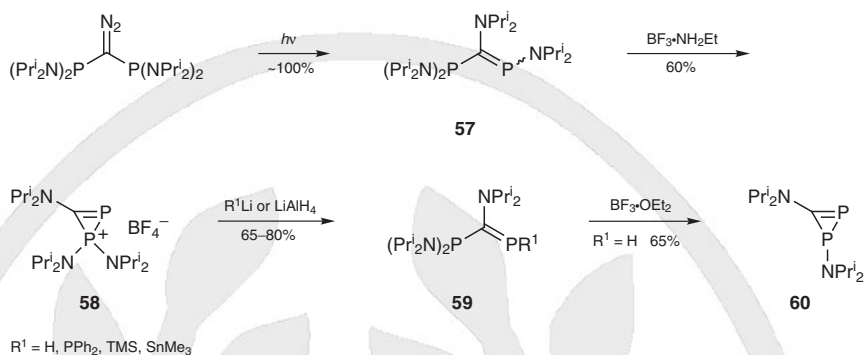
4,4-Difluoro-*N,N*-diisopropyl-1-(trifluoromethyl)-1,4-dihydro-1,3-diphosphet-2-amine (50):^[76]

The phosphalkyne **40** (215 mg, 1.5 mmol), CH_2Cl_2 (5 mL), and $\text{F}_3\text{CP}=\text{CF}_2$ (**49**; 225 mg, 1.5 mmol) were transferred to a dried and evacuated 50-mL Schlenk vessel by vacuum condensation. The reaction began when the mixture was warmed from -78 to 0°C and a color change to yellow-orange was observed. The soln was stirred for a few min at 25°C and was then cooled to -78°C and the solvent was pumped off. Reduced pressure sublimation ($25^\circ\text{C}/0.001$ Torr) on to a cold finger at -78°C gave the product as a colorless solid with a low mp, stable at rt; yield: 149 mg (34%).

18.14.4.1.3

**Method 3:
Rearrangement Reactions**

This synthetic group is based on the formation of the phosphalkene **57**, its cyclization to the diphosphirenium salt **58**, and the opening of this cation (Scheme 21). The phosphalkene **57** is produced in high yield by the photolysis of bis[bis(diisopropylamino)phosphino]diazomethane.^[80] Compound **57** cyclizes to the diphosphirenium salt **58** when treated with boron trifluoride–ethylamine complex^[81,82] (a reaction that can be reversed by the addition of lithium diisopropylamide). Reaction with other organolithium species,^[82,83] or with lithium aluminum hydride,^[84] produces the new phosphalkenes **59**. Compound **59** ($\text{R}^1 = \text{H}$) can be cyclized to the neutral diphosphirene **60**.^[84]

Scheme 21 Formation and Nucleophilic Ring Opening of a Diphosphirenium Cation^[80–84]

{{(Diisopropylamino)[bis(diisopropylamino)phosphino]methylene}(diphenylphosphino)-phosphine (59, R¹ = PPh₂)}.^[83]

To a THF soln (5 mL) of the diphosphirenium salt **58** (0.46 g, 1 mmol) a soln of Ph₂PLi (0.19 g, 1 mmol) in THF (5 mL) was added at –78 °C. The soln was allowed to warm to rt and the solvent was removed under reduced pressure. The residue was mixed with pentane and filtered. After concentration of the filtrate, the phosphalkene was obtained as a yellow oil; yield: 0.44 g (80%).

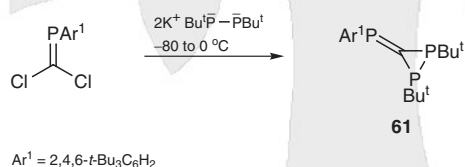
18.14.5

Product Subclass 5:
Alkylidenephosphines with Two Phosphorus Substituents

18.14.5.1

Synthesis of Product Subclass 5

This product subclass is virtually unknown. A synthesis of the diphosphirane **61** has been described (Scheme 22), but the product was impure and in low yield.^[85]

Scheme 22 Synthesis of a Diphosphirane^[85]

References

- [1] Birum, G. H.; Wilson, J. D., *J. Org. Chem.*, (1972) **37**, 2730.
- [2] Schmidpeter, A.; Lochschmidt, S.; Willhalm, A., *Angew. Chem.*, (1983) **95**, 561; *Angew. Chem. Int. Ed. Engl.*, (1983) **22**, 545.
- [3] Coles, M. P.; Hitchcock, P. B., *Chem. Commun. (Cambridge)*, (2002), 2794.
- [4] Issleib, K.; Schmidt, H.; Meyer, H., *J. Organomet. Chem.*, (1980) **192**, 33.
- [5] Tolmachev, A. A.; Merkulov, A. S.; Oshovskii, G. V.; Rozhenko, A. B., *Zh. Obshch. Khim.*, (1996) **66**, 1930; *Russ. J. Gen. Chem. (Engl. Transl.)*, (1996) **66**, 1877.
- [6] Tolmachev, A. A.; Merkulov, A. S.; Oshovsky, G. V., *Khim. Geterotsikl. Soedin.*, (1997), 1000; *Chem. Heterocycl. Compd. (Engl. Transl.)*, (1997), 877.
- [7] Buzykin, B. I.; Sokolov, M. P., *Zh. Obshch. Khim.*, (1990) **60**, 1288; *J. Gen. Chem. USSR (Engl. Transl.)*, (1990) **60**, 1150.
- [8] Pavlov, V. A.; Tkachenko, S. E.; Aristova, N. V.; Moskva, V. V.; Kamalov, R. M.; Pushin, A. N., *Zh. Obshch. Khim.*, (1992) **62**, 1772; *J. Gen. Chem. USSR (Engl. Transl.)*, (1992) **62**, 1457.
- [9] Stec, W. J.; Lesiak, K.; Sudol, M., *Synthesis*, (1975), 785.
- [10] Sokolov, M. P.; Buzykin, B. I., *Zh. Obshch. Khim.*, (1991) **61**, 1267; *J. Gen. Chem. USSR (Engl. Transl.)*, (1991) **61**, 1151.
- [11] Buzykin, B. I.; Bredikhina, Z. A.; Sokolov, M. P.; Gazetdinova, N. G., *Zh. Obshch. Khim.*, (1992) **62**, 551; *J. Gen. Chem. USSR (Engl. Transl.)*, (1992) **62**, 452.
- [12] Buzykin, B. I.; Bredikhina, Z. A., *Synthesis*, (1993), 59.
- [13] Sokolov, M. P.; Buzykin, B. I.; Mavrin, G. V., *Zh. Obshch. Khim.*, (1990) **60**, 1986; *J. Gen. Chem. USSR (Engl. Transl.)*, (1990) **60**, 1773.
- [14] Sokolov, M. P.; Buzykin, B. I.; Zyablikova, T. A., *Zh. Obshch. Khim.*, (1990) **60**, 1293; *J. Gen. Chem. USSR (Engl. Transl.)*, (1990) **60**, 1155.
- [15] Buzykin, B. I.; Sokolov, M. P., *Zh. Obshch. Khim.*, (1990) **60**, 1980; *J. Gen. Chem. USSR (Engl. Transl.)*, (1990) **60**, 1767.
- [16] Tashma, Z., *J. Org. Chem.*, (1983) **48**, 3966.
- [17] Young, R. C.; Ganellin, C. R.; Graham, M. J.; Mitchell, R. C.; Roantree, M. L.; Tashma, Z., *J. Med. Chem.*, (1987) **30**, 1150.
- [18] Kukhar, V. P.; Shevchenko, M. V.; Kirsanova, N. A., *Zh. Org. Khim.*, (1973) **9**, 1815; *J. Org. Chem. USSR (Engl. Transl.)*, (1973) **9**, 1839.
- [19] Dimroth, K.; Greif, N.; Klapproth, A., *Liebigs Ann. Chem.*, (1975), 373.
- [20] Pudovik, A. N.; Romanov, G. V.; Stepanova, T. Y., *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1982), 1416; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1982) **31**, 1263.
- [21] Thewissen, D.; Ambrosius, H., *Recl. Trav. Chim. Pays-Bas*, (1980) **99**, 344.
- [22] Grundy, J.; Coles, M. P.; Hitchcock, P. B., *Dalton Trans.*, (2003), 2573.
- [23] Issleib, K.; Franze, K. D., *J. Prakt. Chem.*, (1973) **315**, 471.
- [24] Afarinkia, K.; Rees, C. W.; Cadogan, J. I. G., *Tetrahedron*, (1990) **46**, 7175.
- [25] Kamalov, R. M.; Makarov, G. M.; Islamov, R. G.; Pudovik, M. A.; Cherkasov, R. A.; Pudovik, A. N., *Zh. Obshch. Khim.*, (1990) **60**, 778; *J. Gen. Chem. USSR (Engl. Transl.)*, (1990) **60**, 680.
- [26] Kennedy, J., *Chem. Ind. (London)*, (1956), 1348.
- [27] Kamalov, R. M.; Khailova, N. A.; Alfonsov, V. A.; Pudovik, M. A., *Zh. Obshch. Khim.*, (1995) **65**, 46; *Russ. J. Gen. Chem. (Engl. Transl.)*, (1995) **65**, 37.
- [28] Nifant'ev, E. E.; Shilov, I. V., *Zh. Obshch. Khim.*, (1973) **43**, 2654; *J. Gen. Chem. USSR (Engl. Transl.)*, (1973) **43**, 2633.
- [29] Hudson, R. F.; Searle, R. J. G., *J. Chem. Soc. B*, (1968), 1349.
- [30] Pudovik, A. N.; Batyeva, E. S., *Zh. Obshch. Khim.*, (1968) **38**, 285; *J. Gen. Chem. USSR (Engl. Transl.)*, (1968) **38**, 288.
- [31] Pudovik, A. N.; Batyeva, E. S.; Ofitserov, E. N., *Zh. Obshch. Khim.*, (1976) **46**, 1441; *J. Gen. Chem. USSR (Engl. Transl.)*, (1976) **46**, 1418.
- [32] Kolodiaznyi, O. I., *Tetrahedron Lett.*, (1982) **23**, 4933.
- [33] Kolodyaznyi, O. I., *Zh. Obshch. Khim.*, (1982) **52**, 2361; *J. Gen. Chem. USSR (Engl. Transl.)*, (1982) **52**, 2101.
- [34] Granier, M.; Baceiredo, A.; Dartiguenave, Y.; Dartiguenave, M.; Menu, M.-J.; Bertrand, G., *J. Am. Chem. Soc.*, (1990) **112**, 6277.
- [35] Appel, R.; Barth, V.; Knoll, F.; Ruppert, I., *Angew. Chem.*, (1979) **91**, 936; *Angew. Chem. Int. Ed. Engl.*, (1979) **18**, 873.

- [36] Appel, R.; Laubach, B., *Tetrahedron Lett.*, (1980) **21**, 2497.
- [37] Appel, R.; Halstenberg, M.; Knoch, F.; Kunze, H., *Chem. Ber.*, (1982) **115**, 2371.
- [38] Appel, R.; Knoch, F.; Laubach, B.; Sievers, R., *Chem. Ber.*, (1983) **116**, 1873.
- [39] Shokol, V. A.; Kozhushko, B. N.; Gumenyuk, A. V., *Zh. Obshch. Khim.*, (1975) **45**, 1965; *J. Gen. Chem. USSR (Engl. Transl.)*, (1975) **45**, 1931.
- [40] Sologub, L. S.; Kisilenko, A. A.; Kukhar, V. P.; Vdovenko, S. I., *Khim. Geterotsikl. Soedin.*, (1983), 798; *Chem. Heterocycl. Compd. (Engl. Transl.)*, (1983), 641.
- [41] Gross, H.; Costisella, B., *J. Prakt. Chem.*, (1972) **314**, 87.
- [42] Gross, H.; Costisella, B.; Gnauk, T.; Brennecke, L., *J. Prakt. Chem.*, (1976) **318**, 116.
- [43] Levkova, L. N.; Alimov, P., *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1966), 2218; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1966), 2149.
- [44] Neidlein, R.; Haussmann, W.; Heukelbach, E., *Chem. Ber.*, (1966) **99**, 1252.
- [45] Foss, V. L.; Lukashev, N. V.; Lutsenko, I. F., *Zh. Obshch. Khim.*, (1982) **52**, 2187; *J. Gen. Chem. USSR (Engl. Transl.)*, (1982) **52**, 1946.
- [46] Shokol, V. A.; Kozhushko, B. N.; Kirsanov, A. V., *Zh. Obshch. Khim.*, (1973) **43**, 544; *J. Gen. Chem. USSR (Engl. Transl.)*, (1973) **43**, 547.
- [47] Appel, R.; Knoll, F.; Ruppert, I., *Angew. Chem.*, (1981) **93**, 771; *Angew. Chem. Int. Ed. Engl.*, (1981) **20**, 731.
- [48] Markovskii, L. N.; Romanenko, V. D., *Zh. Obshch. Khim.*, (1986) **56**, 253; *J. Gen. Chem. USSR (Engl. Transl.)*, (1986) **56**, 221.
- [49] Markovski, L. N.; Romanenko, V. D., *Tetrahedron*, (1989) **45**, 6019.
- [50] Appel, R.; Knoll, F., *Adv. Inorg. Chem.*, (1989) **33**, 259.
- [51] Weber, L., *Eur. J. Inorg. Chem.*, (2000), 2425.
- [52] Schmidpeter, A.; Gebler, W.; Zwaschka, F.; Sheldrick, W. S., *Angew. Chem.*, (1980) **92**, 767; *Angew. Chem. Int. Ed. Engl.*, (1980) **19**, 722.
- [53] Markovskii, L. N.; Romanenko, V. D.; Pidvarko, T. I., *Zh. Obshch. Khim.*, (1982) **52**, 1925; *J. Gen. Chem. USSR (Engl. Transl.)*, (1982) **52**, 1707.
- [54] Povolotskii, M. I.; Negrebetskii, V. V.; Romanenko, V. D.; Ivanchenko, V. I.; Sarina, T. V.; Markovskii, L. N., *Zh. Obshch. Khim.*, (1990) **60**, 2238; *J. Gen. Chem. USSR (Engl. Transl.)*, (1990) **60**, 2000.
- [55] Oehme, H.; Leissring, E.; Meyer, H., *Z. Chem.*, (1981) **21**, 407.
- [56] Issleib, K.; Leissring, E.; Meyer, H., *Tetrahedron Lett.*, (1981) **22**, 4475.
- [57] Issleib, K.; Leissring, E.; Riemer, M.; Oehme, H., *Z. Chem.*, (1983) **23**, 99.
- [58] Weber, L.; Kaminski, O., *Synthesis*, (1995), 158.
- [59] Weber, L.; Meyer, M.; Stammler, H. G.; Neumann, B., *Chem.-Eur. J.*, (2001) **7**, 5401.
- [60] Arduengo, A. J.; Calabrese, J. C.; Cowley, A. H.; Dias, H. V. R.; Goerlich, J. R.; Marshall, W. J.; Riegel, B., *Inorg. Chem.*, (1997) **36**, 2151.
- [61] Arduengo, A. J.; Dias, H. V. R.; Calabrese, J. C., *Chem. Lett.*, (1997), 143.
- [62] Hahn, F. E.; Le Van, D.; Moyes, M. C.; von Fehren, T.; Fröhlich, R.; Würthwein, E.-U., *Angew. Chem.*, (2001) **113**, 3241; *Angew. Chem. Int. Ed.*, (2001) **40**, 3144.
- [63] Romanenko, V. D.; Sarina, T. V.; Kolotilo, N. V.; Markovskii, L. N., *Zh. Obshch. Khim.*, (1985) **55**, 1188; *J. Gen. Chem. USSR (Engl. Transl.)*, (1985) **55**, 1060.
- [64] Markovskii, L. N.; Romanenko, V. D.; Pidvarko, T. V., *Zh. Obshch. Khim.*, (1983) **53**, 1672; *J. Gen. Chem. USSR (Engl. Transl.)*, (1983) **53**, 1502.
- [65] Weber, L.; Uthmann, S.; Bogge, H.; Muller, A.; Stammler, H. G.; Neumann, B., *Organometallics*, (1998) **17**, 3593.
- [66] Weber, L.; Uthmann, S.; Stammler, H. G.; Neumann, B.; Schoeller, W. W.; Boese, R.; Blaser, D., *Eur. J. Inorg. Chem.*, (1999), 2369.
- [67] Romanenko, V. D.; Kachkovskaya, L. S.; Markovskii, L. N., *Zh. Obshch. Khim.*, (1985) **55**, 2140; *J. Gen. Chem. USSR (Engl. Transl.)*, (1985) **55**, 1898.
- [68] Sanchez, M.; Romanenko, V.; Mazieres, M. R.; Gudima, A.; Markowski, L., *Tetrahedron Lett.*, (1991) **32**, 2775.
- [69] Romanenko, V. D.; Sarina, T. V.; Sanshe, M.; Mazier, M. R.; Rozhenko, A. B.; Chernega, A. N.; Polovinko, V. V., *Zh. Obshch. Khim.*, (1994) **64**, 579; *Russ. J. Gen. Chem. (Engl. Transl.)*, (1994) **64**, 526.
- [70] Markovskii, L. N.; Romanenko, V. D.; Sarinapidvarko, T. V.; Povolotskii, M. I., *Zh. Obshch. Khim.*, (1985) **55**, 221; *J. Gen. Chem. USSR (Engl. Transl.)*, (1985) **55**, 194.
- [71] Romanenko, V. D.; Sarina, T. V.; Povolotskii, M. I.; Markovskii, L. N., *Zh. Obshch. Khim.*, (1985) **55**, 1437; *J. Gen. Chem. USSR (Engl. Transl.)*, (1985) **55**, 1280.

- [72] Markovskii, L. N.; Romanenko, V. D.; Kachkovskaya, L. S.; Povolotskii, M. I.; Patsanovskii, I. I.; Stepanova, Y. Z.; Ishmaeva, E. A., *Zh. Obshch. Khim.*, (1987) **57**, 901; *J. Gen. Chem. USSR (Engl. Transl.)*, (1987) **57**, 799.
- [73] Markovskii, L. N.; Romanenko, V. D.; Ruban, A. V.; Sarina, T. V.; Povolotskii, M. I.; Lure, L. F., *Zh. Obshch. Khim.*, (1991) **61**, 401; *J. Gen. Chem. USSR (Engl. Transl.)*, (1991) **61**, 363.
- [74] Weber, L.; Dembeck, G.; Boese, R.; Blaser, D., *Chem. Ber./Recl.*, (1997) **130**, 1305.
- [75] Grobe, J.; Le Van, D.; Pohlmeier, T.; Immel, F.; Pucknat, H.; Krebs, B.; Kuchinke, J.; Lage, M., *Tetrahedron*, (2000) **56**, 27.
- [76] Grobe, J.; Le Van, D.; Broschk, B.; Hegemann, M.; Lüth, B.; Becker, G.; Böhringer, M.; Würthwein, E.-U., *J. Organomet. Chem.*, (1997) **529**, 177.
- [77] Streubel, R.; Frost, M.; Nieger, M.; Niecke, E., *Bull. Soc. Chim. Fr.*, (1993) **130**, 642.
- [78] Hahn, F. E.; Wittenbecher, L.; Le Van, D.; Fröhlich, R.; Wibbeling, B., *Angew. Chem.*, (2000) **112**, 2393; *Angew. Chem. Int. Ed.*, (2000) **39**, 2307.
- [79] Niecke, E.; Streubel, R.; Nieger, M.; Stalke, D., *Angew. Chem.*, (1989) **101**, 1708; *Angew. Chem. Int. Ed. Engl.*, (1989) **28**, 1673.
- [80] Baceiredo, A.; Igau, A.; Bertrand, G.; Menu, M. J.; Dartiguenave, Y.; Bonnet, J. J., *J. Am. Chem. Soc.*, (1986) **108**, 7868.
- [81] Castan, F.; Baceiredo, A.; Fischer, J.; De Cian, A.; Commenges, G.; Bertrand, G., *J. Am. Chem. Soc.*, (1991) **113**, 8160.
- [82] Soleilhavoup, M.; Canac, Y.; Polozov, A. M.; Baceiredo, A.; Bertrand, G., *J. Am. Chem. Soc.*, (1994) **116**, 6149.
- [83] Kato, T.; Polishchuk, O.; Gornitzka, H.; Baceiredo, A.; Bertrand, G., *J. Organomet. Chem.*, (2000) **613**, 33.
- [84] Bourissou, D.; Canac, Y.; Collado, M. I.; Baceiredo, A.; Bertrand, G., *Chem. Commun. (Cambridge)*, (1997), 2399.
- [85] Baudler, M.; Simon, J., *Chem. Ber.*, (1988) **121**, 281.



Product Class 15: Tetraheterosubstituted Methanes with a Carbon—Halogen Bond

A. Y. Il'chenko

General Introduction

Previously published information regarding this product class can be found in *Houben-Weyl*, Vol. 5/3, pp 1–1217; Vol. 5/4, pp 1–894; Vol. E 10a, pp 1–740; Vol. E 10b/1, pp 1–720; and Vol. E 10b/2, pp 1–464.

Product Class 15 (Section 18.15) includes compounds (tetrasubstituted methanes) of general formula $Z-CX_3$, with halogen atoms $Z = F, Cl, Br, I$ and heteroatoms $X = F, Cl, Br, I, O, S, Se, Te, N, P$. Heteroatoms X can be in different oxidation degrees, have different valences, and be combined with hydrogen atoms, alkyls, aryls, or heteroatoms. According to the type of heteroatom X , Product Class 15 is subdivided into seven product subclasses ($X = \text{halo}, O, S, Se, Te, N, P$; Sections 18.15.1–18.15.7).

Many tetrasubstituted methanes belonging to this product class, containing halogen, oxygen, sulfur, selenium, tellurium, nitrogen, and phosphorus heteroatoms, are important reagents, widely used in syntheses of organic compounds.

Carbon tetrahalides are also named as substituted methanes by substitutive IUPAC nomenclature. In this section, the carbon tetrahalide names will only be used when all the halo groups are the same (e.g., carbon tetrachloride). In the other cases, the tetrahalomethane names will be used (e.g., dichlorofluoroiodomethane).

18.15.1

Product Subclass 1: Tetrahalomethanes

Compounds containing fluorine atoms are of great practical importance.^[1–4] Carbon tetrafluoride is used for plasma, ion-beam, or sputter etching of semiconductor devices.^[5] Some chlorofluorocarbons, in particular chlorotrifluoromethane and dichlorodifluoromethane, have important practical and industrial applications as refrigerants, aerosol propellants, blowing agents, and solvents.^[1–4,6] The commercialization of certain chlorofluorohydrocarbons as refrigerating agents in household devices and air-conditioning equipment at around 1930 resulted in increasing interest in the chemistry of tetrahalomethanes. Many of these compounds are commercially available.

Chlorofluoromethanes are stable, relatively inert chemically, particularly in the absence of moisture. They do not react with most metals below temperatures of 200 °C or with acids or oxidizing agents. They react very slowly with alkalis in the presence of water and can be decomposed with molten alkali metals, particularly when dissolved in liquid ammonia. At room temperature, chlorofluoromethanes are stable toward concentrated sulfuric acid as well as toward concentrated alkaline hydroxides. The extreme stability of highly fluorinated compounds to chemical action and heat is one of the principal motivations for the present wide scope of research on the preparation and properties of these substances.

From a biological point of view, fluorinated refrigerants and aerosol propellants are remarkably inert and harmless to man.^[1,2,6] In 1974, the hypothesis, controversial at first,^[6] was forwarded that chlorinated compounds are responsible for the depletion of the ozone in the stratosphere. Therefore, in accordance with the Montreal Protocol, the

first international agreement to protect the global environment, the production and use of chlorofluorocarbons is being decreased.^[1,2]

The nonexplosiveness and nonflammability of fluorinated methane derivatives contributes to their application as fire extinguishers. The brominated products, dibromodifluoromethane, and especially bromotrifluoromethane are very efficient at extinguishing fires by slowing down the chain reactions of burning. The latter compound is particularly suitable for this purpose, since it and its decomposition products are entirely non-toxic. For this reason, it is much safer than carbon tetrachloride, which forms highly toxic carbonyl chloride when used to put out fires. The main applications of fluorinated fire extinguishers are in aircraft and rocket fires, and as safety screens in fuel storage.^[2]

Fluorocarbons containing bromine and iodine atoms are more toxic than the corresponding chlorinated compounds. A higher fluorine to other halogen ratio lowers the toxicity, especially in bromofluorocarbons.^[5]

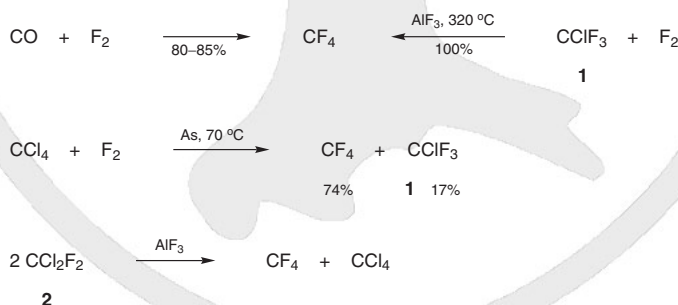
18.15.1.1 Synthesis of Product Subclass 1

18.15.1.1.1 Method 1: Carbon Tetrafluoride

Carbon tetrafluoride is a colorless, odorless, thermally stable, nonflammable, and chemically very inert gas. It was prepared for the first time in 1890 by the interaction of fluorine with carbon, carbon tetrachloride, trichloromethane, or methane,^[7] or by reaction of silver(I) fluoride with carbon tetrachloride at 300 °C.^[8–10]

Carbon tetrafluoride is commercially available. It is prepared in 80–85% yield by combustion of a mixture of carbon monoxide and fluorine (Scheme 1).^[11] The interaction of carbon tetrachloride with fluorine in the presence of arsenic gives carbon tetrafluoride and chlorotrifluoromethane (**1**) (Scheme 1).^[12] Carbon tetrafluoride can also be prepared from carbon and fluorine^[13,14] and from silicon carbide and fluorine.^[15] The substitution of the chlorine atom in chlorotrifluoromethane (**1**) by a fluorine atom under action of fluorine in the presence of aluminum trifluoride catalyst gives carbon tetrafluoride in almost 100% yield (Scheme 1).^[16] Carbon tetrafluoride is obtained when dichlorodifluoromethane (**2**) reacts with anhydrous hydrogen fluoride at elevated temperature,^[17] or by disproportionation of dichlorodifluoromethane (**2**) when heated in the presence of aluminum trifluoride (Scheme 1).^[18,19]

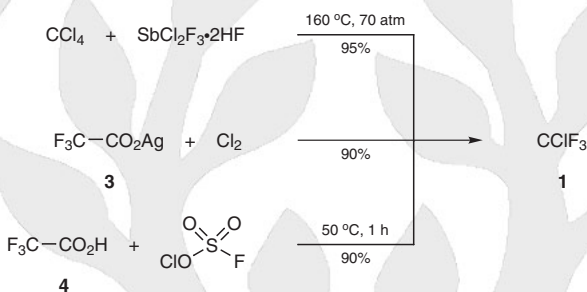
Scheme 1 Synthesis of Carbon Tetrafluoride^[11,12,16–19]



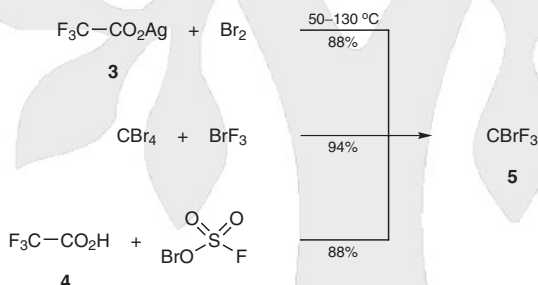
18.15.1.1.2

Method 2:**Chlorotrifluoromethane, Bromotrifluoromethane, and Trifluoroiodomethane**

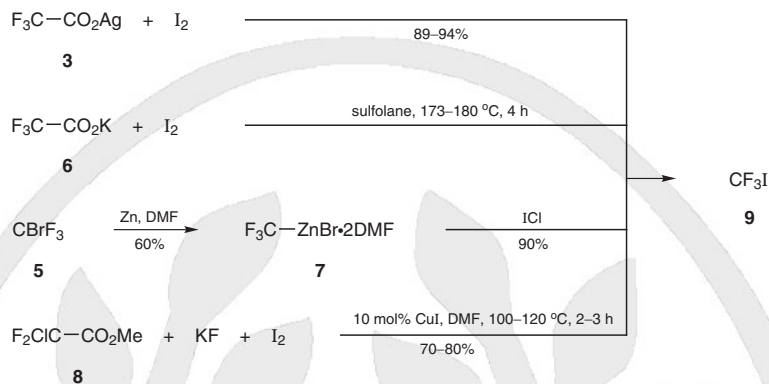
Chlorotrifluoromethane (**1**) is a colorless, odorless gas that can be prepared from carbon tetrachloride and the antimony(V) dichloride trifluoride–bis(hydrogen fluoride) complex (95% yield),^[20] from silver(I) trifluoroacetate (**3**) and chlorine (90% yield),^[21] or from trifluoroacetic acid (**4**) and chlorine fluorosulfate (90% yield) (Scheme 2).^[22]

Scheme 2 Synthesis of Chlorotrifluoromethane^[20–22]

Bromotrifluoromethane (**5**) can be prepared from silver(I) trifluoroacetate (**3**) and bromine (88% yield),^[23,24] from carbon tetrabromide and bromine trifluoride (94% yield),^[25] or from trifluoroacetic acid (**4**) and bromine fluorosulfate (88% yield) (Scheme 3).^[22]

Scheme 3 Synthesis of Bromotrifluoromethane^[22–25]

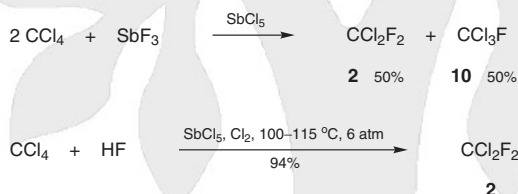
Trifluoroiodomethane (**9**) can be prepared from silver(I) trifluoroacetate (**3**) and iodine (89–94% yield),^[21,26,27] from potassium trifluoroacetate (**6**) and iodine (80% yield),^[28] or from the (trifluoromethyl)zinc(II) bromide–bis(dimethylformamide) complex [**7**; prepared from bromotrifluoromethane (**5**) and zinc] and iodine chloride (90% yield) (Scheme 4).^[29] Treatment of methyl chlorodifluoroacetate (**8**) with potassium fluoride and iodine (1:1:1) in the presence of a catalytic amount of copper(I) iodide also gives trifluoroiodomethane (**9**) (70–80% yield) (Scheme 4).^[30]

Scheme 4 Preparation of Trifluoroiodomethane^[21,26–30]

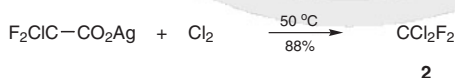
18.15.1.1.3

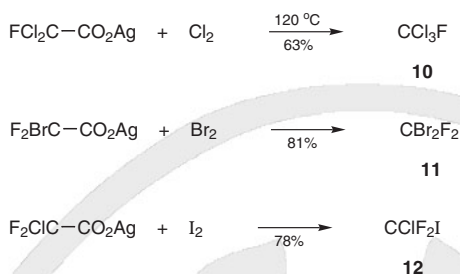
Method 3:**Tetrahalomethanes Containing Zero to Two Fluorides**

Dichlorodifluoromethane (**2**) and trichlorofluoromethane (**10**) are commercially available. They are usually obtained from carbon tetrachloride by replacement of chlorine by fluorine atoms on reaction with antimony(III) fluoride in the presence of antimony(V) chloride (Scheme 5).^[31] Reaction of carbon tetrachloride with hydrogen fluoride in the presence of antimony(V) chloride gives dichlorodifluoromethane (**2**) exclusively (94% yield) (Scheme 5).^[32]

Scheme 5 Syntheses of Dichlorodifluoromethane and Trichlorofluoromethane from Carbon Tetrachloride^[31,32]

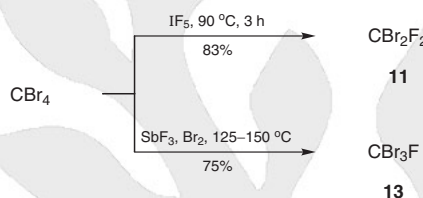
When silver(I) chlorodifluoroacetate or silver(I) dichlorofluoroacetate is heated with dry chlorine in a steel bomb, dichlorodifluoromethane (**2**) and trichlorofluoromethane (**10**) are obtained, respectively (Scheme 6).^[33] Heating of silver(I) trihaloacetates with bromine gives the corresponding bromotrihalomethanes.^[33] In this way, dibromodifluoromethane (**11**) is prepared from silver(I) bromodifluoroacetate and bromine (81% yield) (Scheme 6).^[33] Heating of silver(I) trihaloacetates with iodine gives the corresponding trihaloiodomethanes similarly.^[33] Thus, trifluoroiodomethane (**9**) is obtained from silver(I) trifluoroacetate (**3**) and iodine,^[21] and chlorodifluoroiodomethane (**12**) is prepared from silver(I) chlorodifluoroacetate and iodine (78% yield) (Scheme 6).^[33]

Scheme 6 Syntheses of Trichlorofluoromethane and Difluorodihalomethanes from Silver(I) Trihaloacetates and Elemental Halogens^[33]



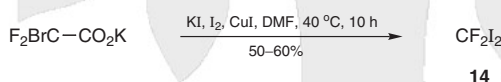
Dibromodifluoromethane (**11**) can be prepared by reaction of carbon tetrabromide with iodine pentafluoride (Scheme 7).^[25] Heating of carbon tetrabromide with antimony(III) fluoride and bromine gives tribromofluoromethane (**13**) (Scheme 7).^[34]

Scheme 7 Syntheses of Dibromodifluoromethane and Tribromofluoromethane from Carbon Tetrabromide^[25,34]



For the synthesis of pure difluorodiiodomethane (**14**), potassium bromodifluoroacetate is the best starting material.^[30] When equimolar amounts of potassium bromodifluoroacetate, potassium iodide, copper(I) iodide, and iodine are heated together in dimethylformamide, difluorodiiodomethane (**14**) is obtained in 50–60% yield (Scheme 8).^[30]

Scheme 8 Synthesis of Difluorodiiodomethane from Potassium Bromodifluoroacetate, Potassium Iodide, Copper(I) Iodide, and Iodine^[30]



Reaction of carbon tetrachloride with aluminum tribromide and bromoethane gives carbon tetrabromide (Scheme 9).^[35] Carbon tetrabromide is also obtainable from carbon disulfide and bromine (Scheme 9).^[36] In a method similar to that used to prepare carbon tetrabromide from carbon tetrachloride, carbon tetraiodide is prepared from carbon tetrachloride and iodomethane in the presence of aluminum trichloride (Scheme 9).^[37]

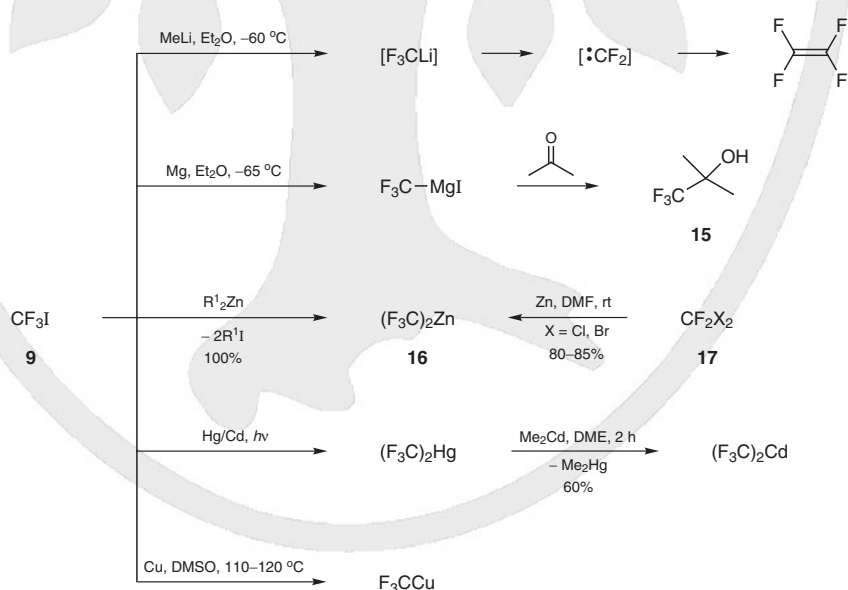
Scheme 9 Syntheses of Carbon Tetrabromide and Carbon Tetrachloride^[35-37]



18.15.1.2 Applications of Product Subclass 1 in Organic Synthesis

18.15.1.2.1 Method 1:
(Trifluoromethyl)metal Reagents

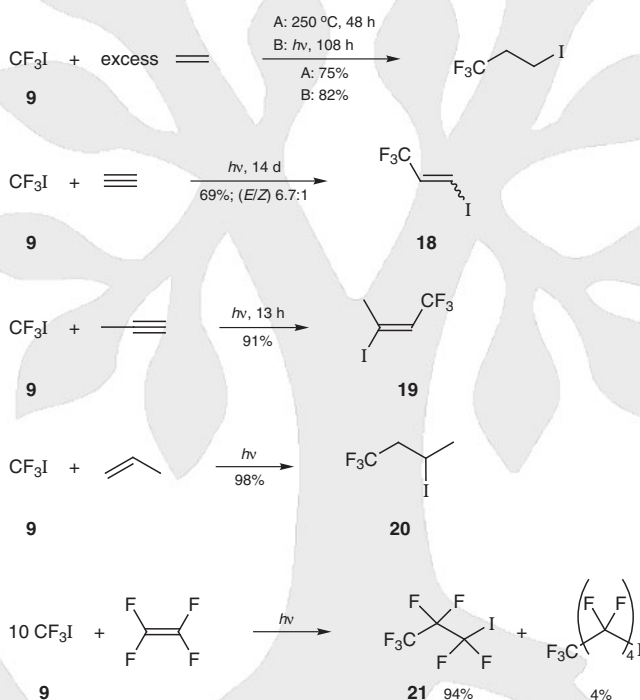
Tetrahalomethanes are widely used for the synthesis of fluorinated organometallic reagents.^[38] (Trifluoromethyl)lithium is prepared from trifluoroiodomethane (**9**) and methylolithium, but is unstable even at low temperatures, and decomposes to yield difluorocarbene, which then forms tetrafluoroethene (Scheme 10).^[39] Trifluoromethyl Grignard reagents (F_3CMgX , $\text{X} = \text{Br}, \text{I}$) are prepared from bromotrifluoromethane (**5**) or trifluoroiodomethane (**9**) and magnesium at low temperatures in the presence of trapping agents (Scheme 10).^[40,41] The trifluoromethyl–acetone adduct **15** has been isolated by reaction between a Grignard reagent and acetone, but is formed in low yield (Scheme 10).^[41] When trifluoroiodomethane (**9**) reacts with a dialkylzinc(II) reagent, bis(trifluoromethyl)zinc(II) (**16**) forms quantitatively (Scheme 10).^[42] Bis(trifluoromethyl)zinc(II) (**16**) has also been prepared from difluorodihalomethanes **17** ($\text{X} = \text{Cl}, \text{Br}$) and zinc in dimethylformamide (Scheme 10).^[43] Dibromodifluoromethane (**11**) and zinc in tetrahydrofuran have been utilized as a difluorocarbene source for the synthesis of *gem*-difluorocyclopropane derivatives.^[44] Irradiation of a mixture of trifluoroiodomethane (**9**) and cadmium amalgam gives bis(trifluoromethyl)mercury(II) (Scheme 10).^[45] The reaction of bis(trifluoromethyl)mercury(II) and dimethylcadmium(II) gives bis(trifluoromethyl)cadmium(II) (Scheme 10).^[46] The bis(trifluoromethyl)cadmium(II)–dimethoxyethane complex is a useful reagent for the introduction of trifluoromethyl groups into inorganic compounds to give products such as tetrakis(trifluoromethyl)stannane^[46] and tris(trifluoromethyl)gold(III).^[47,48] When trifluoroiodomethane (**9**) is heated with copper metal in dimethyl sulfoxide, (trifluoromethyl)copper(I) forms in good yield (Scheme 10).^[49] Although dimethyl sulfoxide is the most generally employed solvent, other solvents such as dimethyl sulfide, dimethylformamide, hexamethylphosphoric triamide, and pyridine have also been utilized.^[49,50]

Scheme 10 Synthesis of (Trifluoromethyl)metal Reagents^[39–43,45,46]

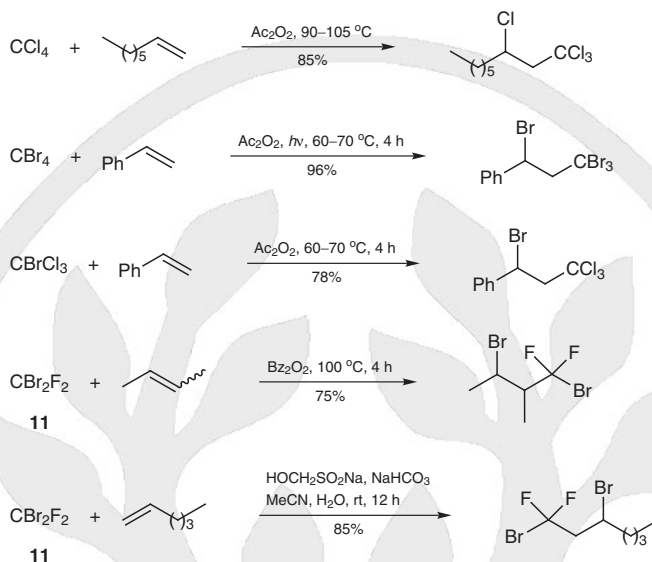
18.15.1.2.2

Method 2:
Addition to Alkenes and Alkynes

When trifluoroiodomethane (**9**) is heated or undergoes ultraviolet irradiation, the trifluoromethyl radical and an iodine atom form, which can add to alkenes or alkynes (Scheme 11).^[51] In this way, trifluoroiodomethane (**9**) reacts with ethene to form 1,1,1-trifluoro-3-iodopropane (Scheme 11).^[52] The light-induced addition of trifluoroiodomethane (**9**) to acetylene yields predominantly the *E*-isomer of 3,3,3-trifluoro-1-iodoprop-1-ene (**18**) (69% yield, *E/Z* 6.7:1) (Scheme 11).^[53] Trifluoroiodomethane (**9**) reacts with propyne when exposed to ultraviolet light to give 1,1,1-trifluoro-3-iodobut-2-ene (**19**) (Scheme 11).^[54] When trifluoroiodomethane (**9**) and propene are irradiated, 1,1,1-trifluoro-3-iodobutane (**20**) forms (Scheme 11).^[52] The thermally or photochemically induced addition of trifluoroiodomethane (**9**) to alkenes tends to result in oligomer formation.^[55] But irradiation of an excess of trifluoroiodomethane (**9**) with tetrafluoroethene gives 1-iodoheptafluoropropane (**21**) predominantly (Scheme 11).^[55] The trifluoromethyl radical adds 1.4 times faster to propene and 6.5 times slower to tetrafluoroethene than to ethene.^[56]

Scheme 11 Addition of Trifluoroiodomethane to Alkenes and Alkynes^[51–55]


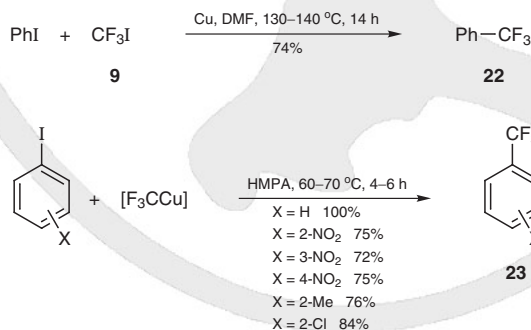
The use of free radical initiators in addition reactions is usually very useful. They allow the reactions to be run at much lower temperatures and with increased efficiency. In the presence of a small amount of either diacetyl peroxide or dibenzoyl peroxide, carbon tetrachloride, carbon tetrabromide, bromotrichloromethane, and dibromodifluoromethane (**11**) undergo addition reactions with alkenes (Scheme 12).^[57–61] This type of addition takes place by a chain reaction initiated by the free radicals generated in the mixture through the decomposition of the organic peroxide.

Scheme 12 Free-Radical-Initiated Addition of Tetrahalomethanes to Alkenes^[57–61]

18.15.1.2.3

**Method 3:
Trifluoromethylation of Arenes and Hetarenes**

Tetrahalomethanes are widely used in the syntheses of trifluoromethylated arenes and hetarenes.^[62–65] The iodo groups of iodoarenes are substituted upon interaction with trifluoroiodomethane (**9**) and copper in a polar aprotic solvent, giving (trifluoromethyl)-arenes in good yields (Scheme 13).^[49,66] Thus, (trifluoromethyl)benzene (**22**) is obtained in 74% yield when iodobenzene, trifluoroiodomethane (**9**), and copper in dimethylformamide are heated in a stainless-steel tube (Scheme 13).^[66,67] Reaction of 1-iodo-2,3,5,6-tetramethylbenzene with trifluoroiodomethane (**9**) and copper in dimethylformamide at 150 °C gives 2,3,5,6-tetramethyl-1-(trifluoromethyl)benzene in 65% yield.^[68] 1-(Trifluoromethyl)naphthalene and 2-(trifluoromethyl)quinoline are also obtained in good yields by this method.^[43,69]

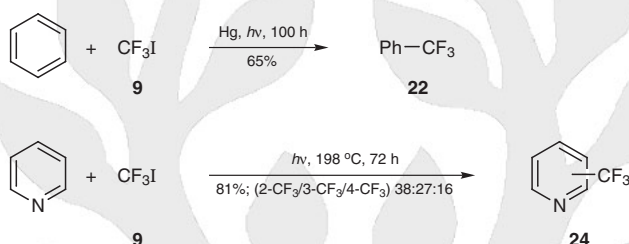
Scheme 13 Trifluoromethylation of Iodobenzenes by Trifluoroiodomethane and Copper or (Trifluoromethyl)copper(I)^[49,66,67,70]

(Trifluoromethyl)copper(I) can be produced from copper(I) salts, such as copper(I) chloride, bromide, or iodide, and bis(trifluoromethyl)cadmium(II), prepared from difluorodihalomethanes **17** (CF_2X_2 , $\text{X} = \text{Cl}, \text{Br}$) and cadmium.^[43] (Trifluoromethyl)copper(I) prepared

by this method reacts with iodoarenes in hexamethylphosphoric triamide to give the corresponding (trifluoromethyl)arenes **23** in good yields (Scheme 13).^[70]

The trifluoromethylation of benzene by trifluoroiodomethane (**9**) and mercury under irradiation gives (trifluoromethyl)benzene (**22**) in 65% yield (Scheme 14).^[71] Heating of trifluoroiodomethane (**9**) with chlorobenzene^[72], bromobenzene^[73], or iodobenzene^[72] in a sealed tube at 190–198 °C produces mixtures of the corresponding 2-, 3-, and 4-halo-(trifluoromethyl)benzenes. Photochemical trifluoromethylation of pyridine by trifluoroiodomethane (**9**) gives a mixture of 2-, 3-, and 4-(trifluoromethyl)pyridines (**24**) (Scheme 14).^[74]

Scheme 14 Photochemical and Thermal Trifluoromethylation of Benzene and Pyridine by Trifluoroiodomethane^[71,74]



Carbon tetrachloride reacts with arenes in the presence of a catalyst to yield trichloromethylated compounds. For example, reaction of carbon tetrachloride and aluminum trichloride with 1,3,5-trimethylbenzene gives 1-(trichloromethyl)-2,4,6-trimethylbenzene,^[75] whose chlorine atoms are replaced by fluorine atoms on reaction with antimony(III) fluoride, to give 1-(trifluoromethyl)-2,4,6-trimethylbenzene in 63% yield.^[76] For introduction of a trifluoromethyl group into arenes, a single-step method based on the action of carbon tetrachloride and hydrogen fluoride can be used (Scheme 15).^[77] This reaction is thought to be of a Friedel–Crafts type and is limited to arenes not substituted by electron-withdrawing groups. (Trifluoromethyl)benzene (**22**) is prepared by this method in 92% yield (Scheme 15).^[77]

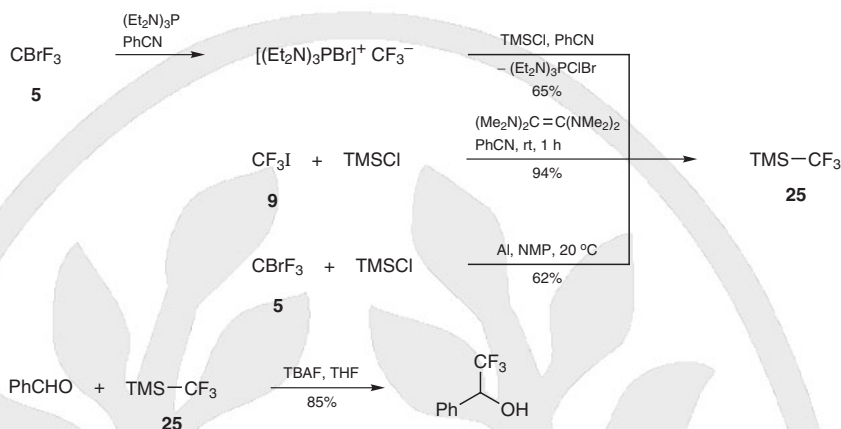
Scheme 15 Trifluoromethylation of Benzene by Carbon Tetrachloride and Hydrogen Fluoride^[77]



18.15.1.2.4

Method 4: Synthesis of Trimethyl(trifluoromethyl)silane (Ruppert's Reagent)

Trimethyl(trifluoromethyl)silane (**25**) (bp 45 °C) is a reagent that can be used for the introduction of the trifluoromethyl group under mild conditions.^[78–80] It can be prepared from bromotrifluoromethane (**5**), hexaethylphosphorous triamide, and chlorotrimethylsilane (Scheme 16);^[78,79] from trifluoroiodomethane (**9**), tetrakis(dimethylamino)ethene, and chlorotrimethylsilane (Scheme 16);^[78] or from bromotrifluoromethane (**5**), chlorotrimethylsilane, and aluminum (Scheme 16).^[81] The use of trimethyl(trifluoromethyl)silane (**25**) in the trifluoromethylation of a carbonyl compound in the presence of the fluoride ion is illustrated in Scheme 16.^[78]

Scheme 16 Synthesis of Trimethyl(trifluoromethyl)silane and Its Reaction with Benzaldehyde^[78–81]**Trimethyl(trifluoromethyl)silane (25):**^[78]

Into a 2-L three-necked flask fitted with an efficient dry ice–acetone cold finger and a mechanical stirrer was placed TMSCl (102 mL, 87.3 g, 0.83 mol) dissolved in PhCN (100 mL). Stirring was started, and the soln was cooled to ca. -30°C . CBrF_3 (5; 261 g, 1.75 mol) was precondensed into a flask and then allowed to evaporate into the reaction flask. The bath was cooled progressively to -60°C . To the resulting slurry was added a soln of $(\text{Et}_2\text{N})_3\text{P}$ (216 g, 0.876 mol) in PhCN (175 mL) over 2 h. After an additional 1 h at -60°C , the bath and cold finger were allowed to warm to rt, and the mixture was stirred overnight. To remove all volatiles, the mildly warmed (45°C) reaction flask was connected to a trap cooled by dry ice–acetone under an aspirator vacuum (20 Torr). The liquid in the trap was washed rapidly with ice-cold H_2O ($3 \times 75\text{ mL}$), the product (top) layer was separated and dried (MgSO_4), and the dry liquid was decanted into a 100-mL flask. Fractional distillation (15-cm column packed with glass helices) afforded TMSCF_3 (25) as a colorless liquid; yield: 77.1 g (65%); bp $55\text{--}55.5^\circ\text{C}$; $^1\text{H NMR}$ (CDCl_3 , δ): 0.25 (s); $^{19}\text{F NMR}$ (CDCl_3 , δ): -66.1 (s).

18.15.2

Product Subclass 2:**Compounds with Carbon–Halogen and Carbon–Oxygen Bonds**

This section deals with aliphatic and aromatic compounds with trifluoromethoxy, trichloromethoxy, and other trihalomethoxy groups. Some of these products are important reagents. Arenes with trifluoromethoxy groups are used as precursors for pharmaceuticals, pesticides, liquid crystals, and dyes.^[63]

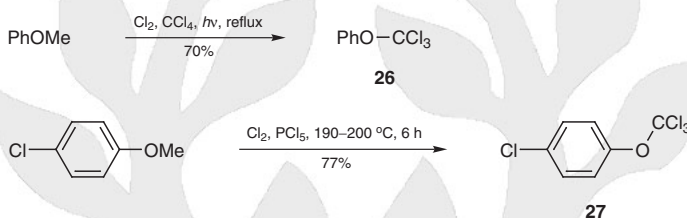
The trifluoromethoxy group is thermally and chemically resistant to attack by acids, bases, organometallic reagents, and oxidizing or reducing agents.^[82,83] Only the simplest compound, trifluoromethanol, prepared from trifluoromethyl hypochlorite and hydrogen chlorite at -120°C , is unstable at room temperature and decomposes into carbonyl difluoride and hydrogen fluoride.^[84]

18.15.2.1 Synthesis of Product Subclass 2

18.15.2.1.1 Method 1:
Trichloromethoxy Derivatives

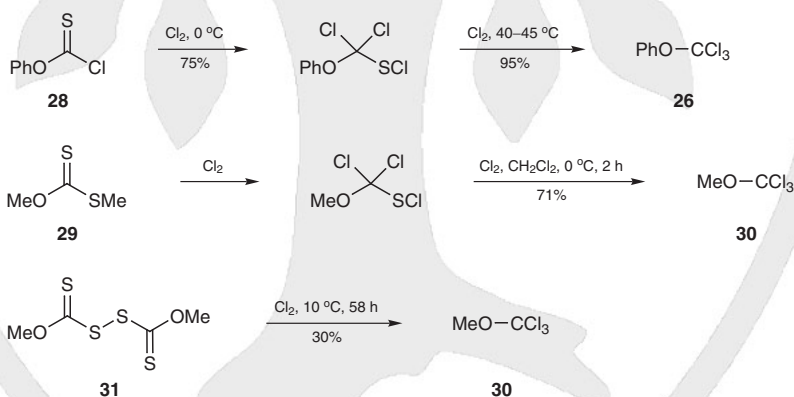
(Trichloromethoxy)benzene (**26**) is prepared in 70% yield by irradiation of a dilute solution of methoxybenzene and chlorine in carbon tetrachloride (Scheme 17).^[85] Chlorination of 1-chloro-4-methoxybenzene by phosphorus pentachloride at 190–200 °C gives 1-chloro-4-(trichloromethoxy)benzene (**27**) (Scheme 17).^[86,87]

Scheme 17 Synthesis of (Trichloromethoxy)benzenes from the Corresponding Methoxybenzenes and Chlorine^[85–87]

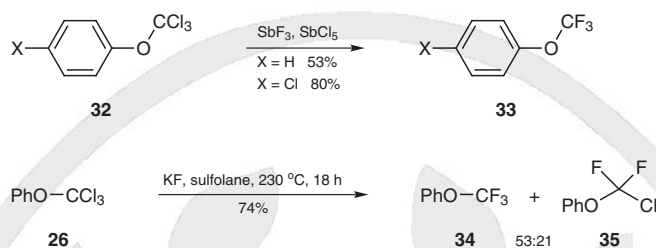


(Trichloromethoxy)benzene (**26**) can also be prepared from *O*-phenyl chlorothioformate (**28**) and chlorine (Scheme 18).^[88] (Dichlorofluoromethoxy)benzene is prepared similarly, in 80% yield, by chlorination of *O*-phenyl fluorothioformate at 40–45 °C.^[89] The reaction of *O,S*-dimethyl dithiocarbonate (**29**) with chlorine affords trichloro(methoxy)methane (**30**) (Scheme 18),^[90,91] which can also be prepared by chlorination of bis(methoxythiocarbonyl) disulfide (**31**) (Scheme 18).^[92]

Scheme 18 Synthesis of (Trichloromethoxy)benzene and Trichloro(methoxy)methane by Chlorination of Thiocarbonate Derivatives^[88,90–92]

18.15.2.1.2 Method 2:
(Trifluoromethoxy)benzenes from the Corresponding
(Trichloromethoxy)benzenes

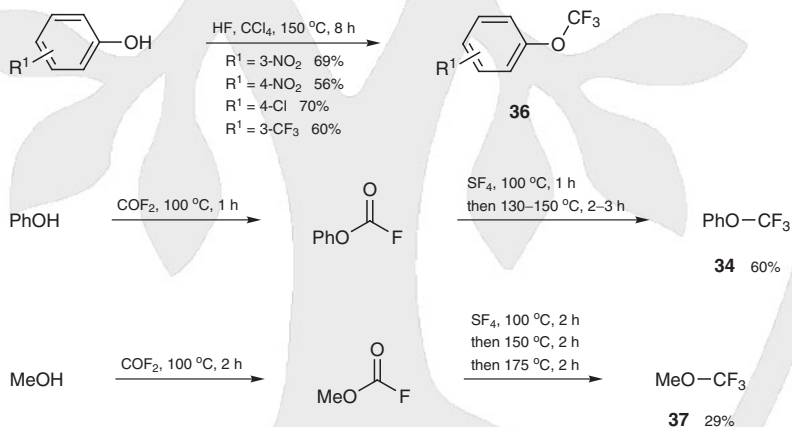
(Trifluoromethoxy)benzene (**33**, X = H)^[88] and 1-chloro-4-(trifluoromethoxy)benzene (**33**, X = Cl)^[87] are prepared in 53% and 80% yield, respectively, from the corresponding (trichloromethoxy)benzenes **32** (X = H, Cl) and antimony(III) fluoride in the presence of antimony(V) chloride (Scheme 19). When (trichloromethoxy)benzene (**26**) is heated with potassium fluoride in sulfolane, (trifluoromethoxy)benzene (**34**) (53%) and (chlorodifluoromethoxy)benzene (**35**) (21%) form (Scheme 19).^[93]

Scheme 19 Syntheses of (Trifluoromethoxy)benzenes from the Corresponding (Trichloromethoxy)benzenes^[87,88,93]

18.15.2.1.3

Method 3:**Trifluoromethoxy Derivatives from the Corresponding Alcohols**

(Trifluoromethoxy)arenes **36** containing ring-deactivating groups such as nitro, chloro, or trifluoromethyl are obtained when the corresponding phenols are heated in an autoclave with carbon tetrachloride and hydrogen fluoride (Scheme 20).^[94] (Trifluoromethoxy)benzene (**34**) is prepared from sulfur tetrafluoride and phenylfluoroformate, prepared from phenol and carbonyl difluoride (Scheme 20).^[82] Trifluoro(methoxy)methane (**37**) is obtained in 29% yield from methanol, carbonyl difluoride, and sulfur tetrafluoride (Scheme 20).^[83]

Scheme 20 Synthesis of (Trifluoromethoxy)benzenes from the Corresponding Phenols and Synthesis of (Trifluoromethoxy)methane from Methanol^[82,83,94]**(Trifluoromethoxy)benzene (34); Typical Procedure:**^[82]

CAUTION: Carbonyl fluoride is a colorless, pungent, and toxic gas. It is highly irritating to all tissues.

CAUTION: Sulfur tetrafluoride is a toxic gas and reacts vigorously with water. Hydrolysis produces hydrogen fluoride, which is highly toxic and irritating to all tissues.

CAUTION: Hydrogen fluoride fumes are severely irritating and extremely destructive to the respiratory system.

PhOH (94.1 g, 1 mol) was placed in a Hastelloy-lined pressure vessel, which was then cooled in dry ice and evacuated; subsequently COF_2 (82.5–85.8 g, 1.25–1.30 mol) was condensed into the vessel. The mixture was heated for 1 h at 100 °C, followed by 2–3 h at 130–

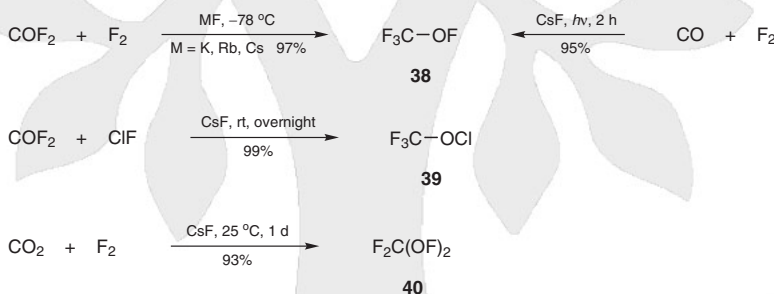
150 °C; it was then cooled to 0 °C and the excess COF₂ was vented. The vessel was again cooled in dry ice, SF₄ (129.7 g, 1.2 mol) was introduced, and the vessel was heated for 2 h at 100, 150, and 175 °C successively. The mixture was then treated with sufficient NaF to remove all of the HF, or, alternatively, washed with H₂O and aq NaHCO₃; fractionation on a 45-cm spinning-band column gave PhOCF₃ (**34**) (>99.9% purity); yield: 60%; mp –50 °C; bp 106 °C; ¹⁹F NMR (CCl₃F, δ): –58.3.^[1]

18.15.2.1.4

Method 4:**Trifluoromethyl Hypofluorite, Trifluoromethyl Hypochlorite, and Difluoromethylene Dihypofluorite**

Trifluoromethyl hypofluorite (**38**) is prepared in a continuous process by the reaction of fluorine with carbon monoxide over a cesium fluoride catalyst (Scheme 21).^[95] Alternatively, trifluoromethyl hypofluorite (**38**) can be prepared from carbonyl difluoride and fluorine in the presence of potassium, rubidium, or cesium fluoride (Scheme 21).^[96] A stainless-steel Hoke cylinder is generally employed in this preparation, although dried glass bulbs can also be used. Trifluoromethyl hypofluorite (**38**) is a gas (mp –215 °C, bp –95 °C) with an odor similar to that of fluorine or oxygen fluoride. The liquid has a pale straw color. The gas is stable up to 450 °C and is a strong oxidizing agent of high reactivity.^[97,98] At room temperature, trifluoromethyl hypofluorite (**38**) is inert to Pyrex glass and can be stored under pressure in pretreated steel cylinders. Trifluoromethyl hypofluorite (**38**) is an extremely reactive and toxic gas, and proper safety precautions are essential when it is used.

Scheme 21 Synthesis of Trifluoromethyl Hypofluorite, Trifluoromethyl Hypochlorite, and Difluoromethylene Dihypofluorite^[95,96,99,100]



Trifluoromethyl hypochlorite (**39**) is prepared by addition of chlorine fluoride across the carbonyl bond of carbonyl difluoride in the presence of cesium fluoride as catalyst (Scheme 21).^[99,100] Trifluoromethyl hypochlorite (**39**) (mp –142 °C, bp –45.8 °C) is colorless and stable at room temperature in clean and dry stainless steel or glass apparatus.

Difluoromethylene dihypofluorite (**40**) is obtained almost quantitatively from carbon dioxide and fluorine in the presence of cesium fluoride (Scheme 21).^[95,101–104]

Trifluoromethyl Hypochlorite (39):^[100]

CAUTION: Carbonyl difluoride is a colorless, pungent, and toxic gas. It is highly irritating to all tissues.

Dry CsF powder (4.8 g, 30.2 mmol) was loaded into a 30-mL pre-passivated cylinder in a drybox. After evacuation of the cylinder, COF₂ (263 mL, 11.7 mmol) and ClF (277 mL, 12.4 mmol) were separately condensed into the reactor at –196 °C. The cold bath was changed to –78 °C for 15 min, before the temperature was allowed to rise to rt. After standing overnight, the reactor was opened, and the products were separated by fractional con-

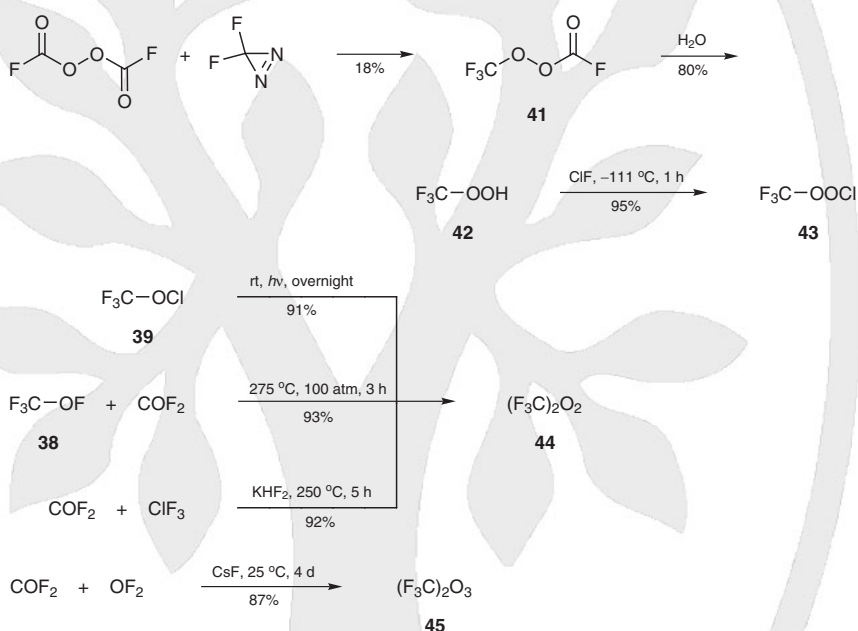
densation at -142°C and -196°C . The trap cooled at -142°C contained F_3COCl (**39**), a colorless liquid; yield: 262 mL (99%); bp -45.8°C ; mp -142°C ; ^{19}F NMR (δ): 64 (s).

18.15.2.1.5

Method 5: Trifluoromethyl Peroxides

Hydrolysis of fluorocarbonyl trifluoromethyl peroxide (**41**), obtained from bis(fluorocarbonyl) peroxide and 3,3-difluorodiazirine, gives trifluoromethyl hydroperoxide (**42**), a clear liquid, which is stable for several months at room temperature when stored in a glass ampule (Scheme 22).^[105,106] The reaction of chlorine monofluoride with trifluoromethyl hydroperoxide (**42**) produces (chloroperoxy)trifluoromethane (**43**), at room temperature a stable yellow gas, which can be stored without decomposition as a liquid in a glass container (Scheme 22).^[107]

Scheme 22 Synthesis of Trifluoromethyl Peroxides^[105–110]



Bis(trifluoromethyl) peroxide (**44**)^[105] is prepared by photolysis of trifluoromethyl hypochlorite (**39**)^[100] or by the reaction of trifluoromethyl hypofluorite (**38**) with carbonyl difluoride at approximately 100 atmospheres and 275°C (Scheme 22).^[108] The reaction of carbonyl difluoride with chlorine trifluoride in the presence of an alkali metal fluoride or alkali metal hydrogen fluoride also gives bis(trifluoromethyl) peroxide (**44**) (Scheme 22).^[109]

Oxygen difluoride reacts with carbonyl difluoride in the presence of cesium fluoride as catalyst to give bis(trifluoromethyl) trioxide (**45**) in good yield (Scheme 22).^[110,111]

18.15.2.2

Applications of Product Subclass 2 in Organic Synthesis

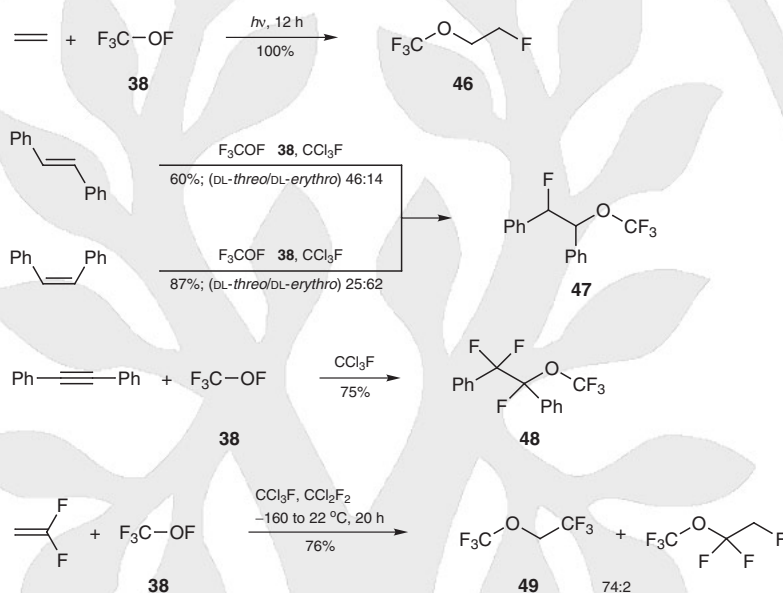
18.15.2.2.1

Method 1: Addition of Trifluoromethyl Hypofluorite or Hypochlorite or Chloroperoxytrifluoromethane to Alkenes and Alkynes

With nitrogen dilution, or at low temperature and under irradiation, trifluoromethyl hypofluorite (**38**) adds across the double bond of ethene to give 1-fluoro-2-(trifluorometh-

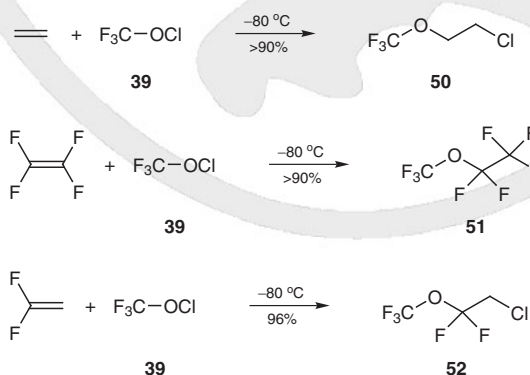
oxy)ethane (**46**) (Scheme 23).^[112,113] (*Z*)- and (*E*)-1,2-diphenylethene each react smoothly with trifluoromethyl hypofluorite (**38**) in trichlorofluoromethane to afford mainly the *syn*-addition products **47** (Scheme 23).^[114] 1,1,2-Trifluoro-1,2-diphenyl-2-(trifluoromethoxy)ethane (**48**) forms in 75% yield when diphenylacetylene in trichlorofluoromethane reacts with 2.5 equivalents of trifluoromethyl hypofluorite (**38**) in the presence of calcium oxide (Scheme 23).^[115] The reactions of trifluoromethyl hypofluorite (**38**) with a variety of simple alkenes are consistent with a free-radical addition mechanism.^[116] The main product of addition of trifluoromethyl hypofluorite (**38**) to 1,1-difluoroethene is 1,1,1-trifluoro-2-(trifluoromethoxy)ethane (**49**) (Scheme 23).^[113,116]

Scheme 23 Addition of Trifluoromethyl Hypofluorite to Alkenes or Alkynes^[112–116]



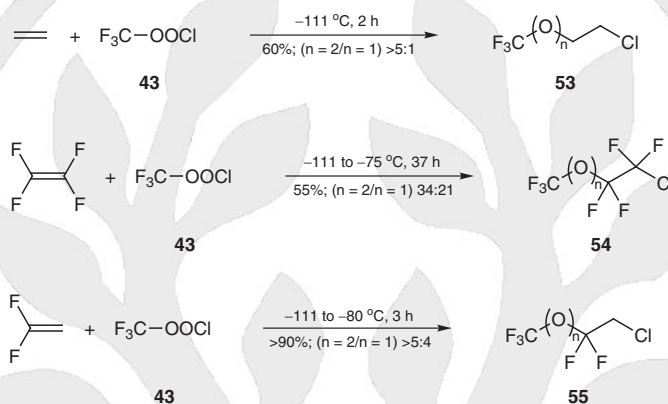
Trifluoromethyl hypochlorite (**39**) adds readily and nearly quantitatively to ethene, tetrafluoroethene, and 1,1-difluoroethene to give 1-chloro-2-(trifluoromethoxy)ethanes **50**, **51**, and **52**, respectively (Scheme 24).^[117] Addition of trifluoromethyl hypochlorite (**39**) to an unsymmetrical alkene gives as principal product an ether in which the chlorine atom of the hypochlorite has attached to the alkenic carbon bearing the greatest electron density.^[117]

Scheme 24 Addition of Trifluoromethyl Hypochlorite to Alkenes^[117]



(Chloroperoxy)trifluoromethane (**43**) adds to ethene, tetrafluoroethene, and 1,1-difluoroethene to yield trifluoromethyl 2-chloroethyl peroxides **53** ($n=2$), **54** ($n=2$), and **55** ($n=2$), respectively (Scheme 25).^[118] In addition to peroxides **53–55** ($n=2$), significant amounts of the corresponding ethers **53–55** ($n=1$) form. They probably form as a result of trifluoromethyl hypochlorite (**39**), a decomposition product of (chloroperoxy)trifluoromethane (**43**), adding to the alkenes.

Scheme 25 Addition of (Chloroperoxy)trifluoromethane to Alkenes^[118]

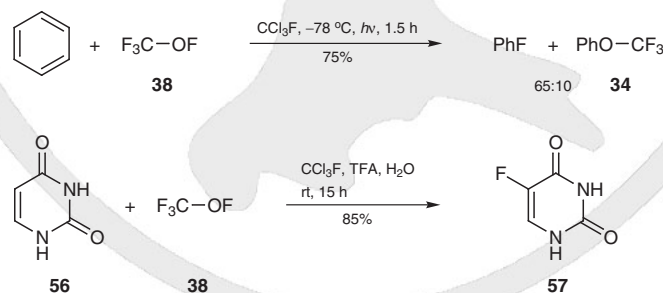


18.15.2.2.2

Method 2: Fluorination by Trifluoromethyl Hypofluorite and Hypochlorite

Trifluoromethyl hypofluorite (**38**) is a useful reagent for the direct electrophilic fluorination of arenes and heteroarenes. The photochemical reaction of trifluoromethyl hypofluorite (**38**) with benzene thus gives fluorobenzene as the main product together with (trifluoromethoxy)benzene (**34**) (Scheme 26).^[119] 5-Fluorouracil (**57**), a cytotoxic analogue of uracil (**56**), and of use in biochemical research and in medicine, can be prepared in 85% yield from uracil (**56**) and trifluoromethyl hypofluorite (**38**) (Scheme 26).^[120] The reaction between adamantane and trifluoromethyl hypofluorite (**38**) gives 1-fluoroadamantane in 75% yield.^[121]

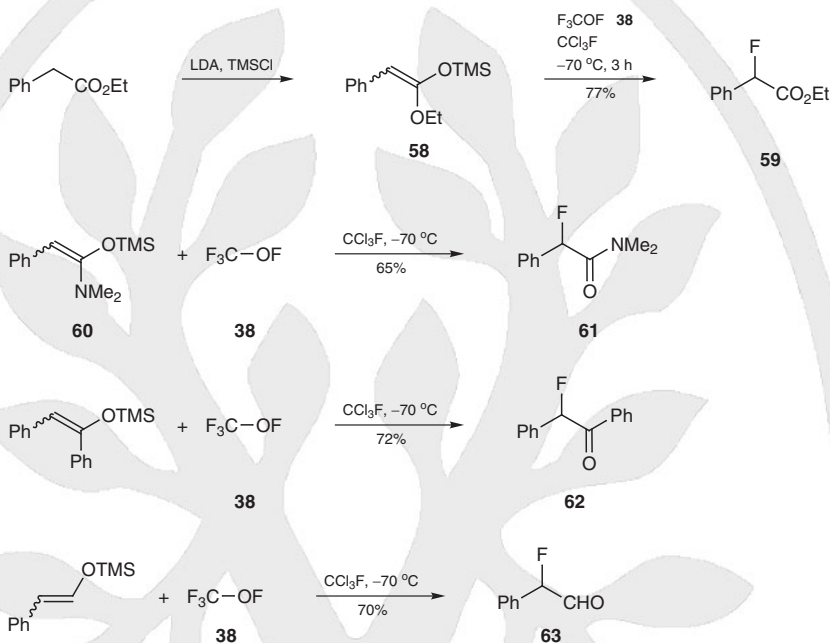
Scheme 26 Electrophilic Fluorination of Benzene and Uracil by Trifluoromethyl Hypofluorite^[119,120]



Trimethylsilyl enol ethers are useful reagents in fluorination reactions with trifluoromethyl hypofluorite (**38**) for the preparation of α -fluoro esters, amides, acids, ketones, and aldehydes.^[122] For example, ethyl phenylacetate is converted into its silyl enol ether **58** by treatment with lithium diisopropylamide and chlorotrimethylsilane (Scheme 27),^[123] and this silyl enol ether **58** reacts with trifluoromethyl hypofluorite (**38**) to give

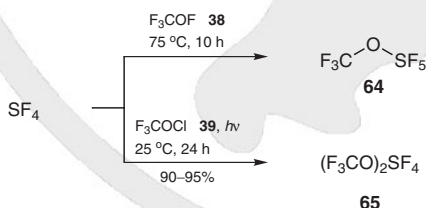
ethyl 2-fluoro-2-phenylacetate (**59**) in 77% yield (Scheme 27).^[122] The fluorination reactions of 1-(dimethylamino)-2-phenyl-1-(trimethylsiloxy)ethene (**60**), 1,2-diphenyl-1-(trimethylsiloxy)ethene, and 2-phenyl-1-(trimethylsiloxy)ethene by trifluoromethyl hypofluorite (**38**) proceed similarly, to give α -fluoro amide **61**, α -fluoro ketone **62**, and α -fluoro aldehyde **63**, respectively (Scheme 27).^[122]

Scheme 27 Fluorination of Silyl Enol Ethers by Trifluoromethyl Hypofluorite^[122,123]



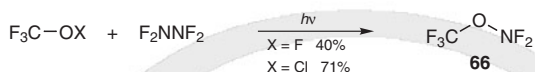
Trifluoromethyl hypofluorite (**38**) can be used for the oxidative fluorination of sulfides, disulfides, and many other compounds. For example, the reaction of trifluoromethyl hypofluorite (**38**) with sulfur tetrafluoride at 75 °C gives (trifluoromethoxy)sulfur pentafluoride (**64**) (Scheme 28).^[124] Trifluoromethyl hypochlorite (**39**) and sulfur tetrafluoride under ultraviolet irradiation give *cis*-bis(trifluoromethoxy)sulfur tetrafluoride (**65**) (Scheme 28).^[125]

Scheme 28 Oxidative Fluorination of Sulfur Tetrafluoride by Trifluoromethyl Hypofluorite or Hypochlorite^[124,125]



Difluoro(trifluoromethoxy)amine (**66**), a colorless, gaseous compound, which does not react with glass at room temperature, is prepared by the reaction of tetrafluorohydrazine with trifluoromethyl hypofluorite (**38**) (Scheme 29),^[126,127] trifluoromethyl hypochlorite (**39**) (Scheme 29),^[126] bis(trifluoromethyl) peroxide (**44**),^[128] or bis(trifluoromethyl) trioxide (**45**).^[129]

Scheme 29 Reaction of Tetrafluorohydrazine with Trifluoromethyl Hypofluorite or Hypochlorite^[126,127]



5-Fluorouracil (57):^[120]

CAUTION: Trifluoromethyl hypofluorite is highly toxic and a powerful oxidant. It explodes on contact with hydrogen-containing solvents and should be handled in all-glass apparatus.

Uracil (**56**; 0.336 g, 3 mmol) in a mixture of TFA (6 mL) and H₂O (20 mL) was added to a soln of F₃COF (**38**; 4.5 mmol) in CCl₃F (50 mL) at −78 °C in a pressure bottle. The precipitated uracil (**56**) redissolved in the aqueous layer when the mixture was warmed to rt. The mixture was vigorously stirred for 15 h. The excess F₃COF (**38**) was removed with N₂, and the solvents were removed under reduced pressure. The solid residue was sublimed (210–230 °C/0.5 Torr) to give crude 5-fluorouracil (**57**) (0.365 g; mp 260–270 °C). Recrystallization (MeOH/Et₂O) gave pure 5-fluorouracil (**57**); yield: 0.33 g (85%); mp 282–283 °C.

Ethyl 2-Fluoro-2-phenylacetate (59):^[122]

CAUTION: Trifluoromethyl hypofluorite is highly toxic and a powerful oxidant. It explodes on contact with hydrogen-containing solvents and should be handled in all-glass apparatus.

A soln of 1-ethoxy-2-phenyl-1-(trimethylsiloxy)ethene (**58**; 21.28 g, 90 mmol; prepared by treatment of ethyl phenylacetate with LDA and TMSCl^[123]) in CCl₃F (200 mL) was cooled to −70 °C. F₃COF (**38**; 9.4 g, 90 mmol) was passed into the soln for 3 h. The mixture was warmed to rt and distilled; yield: 12.52 g (77%); bp 96–98 °C/4.8 Torr; ¹⁹F NMR (CDCl₃, δ): −180.1 (d, J = 48 Hz).

18.15.3

Product Subclass 3:

Compounds with Carbon–Halogen and Carbon–Sulfur Bonds

Compounds with halogen and sulfur functional groups on the same carbon are very important reagents for syntheses in organic chemistry. The introduction of trifluoromethylsulfanyl groups into aliphatic and aromatic reagents is of interest to the agricultural and pharmaceutical industries. Trifluoromethanesulfonic acid and its derivatives have found extensive applications in synthetic chemistry.

18.15.3.1

Synthesis of Product Subclass 3

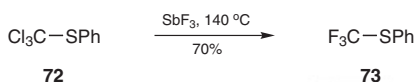
18.15.3.1.1

Method 1:

Trifluoromethanethiol from Bis(trifluoromethylsulfanyl)mercury(II) and Hydrogen Chloride or Bis(trifluoromethyl) Disulfide and Hydrogen Sulfide

Trifluoromethanethiol (**68**) can be prepared at room temperature in 99% yield from bis(trifluoromethylsulfanyl)mercury(II) (**67**) and hydrogen chloride,^[130,131] or, alternatively, in 90–99% yield by ultraviolet irradiation of bis(trifluoromethyl) disulfide (**69**) and hydrogen sulfide (Scheme 30).^[132] Bis(trifluoromethylsulfanyl)mercury(II) (**67**) is prepared at 250 °C in an autoclave from carbon disulfide and mercury(II) fluoride,^[133] or from bis(trifluoromethyl) disulfide (**69**) and mercury under ultraviolet irradiation (Scheme 30).^[130]

Scheme 30 Synthesis of Trifluoromethanethiol^[130–133]


Trifluoro(methylsulfanyl)methane (71):^[134]

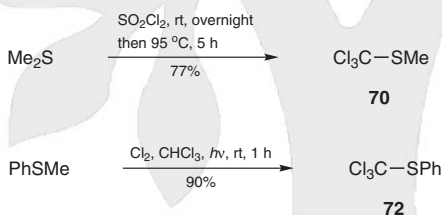
CAUTION: Antimony(V) chloride is a severe irritant of the lungs, eyes, and skin.

Finely pulverized SbF₃ (150 g, 0.84 mol) and SbCl₅ (2 g) were placed in a 500-mL, three-necked flask equipped with a sealed stirrer, a dropping funnel, and a condenser connected to a dry ice trap. MeSCCl₃ (**70**; 46 g, 0.28 mol) was added over 15 min. The flask was warmed in a water bath at 95 °C until refluxing stopped (ca. 1 h). The liquid (28 g) that had collected in the dry ice trap was purified by distillation over a low-temperature column; yield: 24.3 g (73%); bp 11.5–11.7 °C/750 Torr.

18.15.3.1.3
**Method 3:
Trichloromethyl Sulfides by Chlorination of
the Corresponding Methyl Sulfides**

The simplest and most often used method for the preparation of trichloromethyl sulfides is the chlorination of the corresponding methyl sulfides with chlorine, or occasionally with sulfuryl chloride, thionyl chloride, or phosphorus pentachloride. For example, trichloro(methylsulfanyl)methane (**70**) is prepared in 77% yield by chlorination of dimethyl sulfide by sulfuryl chloride (Scheme 32).^[134] Chlorination of (methylsulfanyl)benzene under irradiation gives (trichloromethylsulfanyl)benzene (**72**) in 90% yield (Scheme 32).^[135]

Scheme 32 Synthesis of Trichloromethyl Sulfides by Chlorination of the Corresponding Methyl Sulfides^[134,135]


Trichloro(methylsulfanyl)methane (70); Typical Procedure:^[134]

CAUTION: Sulfuryl chloride can react explosively with alkalis and is an irritant.

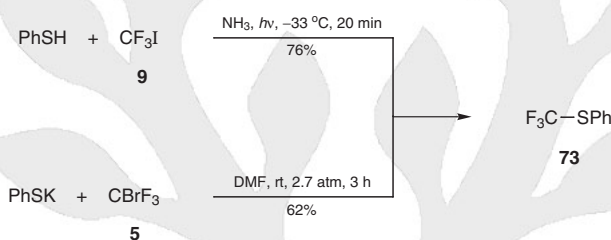
Me₂S (100 g, 1.61 mol) was placed in a 1-L, three-necked flask equipped with a sealed stirrer, a dropping funnel, and a dry ice condenser. The flask was cooled in an ice bath, and SO₂Cl₂ (762 g, 5.65 mol) was added over 2 h. The ice bath was removed soon after the addition of SO₂Cl₂ had begun. When the addition of SO₂Cl₂ was completed, the dry ice condenser was replaced with a tap-water condenser, so that SO₂ could escape. After standing overnight at rt, the mixture was slowly warmed to 95 °C and maintained at that temperature for 5 h. The crude product was purified by fractional distillation; yield: 204 g (77%); bp 146.0 °C/750 Torr; 67.7 °C/50 Torr.

18.15.3.1.4

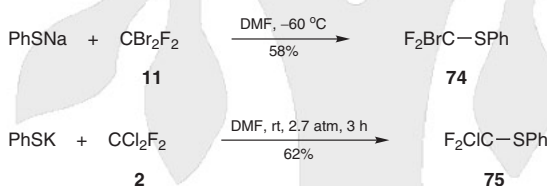
Method 4:**Phenyl Trihalomethyl Sulfides by Trihalomethylation of Benzenethiols or Benzenethiolates**

Trifluoromethylation of benzenethiols by trifluoroiodomethane (**9**) can be performed in liquid ammonia under ultraviolet irradiation.^[136] Under these conditions, benzenethiol and trifluoroiodomethane (**9**) give (trifluoromethylsulfanyl)benzene (**73**) in 76% yield (Scheme 33).^[136] This photochemical reaction also occurs with thiolates in acetonitrile or under phase-transfer conditions.^[136,137] Even the poorly reactive bromotrifluoromethane (**5**) reacts with benzenethiolate in dimethylformamide under slight pressure^[138] or ultraviolet irradiation^[139] (Scheme 33). Benzenethiolate also reacts with dibromodifluoromethane (**11**) and dichlorodifluoromethane (**2**) to give (bromodifluoromethylsulfanyl)benzene (**74**), and (chlorodifluoromethylsulfanyl)benzene (**75**), respectively (Scheme 34).^[138,140]

Scheme 33 Synthesis of (Trifluoromethylsulfanyl)benzene by Trifluoromethylation of Benzenethiol or Benzenethiolate^[136,139]



Scheme 34 Synthesis of (Trihalomethylsulfanyl)benzenes by Trihalomethylation of Benzenethiol or Benzenethiolate^[138,140]

**(Trifluoromethylsulfanyl)benzene (73); Typical Procedure:**^[136]

Benzenethiol (2.20 g, 0.02 mol) was placed into a Pyrex flask equipped with a dry ice condenser. The flask was cooled by dry ice, and NH₃ (20 mL) followed by CF₃I (**9**; 5.88 g, 0.03 mol) were condensed into it. The mixture was exposed to a Hg lamp (PRK-4) at a distance of 25–30 cm from the flask. The reaction was carried out under argon or N₂ free from O₂ at the reflux temperature of NH₃ for 30 min. After elimination of NH₃, a 5% NaOH soln (25 mL) was added, and the mixture was extracted with Et₂O. The Et₂O soln was washed with H₂O and dried (MgSO₄). The solvent was removed by distillation, and the product was purified by distillation; yield: 2.79 g (76%); bp 141.5 °C;^[135] ¹⁹F NMR (CCl₃F, δ): –63.2.^[1]

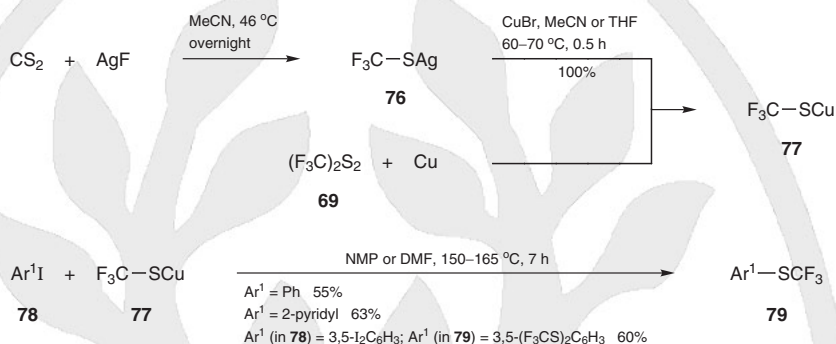
18.15.3.1.5

Method 5:**Aryl or Methyl Trifluoromethyl Sulfides by Cross-Coupling Reactions between Iodoarenes or Iodomethane and (Trifluoromethylsulfanyl)metal Reagents**

Aryl and hetaryl trifluoromethyl sulfides **79** [Ar¹ = Ph, 2-pyridyl, 3,5-(F₃CS)₂C₆H₃] can be prepared from aryl and hetaryl iodides **78** (Ar¹ = Ph, 2-pyridyl, 3,5-I₂C₆H₃) and (trifluoro-

methylsulfanyl)copper(I) (**77**) (Scheme 35).^[141] (Trifluoromethylsulfanyl)copper(I) (**77**) is obtainable from (trifluoromethylsulfanyl)silver(I) (**76**), prepared from carbon disulfide and silver(I) fluoride,^[133,142,143] and copper(I) bromide^[141] or from bis(trifluoromethyl) disulfide (**69**) and copper metal (Scheme 35).^[144]

Scheme 35 Synthesis of (Trifluoromethylsulfanyl)copper(I) and (Trifluoromethylsulfanyl)silver(I) Reagents and Cross-Coupling Reaction of (Trifluoromethylsulfanyl)copper(I) with Iodoarenes To Give the Corresponding (Trifluoromethylsulfanyl)arenes^[133,141–144]



Trifluoro(methylsulfanyl)methane (**71**) is prepared quantitatively by the reaction of bis(trifluoromethylsulfanyl)mercury(II) (**67**) and iodomethane (Scheme 36).^[145]

Scheme 36 Synthesis of Trifluoro(methylsulfanyl)methane from Bis(trifluoromethylsulfanyl)mercury(II) and Iodomethane^[145]



(Trifluoromethylsulfanyl)copper(I) (**77**):^[141]

CuBr (1.43 g, 10 mmol) was added to a soln of F_3CSAg (**76**; 2.09 g, 10 mmol) in anhyd MeCN (10 mL). The mixture was stirred under a stream of N_2 at $60\text{--}70^\circ\text{C}$ for 0.5 h. AgBr was removed by filtration and the MeCN was removed under reduced pressure; yield: 1.64 g (100%).

(Trifluoromethylsulfanyl)arenes and (Trifluoromethylsulfanyl)hetarenes **79** [$\text{Ar}^1 = \text{Ph}$, 2-Pyridyl, 3,5-(F_3CS) $_2\text{C}_6\text{H}_3$]; **General Procedure**:^[141]

Under anhyd N_2 , iodoarene **78** (0.005 mol) was stirred with F_3CSCu (**77**; 0.01 mol) in NMP or DMF (10 mL) at $150\text{--}165^\circ\text{C}$ for 7 h. The mixture was then cooled and diluted with H_2O , and the product was extracted with Et_2O . The Et_2O soln was washed with H_2O and then dried. In case of di- and triiodoarenes, the reaction was run in a similar way, the quantity of F_3CSCu (**77**) being increased proportionally to give the correct stoichiometry.

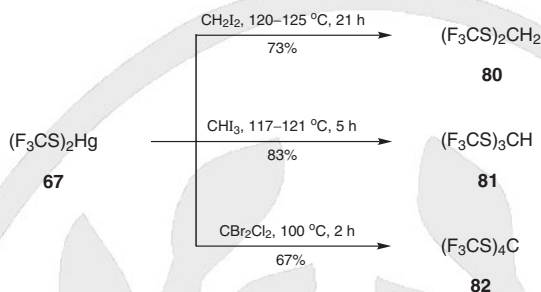
18.15.3.1.6

Method 6:

Bis-, Tris-, and Tetrakis(trifluoromethylsulfanyl)methanes and Halotris(trifluoromethylsulfanyl)methanes

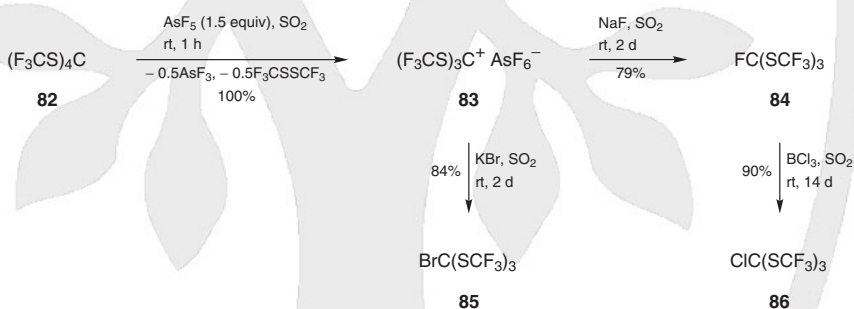
Bis-, tris-, and tetrakis(trifluoromethylsulfanyl)methane (**80–82**) are prepared from bis(trifluoromethylsulfanyl)mercury(II) (**67**) and diiodomethane, triiodomethane, and dibromodichloromethane, respectively (Scheme 37).^[131,146,147]

Scheme 37 Synthesis of Bis-, Tris-, and Tetrakis(trifluoromethylsulfanyl)methane by Substitution of the Halo Groups of Di-, Tri-, and Tetrahalomethanes by Bis(trifluoromethylsulfanyl)mercury(II)^[131]



Tris(trifluoromethylsulfanyl)methylum hexafluoroarsenate (**83**) is prepared in quantitative yield from tetrakis(trifluoromethylsulfanyl)methane (**82**) and arsenic(V) fluoride (Scheme 38).^[147] Reaction of tris(trifluoromethylsulfanyl)methylum hexafluoroarsenate (**83**) with sodium fluoride gives fluorotris(trifluoromethylsulfanyl)methane (**84**) (79% yield), whose reaction with boron trichloride gives chlorotris(trifluoromethylsulfanyl)methane (**86**) (90% yield) (Scheme 38).^[147] Bromotris(trifluoromethylsulfanyl)methane (**85**) is obtained in 84% yield from tris(trifluoromethylsulfanyl)methylum hexafluoroarsenate (**83**) and potassium bromide (Scheme 38).^[147]

Scheme 38 Synthesis of Halotris(trifluoromethylsulfanyl)methanes from Tris(trifluoromethylsulfanyl)methylum Hexafluoroarsenate^[147]



18.15.3.1.7

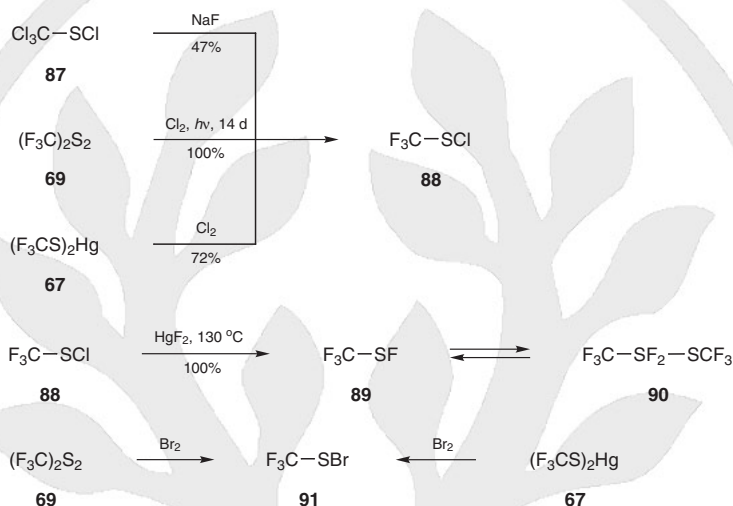
Method 7:**Trifluoro- and Trichloromethanesulfenyl Halides**

Trifluoromethanesulfenyl chloride (**88**) can be prepared from trichloromethanesulfenyl chloride (**87**) and sodium fluoride (47% yield),^[148] bis(trifluoromethyl) disulfide (**69**) and chlorine under ultraviolet irradiation (quantitative yield),^[130] or bis(trifluoromethylsulfanyl)mercury(II) (**67**) and chlorine (72% yield)^[130] (Scheme 39).

Trifluoromethanesulfenyl fluoride (**89**) is prepared in quantitative yield from trifluoromethanesulfenyl chloride (**88**) and mercury(II) fluoride (Scheme 39).^[149] That the gaseous compound is trifluoromethanesulfenyl fluoride (**89**) has been confirmed by ^{19}F NMR and IR spectroscopy,^[149] but in the liquid state, sulfenyl fluoride **89** is in equilibrium with (trifluoromethyl)(trifluoromethylsulfanyl)sulfur difluoride (**90**) (Scheme 39).^[149,150]

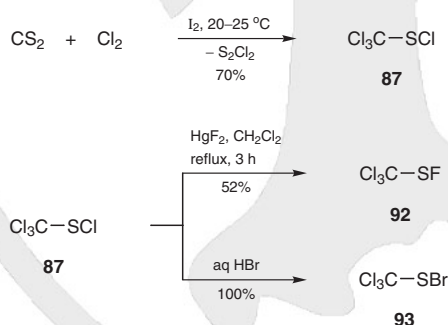
Trifluoromethanesulfonyl bromide (**91**) is prepared from bromine and bis(trifluoromethyl) disulfide (**69**)^[151] or bis(trifluoromethylsulfanyl)mercury(II) (**67**) (Scheme 39).^[89] Trifluoromethanesulfonyl bromide (**91**) is an orange-red liquid, stable up to 25 °C in a sealed glass tube, but decomposes in sunlight to bis(trifluoromethyl) disulfide (**69**) and bromine.

Scheme 39 Synthesis of Trifluoromethanesulfonyl Halides^[89,130,148–151]



Trichloromethanesulfonyl chloride (**87**) is prepared from carbon disulfide and chlorine in the presence of a catalytic quantity of iodine (Scheme 40).^[152,153] Trichloromethanesulfonyl fluoride (**92**) is prepared from trichloromethanesulfonyl chloride (**87**) and mercury(II) fluoride (Scheme 40).^[154] Trichloromethanesulfonyl bromide (**93**) is prepared from trichloromethanesulfonyl chloride (**87**) and an aqueous solution of hydrogen bromide (Scheme 40).^[155]

Scheme 40 Synthesis of Trichloromethanesulfonyl Halides^[152–155]



Trichloromethanesulfonyl Chloride (**87**):^[153]

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

CS_2 was chlorinated in the presence of 0.1% I_2 at 20–25 °C until enough Cl_2 had been absorbed to give a Cl_2/CS_2 molar ratio of ca. 2.5:1. The mixture was distilled through a short column to remove most of the sulfur chlorides until a head temperature of 140 °C was reached. The remaining oil could then be washed safely with cold and then hot H_2O until

no more S was deposited. Distillation of the remaining mixture gave Cl_3CSCl (**87**) in approximately $\geq 90\%$ purity, satisfactory for most preparative work; yield: 70%; bp 149°C , $38^\circ\text{C}/13\text{ Torr}$; $83^\circ\text{C}/100\text{ Torr}$.

Trichloromethanesulfonyl Fluoride (**92**):^[154]

CAUTION: Mercury(II) salts are toxic.

HgF_2 (100 g, 0.42 mol) was added portionwise, with stirring, to Cl_3CSCl (**87**; 90 g, 0.48 mol) in CH_2Cl_2 (200 mL) at rt. The addition required ca. 10 min and was slightly exothermic. The mixture was refluxed for 3 h and, after cooling, filtered by suction. Fractional distillation of the filtrate through a Widmor column gave, after removal of CH_2Cl_2 , a first fraction (bp $96\text{--}101^\circ\text{C}$) consisting of Cl_3CSF (**92**); yield: 42.2 g (52%). Redistillation gave analytically pure product; bp $97\text{--}99^\circ\text{C}$.

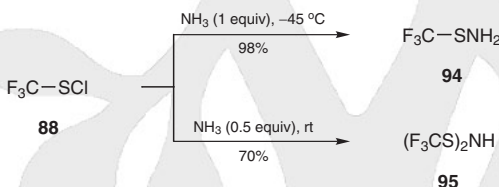
18.15.3.1.8

Method 8:

Mono- and Bis(trifluoromethylsulfonyl)amines from Trifluoromethanesulfonyl Chloride and Ammonia

(Trifluoromethylsulfonyl)amine (**94**) and bis(trifluoromethylsulfonyl)amine (**95**) are prepared in 98 and 70% yield, respectively, from trifluoromethanesulfonyl chloride (**88**) and 1 and 0.5 equivalents of ammonia, respectively (Scheme 41).^[156]

Scheme 41 Synthesis of Mono- and Bis(trifluoromethylsulfonyl)amines from Trifluoromethanesulfonyl Chloride and Ammonia^[156]



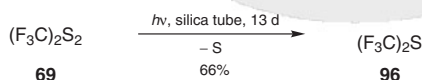
18.15.3.1.9

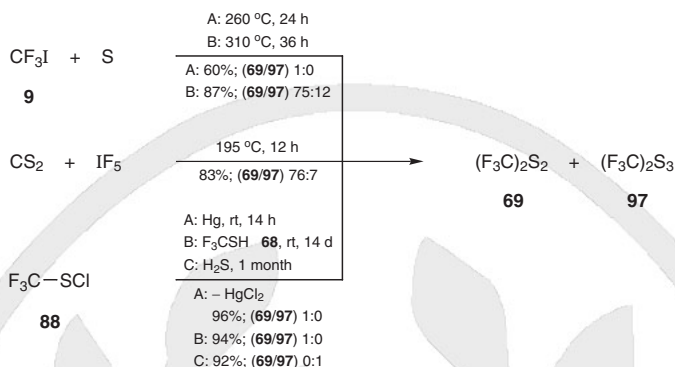
Method 9:

Bis(trifluoromethyl) Sulfide, Disulfide, and Trisulfide

Bis(trifluoromethyl) sulfide (**96**), a colorless liquid, stable to aqueous alkali up to 150°C , is prepared in 66% yield by the photolysis of bis(trifluoromethyl) disulfide (**69**) in a silica vessel (Scheme 42).^[1,157,158] Bis(trifluoromethyl) disulfide (**69**),^[149] a colorless, dense liquid with a sharp odor, stable in air and glass, is prepared in 60–75% yield from trifluoroiodomethane (**9**) and sulfur.^[130,157] The reaction of trifluoromethanesulfonyl chloride (**88**) and mercury or trifluoromethanethiol (**68**) also gives bis(trifluoromethyl) disulfide, but bis(trifluoromethyl) trisulfide (**97**) is obtained when trifluoromethanesulfonyl chloride (**88**) reacts with hydrogen sulfide (Scheme 42).^[130] Extreme care should be exercised when bis(trifluoromethyl) disulfide and bis(trifluoromethyl) trisulfide are handled, as they are both highly toxic by inhalation.

Scheme 42 Synthesis of Bis(trifluoromethyl) Sulfide, Disulfide, and Trisulfide^[130,157]





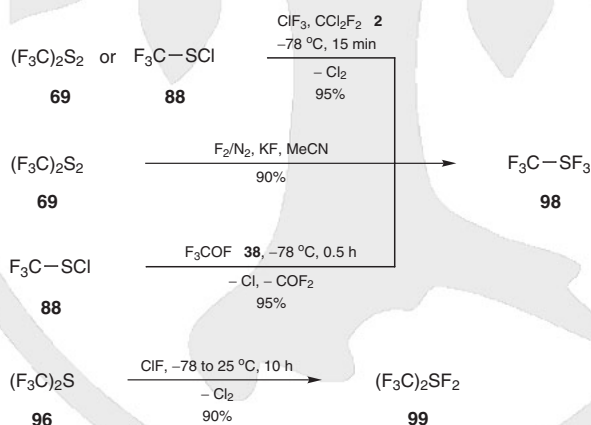
18.15.3.1.10

Method 10:

(Trifluoromethyl)sulfur Trifluoride, Bis(trifluoromethyl)sulfur Difluoride, and Difluorobis(trifluoro- λ^4 -sulfanyl)methane

(Trifluoromethyl)sulfur trifluoride (**98**) is prepared in 95% yield from bis(trifluoromethyl) disulfide (**69**) or trifluoromethanesulfonyl chloride (**88**) and chlorine trifluoride (Scheme 43).^[158] Alternatively, (trifluoromethyl)sulfur trifluoride (**98**) can be prepared in 90% yield from bis(trifluoromethyl) disulfide (**69**) and fluorine diluted with nitrogen in acetonitrile in the presence of potassium fluoride (Scheme 43).^[159] The reaction of trifluoromethanesulfonyl chloride (**88**) and trifluoromethyl hypofluorite (**38**) also gives (trifluoromethyl)sulfur trifluoride (**98**), in 95% yield (Scheme 43).^[159] (Trifluoromethyl)sulfur trifluoride (**98**) is stable in glass at -183°C for an indefinite period or for a few days at -78°C , but it decomposes in glass at room temperature. Bis(trifluoromethyl)sulfur difluoride (**99**) is prepared in 90% yield from bis(trifluoromethyl) sulfide (**96**) and chlorine monofluoride (Scheme 43).^[160]

Scheme 43 Synthesis of (Trifluoromethyl)sulfur Trifluoride and Bis(trifluoromethyl)sulfur Difluoride^[158–160]



Difluorobis(trifluoro- λ^4 -sulfanyl)methane (**100**) is prepared from carbon disulfide and fluorine (Scheme 44).^[161–164]

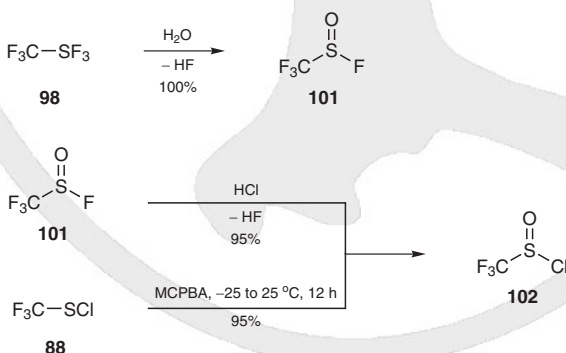
Scheme 44 Synthesis of Difluorobis(trifluoro- λ^4 -sulfanyl)methane from Carbon Disulfide and Fluorine^[161–164]**(Trifluoromethyl)sulfur Trifluoride (98):**^[158]**CAUTION:** Mercury vapor is readily absorbed by inhalation and is neurotoxic.

(F_3C) $_2\text{S}_2$ (**69**; 2.0 g, 10 mmol) or F_3CSCl (**88**; 2.7 g, 20 mmol) and CCl_2F_2 (**2**; 10 mL) were co-condensed at -196°C into a long-necked, 25-mL round-bottomed flask containing a magnetic stirring bar and equipped with a greased glass stopcock. The mixture was allowed to warm to -78°C and stirred for a few min to ensure complete mixing. Next, the soln was recooled to -196°C and ClF_3 (2 mmol) was condensed into the reactor. The mixture was then allowed to warm slowly to -78°C and stirred for 15 min at this temperature. ClF_3 (2.04 g, 22 mmol) was added in successive 2-mmol aliquots as described above. The mixture was separated by vacuum fractionation, the crude product of F_3CSF_3 (**98**) contaminated with ClF_3 and traces of Cl_2 and CCl_2F_2 (**2**) condensing in U-traps held at -98 and -105°C . [Pure F_3CSF_3 (**98**) passes a -98°C trap and condenses at -105°C .] Traces of Cl_2 and ClF_3 were removed by treatment of the crude product with Hg. Successive refractionation gave pure F_3CSF_3 (**98**); yield: 95%; ^{19}F NMR (CCl_3F , δ): -72.8 (d, CF_3), -49.6 (t, 1F, SF), 47.4 (dq, 2F, SF_2).^[159]

18.15.3.1.11

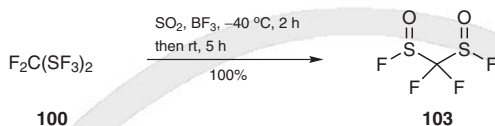
Method 11:
Trifluoromethanesulfinyl Fluoride and Chloride and
Difluoromethanedisulfinyl Fluoride

Trifluoromethanesulfinyl fluoride (**101**) is prepared quantitatively by the mild hydrolysis of (trifluoromethyl)sulfur trifluoride (**98**) (Scheme 45),^[159] and can be used to prepare trifluoromethanesulfinyl chloride (**102**) by reaction with gaseous hydrogen chloride (Scheme 45).^[159] Trifluoromethanesulfinyl chloride (**102**) is also prepared in high yield by oxidation of trifluoromethanesulfinyl fluoride (**101**) with 3-chloroperoxybenzoic acid (Scheme 45).^[165]

Scheme 45 Synthesis of Trifluoromethanesulfinyl Fluoride and Trifluoromethanesulfinyl Chloride^[159,165]

Difluoromethanedisulfinyl fluoride (**103**), consisting of a mixture of two diastereomers (*meso*/*rac* 1:1),^[163] is prepared in quantitative yield from difluorobis(trifluoro- λ^4 -sulfanyl)-methane (**100**), sulfur dioxide, and boron trifluoride (Scheme 46).^[162]

Scheme 46 Synthesis of Difluoromethanedisulfinyl Fluoride from Difluorobis(trifluoro- λ^4 -sulfanyl)methane and Sulfur Dioxide^[162]

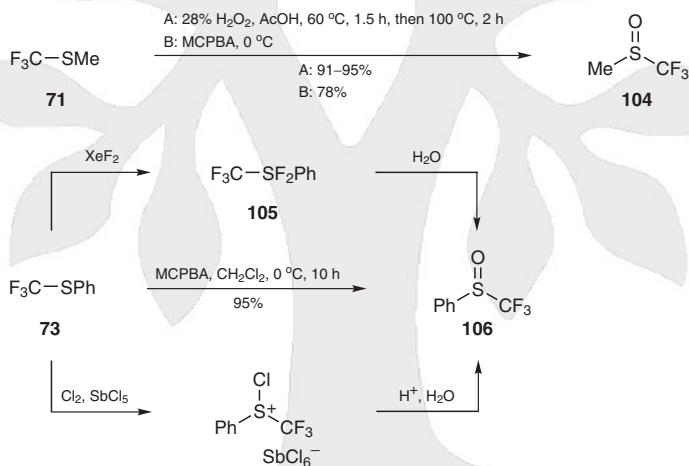


18.15.3.1.12

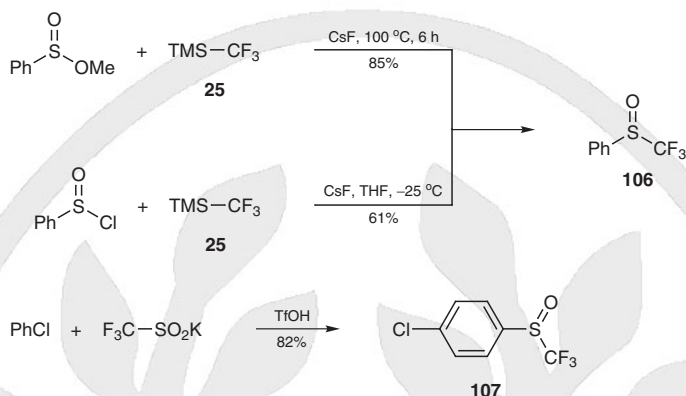
Method 12:
Trifluoromethyl Sulfoxides

Trifluoro(methylsulfinyl)methane (**104**) is prepared by oxidation of trifluoro(methylsulfinyl)methane (**71**) by hydrogen peroxide in acetic acid^[166,167] or by 3-chloroperoxybenzoic acid (Scheme 47).^[145] (Trifluoromethylsulfinyl)benzene (**106**)^[168] is prepared by hydrolysis of [difluoro(trifluoromethyl)- λ^4 -sulfanyl]benzene (**105**), prepared from (trifluoromethylsulfinyl)benzene (**73**) and xenon difluoride (Scheme 47).^[169] (Trifluoromethylsulfinyl)benzene (**106**) is also prepared by the oxidation of (trifluoromethylsulfinyl)benzene (**73**) by 3-chloroperoxybenzoic acid,^[170] or by the hydrolysis of the sulfonium antimonate salt formed from (trifluoromethylsulfinyl)benzene (**73**) and chlorine in the presence of antimony(V) chloride (Scheme 47).^[171]

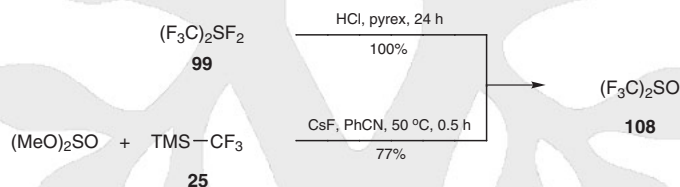
Scheme 47 Synthesis of Trifluoromethyl Sulfoxides by Oxidation of Trifluoromethyl Sulfides^[145,166,167,169–171]



(Trifluoromethylsulfinyl)benzene (**106**) can also be prepared by trifluoromethylation of methyl benzenesulfinate^[172] or benzenesulfinyl chloride^[173] by trimethyl(trifluoromethyl)silane (**25**) and cesium fluoride (Scheme 48). For the trifluoromethylation of benzenesulfinyl chloride, [tris(dimethylamino)sulfonium] difluorotrimethylsilicate can also be used as the fluoride source.^[173] Substituted benzenes, for example, chlorobenzene, are sulfinylated with trifluoromethanesulfinate salts in strongly acidic media to form (trifluoromethylsulfinyl)benzenes, e.g. **107** (Scheme 48).^[174]

Scheme 48 Synthesis of Trifluoromethyl Sulfoxides from Chloride, Ester, or Metalated Derivatives of Sulfinic Acids^[172–174]

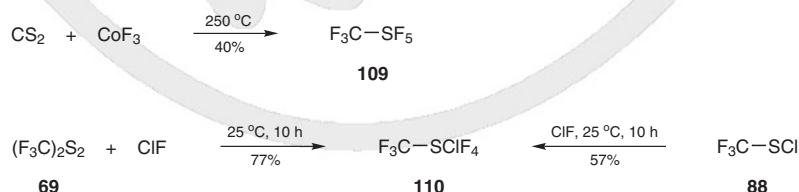
Bis(trifluoromethyl) sulfoxide (**108**) is prepared from the reaction of bis(trifluoromethyl)-sulfur difluoride (**99**) with hydrogen chloride in a Pyrex vessel (Scheme 49),^[160] or from dimethyl sulfite, trimethyl(trifluoromethyl)silane (**25**), and cesium fluoride (Scheme 49).^[172]

Scheme 49 Synthesis of Bis(trifluoromethyl) Sulfoxide from Bis(trifluoromethyl)sulfur Difluoride or Dimethyl Sulfite and Trimethyl(trifluoromethyl)silane^[160,172]

18.15.3.1.13

Method 13:
(Trifluoromethyl)sulfur Pentafluoride and
(Trifluoromethyl)sulfur Chloride Tetrafluoride

(Trifluoromethyl)sulfur pentafluoride (**109**) is prepared in 40% yield from carbon disulfide and cobalt(III) fluoride (Scheme 50).^[175,176] (Trifluoromethyl)sulfur chloride tetrafluoride (**110**) is prepared from the reaction of chlorine monofluoride with bis(trifluoromethyl) disulfide (**69**) (77% yield) or trifluoromethanesulfonyl chloride (**88**) (57% yield) (Scheme 50).^[176]

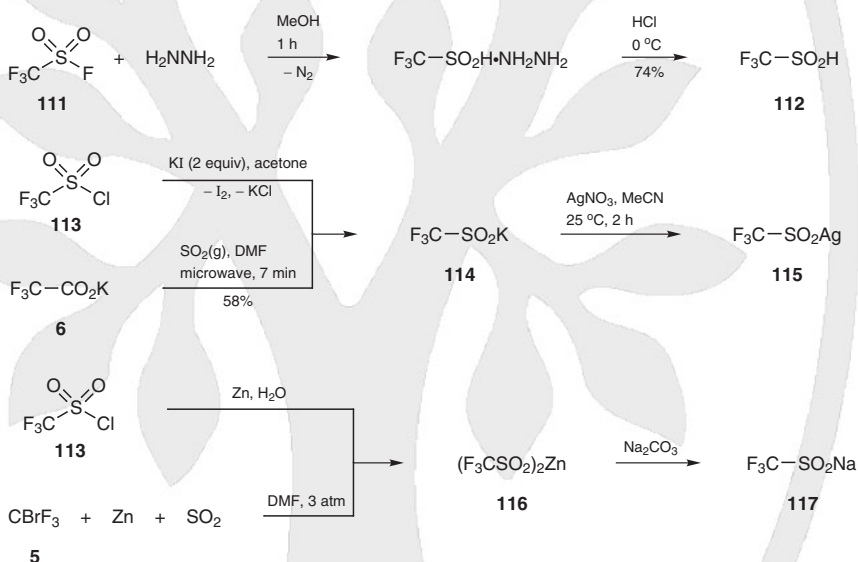
Scheme 50 Synthesis of (Trifluoromethyl)sulfur Pentafluoride and (Trifluoromethyl)sulfur Chloride Tetrafluoride^[175,176]

18.15.3.1.14

Method 14:**Trifluoromethanesulfinic Acid, Metal Trifluoromethanesulfonates, and Difluoromethanedisulfinic Acid**

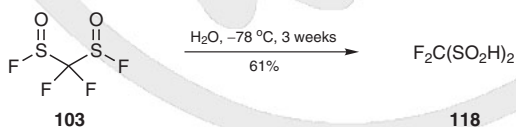
Trifluoromethanesulfinic acid (**112**) can be prepared in 74% yield from trifluoromethanesulfonyl fluoride (**111**), hydrazine, and hydrogen chloride (Scheme 51).^[177] Potassium trifluoromethanesulfinate (**114**) is prepared from the reaction between trifluoromethanesulfonyl chloride (**113**) and 2 equivalents of potassium iodide (Scheme 51),^[178] or by microwave irradiation of potassium trifluoroacetate (**6**) and sulfur dioxide in dimethylformamide (Scheme 51).^[179] Silver(I) trifluoromethanesulfinate (**115**) is prepared from potassium trifluoromethanesulfinate (**114**) and silver(I) nitrate (Scheme 51).^[180] Sodium trifluoromethanesulfinate (**117**) is prepared from sodium carbonate and zinc(II) trifluoromethanesulfinate (**116**), which is prepared from trifluoromethanesulfonyl chloride (**113**) and zinc (Scheme 51).^[181] Zinc(II) trifluoromethanesulfinate (**116**) can also be prepared from bromotrifluoromethane (**5**), zinc, and sulfur dioxide (Scheme 51).^[182]

Scheme 51 Synthesis of Trifluoromethanesulfinic Acid and Potassium, Silver(I), Zinc(II), and Sodium Trifluoromethanesulfinate^[177–182]



Difluoromethanedisulfinic acid (**118**) is prepared by the hydrolysis of difluoromethanedisulfinyl fluoride (**103**) by moist air (Scheme 52).^[164]

Scheme 52 Synthesis of Difluoromethanedisulfinic Acid from Difluoromethanedisulfinyl Fluoride^[164]

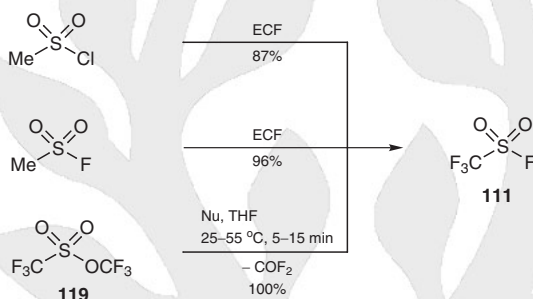


18.15.3.1.15

Method 15:**Trifluoromethanesulfonyl Fluoride from Alkanesulfonic Acid Halides or Esters**

Trifluoromethanesulfonyl fluoride (**111**) can be prepared from methanesulfonyl chloride or fluoride by electrochemical fluorination (ECF) in 87 and 96% yield, respectively (Scheme 53),^[1,183,184] or in quantitative yield by the reaction of trifluoromethyl trifluoromethanesulfonate (**119**) with a neutral or anionic nucleophile (e.g., pyridine, triethylamine, cesium fluoride) with elimination of carbonyl difluoride (Scheme 53).^[185]

Scheme 53 Synthesis of Trifluoromethanesulfonyl Fluoride from Methanesulfonyl Chloride or Fluoride by Electrochemical Fluorination or from Trifluoromethyl Trifluoromethanesulfonate by Nucleophilic Substitution^[183–185]

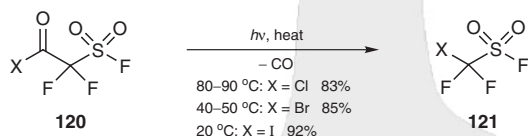


18.15.3.1.16

Method 16:**Difluorohalomethanesulfonyl Fluorides by Photolytic Decarbonylation of the Corresponding Difluoro(halocarbonyl)methanesulfonyl Fluorides**

Difluorohalomethanesulfonyl fluorides **121** (X = Cl, Br, I) can be prepared from the corresponding difluoro(halocarbonyl)methanesulfonyl fluorides **120** (X = Cl, Br, I) by photolysis (Scheme 54).^[186–188]

Scheme 54 Synthesis of Difluorohalomethanesulfonyl Fluorides by Photolytic Decarbonylation of the Corresponding Difluoro(halocarbonyl)methanesulfonyl Fluorides^[186,187]

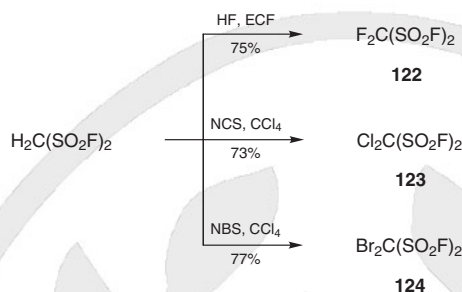


18.15.3.1.17

Method 17:**Dihalomethanedisulfonyl Difluorides by Halogenation of Methanedisulfonyl Difluoride**

Methanedisulfonyl difluoride can be fluorinated, chlorinated, or brominated to give dihalomethanedisulfonyl difluorides **122–124**. Difluoromethanedisulfonyl difluoride (**122**) is prepared by electrochemical fluorination of methanedisulfonyl difluoride in anhydrous hydrogen fluoride (Scheme 55).^[189] Dichloromethanedisulfonyl difluoride (**123**) is prepared by chlorination of methanedisulfonyl difluoride by *N*-chlorosuccinimide in carbon tetrachloride (Scheme 55).^[189] Dibromomethanedisulfonyl difluoride (**124**) is prepared from methanedisulfonyl difluoride and *N*-bromosuccinimide in carbon tetrachloride (Scheme 55).^[189]

Scheme 55 Synthesis of Dihalomethanedisulfonyl Difluorides by Halogenation of Methanedisulfonyl Difluoride^[189]

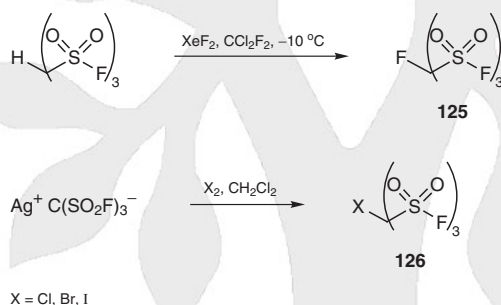


18.15.3.1.18

Method 18:**Halomethanetrisulfonyl Trifluorides from Methanetrisulfonyl Trifluoride**

Fluoromethanetrisulfonyl trifluoride (**125**) is prepared from methanetrisulfonyl trifluoride and xenon difluoride (Scheme 56).^[190] Chloro-, bromo-, and iodomethanetrisulfonyl trifluorides **126** (X = Cl, Br, I) are prepared from silver(I) tris(fluorosulfonyl)methanide and the corresponding elemental halogen (Scheme 56).^[190]

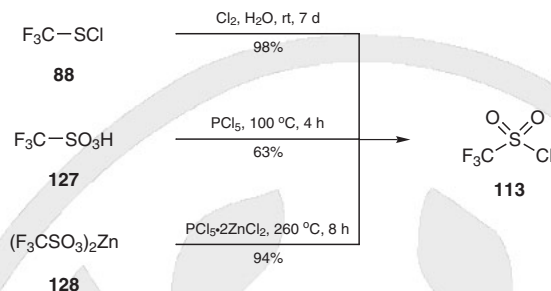
Scheme 56 Synthesis of Halomethanetrisulfonyl Trifluorides by Halogenation of Methanetrisulfonyl Trifluoride^[190]



18.15.3.1.19

Method 19:**Trifluoromethanesulfonyl Chloride**

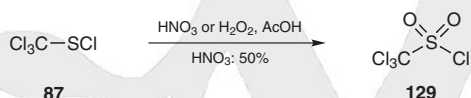
Trifluoromethanesulfonyl chloride (**113**) is prepared in 98% yield from trifluoromethanesulfonyl chloride (**88**), chlorine, and water (Scheme 57).^[1,181] or in 63% yield when trifluoromethanesulfonic acid (**127**) and phosphorus pentachloride are heated together (Scheme 57).^[181] Alternatively, zinc(II) precursors can be used. Thus, heating of dried zinc(II) trifluoromethanesulfonate (**128**) with the phosphorus pentachloride–bis[zinc(II) dichloride] complex also gives trifluoromethanesulfonyl chloride (**113**) (Scheme 57).^[191,192]

Scheme 57 Synthesis of Trifluoromethanesulfonyl Chloride^[191–193]

18.15.3.1.20

Method 20:
Trichloromethanesulfonyl Chloride by Oxidation of
Trichloromethanesulfenyl Chloride

Oxidation of trichloromethanesulfenyl chloride (**87**) by nitric acid^[194] or hydrogen peroxide^[153] in acetic acid gives trichloromethanesulfonyl chloride (**129**) (Scheme 58). The product is obtained in good yield and quality when hydrogen peroxide is used, and this method is very suitable for laboratory purposes.^[153]

Scheme 58 Synthesis of Trichloromethanesulfonyl Chloride by Oxidation of Trichloromethanesulfenyl Chloride^[153,194]

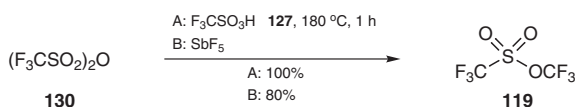
Trichloromethanesulfonyl Chloride (129):^[194]

Cl_3CSCl (**87**; 10 g, 53.8 mmol) dissolved in glacial AcOH (30 mL) was refluxed gently, and concd HNO_3 (15 mL) was added dropwise over 10–15 min. After all the HNO_3 had been added, the soln was refluxed for a further 20 min, after which it was diluted with several volumes of H_2O . The separated product was collected by filtration, washed well with H_2O , and dried. To recrystallize the crude product, it was dissolved in warm EtOH and then diluted with H_2O ; yield: 5.86 g (50%); mp 140–140.5 °C.

18.15.3.1.21

Method 21:
Trifluoromethyl Trifluoromethanesulfonate from
Trifluoromethanesulfonic Anhydride

Trifluoromethyl trifluoromethanesulfonate (**119**) can be prepared by the reaction of trifluoromethanesulfonic anhydride (**130**) with trifluoromethanesulfonic acid (**127**) at 180 °C (100% yield) (Scheme 59)^[195] or with antimony(V) fluoride at 25 °C (80% yield) (Scheme 59).^[185] This reaction gives pure trifluoromethyl trifluoromethanesulfonate (**119**) conveniently and economically in large quantities.^[185]

Scheme 59 Synthesis of Trifluoromethyl Trifluoromethanesulfonate from Trifluoromethanesulfonic Anhydride^[185,195]

Trifluoromethyl Trifluoromethanesulfonate (119):^[185]

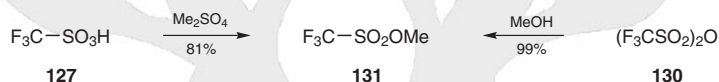
Tf₂O (**130**; 121 g, 0.43 mol) was slowly added to SbF₅ (0.60 g, 2.8 mmol) with stirring. The temperature of the bath was kept near 25 °C. The volatile products produced in the rapid and exothermic reaction were carried away by a slow stream of N₂ through a water-cooled condenser and then bubbled through a rapidly stirred 3 M aq KOH soln in a –15 °C bath. After addition of the Tf₂O (**130**), the reaction flask was heated to 60 °C for 15 min. The product, TfOCF₃ (**119**) (bottom layer), was then separated from the KOH soln in the receiver, dried (P₂O₅), and distilled; yield: 75 g (80%), bp 21.1 °C; ¹⁹F NMR (CCl₃F, δ): –53.3 (q, ⁵J_{FF} = 3.5 Hz, CF₃O), –74.0 (q, CF₃S).

18.15.3.1.22

Method 22:**Methyl Trifluoromethanesulfonate from Trifluoromethanesulfonic Acid and Dimethyl Sulfate**

Methyl trifluoromethanesulfonate (**131**) is most conveniently prepared by the reaction of trifluoromethanesulfonic acid (**127**) with dimethyl sulfate (Scheme 60).^[196,197] It can also be prepared from trifluoromethanesulfonic anhydride (**130**) and methanol (Scheme 60).^[198]

Scheme 60 Synthesis of Methyl Trifluoromethanesulfonate from Trifluoromethanesulfonic Acid and Dimethyl Sulfate or from Trifluoromethanesulfonic Anhydride and Methanol^[196–198]

**Methyl Trifluoromethanesulfonate (131):**^[196]

CAUTION: Methyl trifluoromethanesulfonate is a powerful methylating agent and is corrosive and irritating to the skin, eyes, and respiratory system.

CAUTION: Dimethyl sulfate is corrosive and irritating to the skin, eyes, and respiratory system and is a probable human carcinogen.

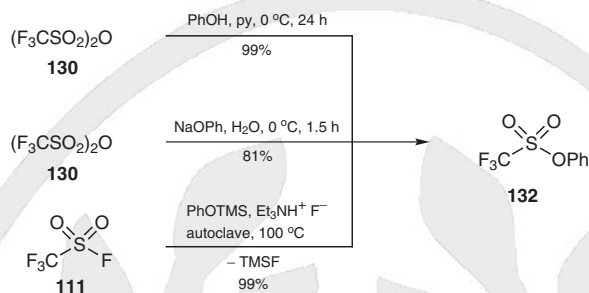
TfOH (**127**; 50 g, 0.3 mol) was added with stirring to Me₂SO₄ (45.5 g, 0.36 mol) at rt. Distillation gave methyl trifluoromethanesulfonate (**131**); yield: 42.2 g (81%); bp 98–99 °C; ¹⁹F NMR (CCl₃F, δ): –74.8 (s).

18.15.3.1.23

Method 23:**Phenyl Trifluoromethanesulfonate from Trifluoromethanesulfonic Anhydride or Trifluoromethanesulfonyl Fluoride**

Phenyl trifluoromethanesulfonate (**132**) can be prepared in 99% yield from phenol and trifluoromethanesulfonic anhydride (**130**) in pyridine (Scheme 61).^[199] Alternatively, phenyl trifluoromethanesulfonate (**132**) has been prepared in 81% yield from sodium phenolate and trifluoromethanesulfonic anhydride (**130**) in water (Scheme 61).^[200] The reaction of trifluoromethanesulfonyl fluoride (**111**) and trimethyl(phenoxy)silane in the presence of a catalyst, for example a tertiary amine or fluoride ion, also gives phenyl trifluoromethanesulfonate (**132**), in 99% yield (Scheme 61).^[201]

Scheme 61 Synthesis of Phenyl Trifluoromethanesulfonate from Phenol or Phenolate and Trifluoromethanesulfonic Anhydride or from Trifluoromethanesulfonyl Fluoride and Trimethyl(phenoxy)silane^[199–201]

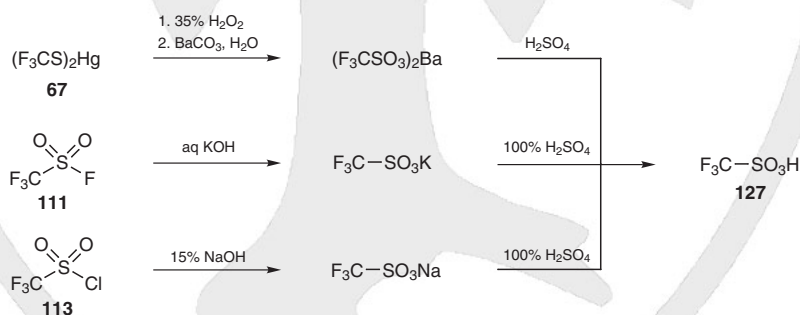


18.15.3.1.24

Method 24:
Trifluoromethanesulfonic Acid

Trifluoromethanesulfonic acid (**127**) is one of the strongest of all known acids. Its first synthesis, reported in 1954, was from bis(trifluoromethylsulfanyl)mercury(II) (**67**) and hydrogen peroxide (Scheme 62).^[202] Trifluoromethanesulfonic acid (**127**) is usually purified by distillation from anhydrous potassium, sodium, or barium salts and 100% sulfuric acid. The salts must be thoroughly dried by heating under reduced pressure prior to addition of sulfuric acid, since trifluoromethanesulfonic acid (**127**) forms a stable monohydrate complex,^[198] which can also be distilled. Pure trifluoromethanesulfonic acid (**127**) is a clear, colorless liquid. It fumes in moist air until it is converted into the monohydrate. Trifluoromethanesulfonic acid (**127**) is also obtained when anhydrous potassium trifluoromethanesulfonate, formed by hydrolysis of trifluoromethanesulfonyl fluoride (**111**) by potassium hydroxide, is treated with sulfuric acid (Scheme 62).^[203] An alternative synthesis is from trifluoromethanesulfonyl chloride (**113**) via sodium trifluoromethanesulfonate (Scheme 62).^[193]

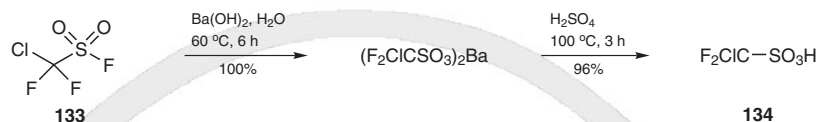
Scheme 62 Synthesis of Trifluoromethanesulfonic Acid^[193,202,203]



18.15.3.1.25

Method 25:
Chlorodifluoromethanesulfonic Acid and Trichloromethanesulfonic Acid

Chlorodifluoromethanesulfonic acid (**134**) is obtained from barium chlorodifluoromethanesulfonate, prepared from chlorodifluoromethanesulfonyl fluoride (**133**) (Scheme 63).^[187]

Scheme 63 Synthesis of Chlorodifluoromethanesulfonic Acid from Chlorodifluoromethanesulfonyl Fluoride^[187]

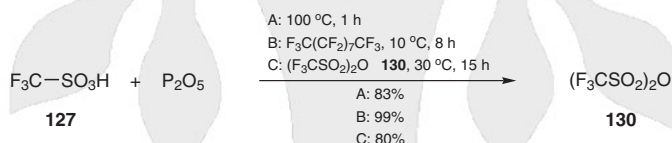
Trichloromethanesulfonic acid (**135**), a strong acid with an acidity between that of perchloric acid and 4-toluenesulfonic acid, is prepared by alkaline hydrolysis of trichloromethanesulfonyl chloride (**129**) (Scheme 64).^[204] It is obtained as a monohydrate.

Scheme 64 Trichloromethanesulfonic Acid from Trichloromethanesulfonyl Chloride by Substitution of the Chloro Group with Sodium Hydroxide^[204]

18.15.3.1.26

Method 26:**Trifluoromethanesulfonic Anhydride from Trifluoromethanesulfonic Acid and Phosphorus Pentoxide**

Trifluoromethanesulfonic anhydride (**130**) can be prepared from trifluoromethanesulfonic acid (**127**) and phosphorus pentoxide (Scheme 65).^[196,198,205–207]

Scheme 65 Synthesis of Trifluoromethanesulfonic Anhydride from Trifluoromethanesulfonic Acid and Phosphorus Pentoxide^[196,198,205–207]**Trifluoromethanesulfonic Anhydride (130):**^[205]

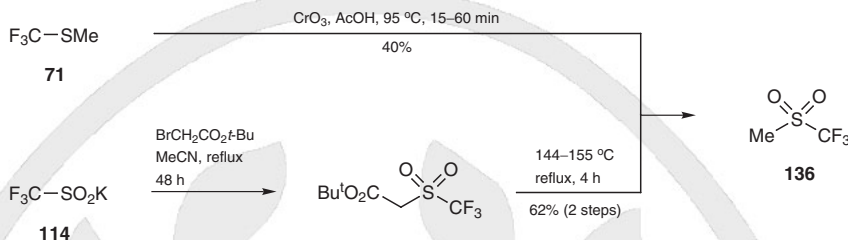
P_2O_5 (25 g, 0.18 mol) was added in three portions to TfOH (**127**; 32.1 g, 0.21 mol) cooled to 0°C . Anhydride **130** was distilled by gradual heating of the mixture for 1 h until it reached 110°C (bath temperature). The fraction boiling at $80\text{--}100^\circ\text{C}$ was redistilled repeatedly from P_2O_5 (ca. 8 g, 0.06 mol), to remove traces of acid, until it no longer fumed when a glass rod was dipped into the distillate and exposed to air; yield: 25 g (83%); bp 84°C .

18.15.3.1.27

Method 27:**Trifluoromethyl Sulfones**

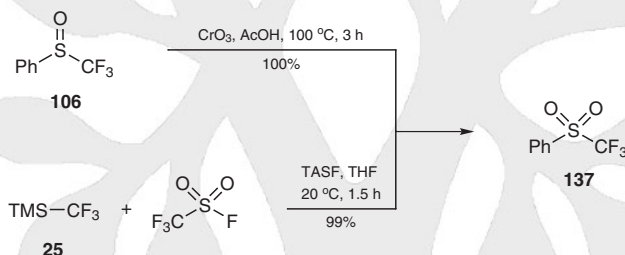
Trifluoro(methylsulfonyl)methane (**136**) may be obtained in 40% yield by oxidation of trifluoro(methylsulfonyl)methane (**71**) by chromium(VI) oxide in acetic acid (Scheme 66),^[134] or in 62% yield from potassium trifluoromethanesulfinate (**114**) and *tert*-butyl bromoacetate (Scheme 66).^[180]

Scheme 66 Synthesis of Trifluoro(methylsulfonyl)methane from trifluoro(methylsulfonyl)methane and Chromium(VI) Oxide or from Potassium Trifluoromethanesulfinate and *tert*-Butyl Bromoacetate^[134,180]



(Trifluoromethylsulfonyl)benzene (**137**) may be prepared in quantitative yield from (trifluoromethylsulfinyl)benzene (**106**) and chromium(VI) oxide in acetic acid (Scheme 67).^[168] The reaction of benzenesulfonyl fluoride and trimethyl(trifluoromethyl)silane (**25**) in tetrahydrofuran or petroleum ether in the presence of tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF) also gives (trifluoromethylsulfonyl)benzene (**137**), in 99% yield (Scheme 67).^[208]

Scheme 67 Synthesis of (Trifluoromethylsulfonyl)benzene from (Trifluoromethylsulfinyl)benzene and Chromium(VI) Oxide or from Benzenesulfonyl Fluoride and Trimethyl(trifluoromethyl)silane^[168,208]



Trifluoro(methylsulfonyl)methane (**136**):^[180]

$\text{F}_3\text{CS}(\text{O})\text{OK}$ (**114**; 24.08 g, 0.131 mol) and *tert*-butyl bromoacetate (25.5 g, 0.131 mol) were dissolved in MeCN (250 mL). The soln was refluxed for 48 h under N_2 . After cooling, it was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and filtered. Removal of the solvent under reduced pressure afforded a brown oil (26.8 g), which was refluxed for 4 h in a bath kept at 145–155 °C. Subsequent distillation afforded trifluoro(methylsulfonyl)methane (**136**); yield: 12.0 g (62%); bp 128.9 °C/737 Torr; mp 14 °C.

(Trifluoromethylsulfonyl)benzene (**137**):^[208]

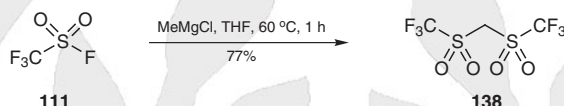
A soln of F_3CTMS (**25**; 2.84 g, 20 mmol) in THF (10 mL) was added portionwise to a stirred suspension of PhSO_2F (1.60 g, 10 mmol) and TASF (0.28 g, 1 mmol) in THF or petroleum ether (bp 60–80 °C; 10 mL) at 25 °C over 10–15 min under argon. The mixture was stirred for 0.5 h, then treated with H_2O (30 mL), and extracted with petroleum ether (30 mL). The organic phase was washed with H_2O (4 × 50 mL), dried (MgSO_4), and concentrated. The product was distilled; yield: 99%; bp 118–119 °C/20 Torr; ^{19}F NMR (acetone- d_6 / CCl_3D / CCl_3F , δ): –78.13.

18.15.3.1.28

Method 28:**Bis- and Tris(trifluoromethylsulfonyl)methanes**

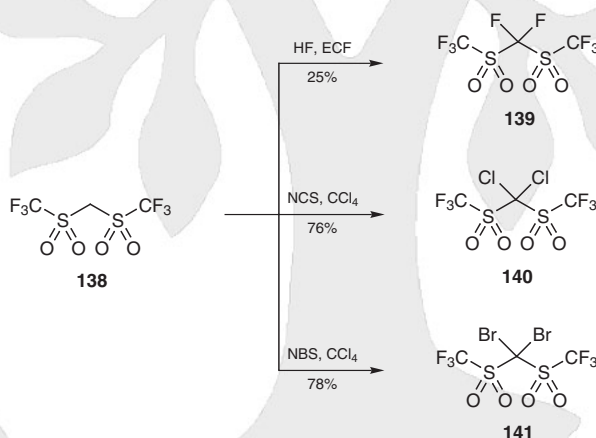
Bis(trifluoromethylsulfonyl)methane (**138**), the strongest known carbon acid of the methylene series ($pK_a -1$),^[209] is prepared from trifluoromethanesulfonyl fluoride (**111**) and methylmagnesium chloride (Scheme 68).^[209,210]

Scheme 68 Synthesis of Bis(trifluoromethylsulfonyl)methane from Trifluoromethanesulfonyl Fluoride and Methylmagnesium Chloride^[209,210]

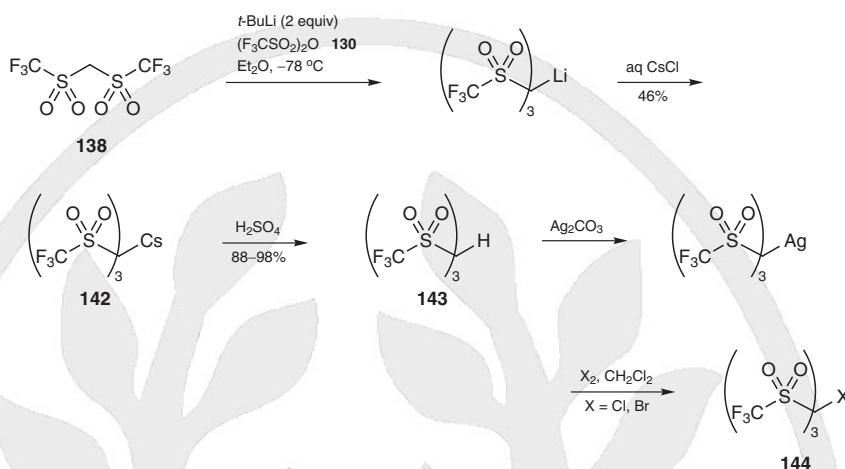


By procedures similar to those used for the preparation of dihalomethanedisulfonyl difluorides from methanedisulfonyl difluoride (Section 18.15.3.1.17), difluoro-, dichloro-, and dibromobis(trifluoromethylsulfonyl)methane (**139–141**) are accessible by halogenation of the methylene group of bis(trifluoromethylsulfonyl)methane (**138**).^[210] Thus, electrochemical fluorination (ECF) of bis(trifluoromethylsulfonyl)methane (**138**) in anhydrous hydrogen fluoride gives difluorobis(trifluoromethylsulfonyl)methane (**139**), chlorination by *N*-chlorosuccinimide in carbon tetrachloride gives dichlorobis(trifluoromethylsulfonyl)methane (**140**), and bromination by *N*-bromosuccinimide in carbon tetrachloride gives dibromobis(trifluoromethylsulfonyl)methane (**141**) (Scheme 69).^[210]

Scheme 69 Synthesis of Dihalobis(trifluoromethylsulfonyl)methanes by Dihalogenation of Bis(trifluoromethylsulfonyl)methane^[210]



From bis(trifluoromethylsulfonyl)methane (**138**), tris(trifluoromethylsulfonyl)methane (**143**) and its metalated and halogenated derivatives can be prepared. Thus, the reaction of bis(trifluoromethylsulfonyl)methane (**138**) with *tert*-butyllithium and trifluoromethanesulfonic anhydride (**130**) gives [tris(trifluoromethylsulfonyl)methyl]lithium, which reacts with aqueous cesium chloride to give cesium tris(trifluoromethylsulfonyl)methanide (**142**).^[211] Cesium salt **142** reacts with sulfuric acid to give tris(trifluoromethylsulfonyl)methane (**143**) in 88–98% yield (Scheme 70).^[211,212] From tris(trifluoromethylsulfonyl)methane (**143**) and silver(I) carbonate, [tris(trifluoromethylsulfonyl)methyl]silver(I) forms, which is halogenated by chlorine or bromine to give chloro- and bromotris(trifluoromethylsulfonyl)methane (**144**, X = Cl, Br) (Scheme 70).^[212]

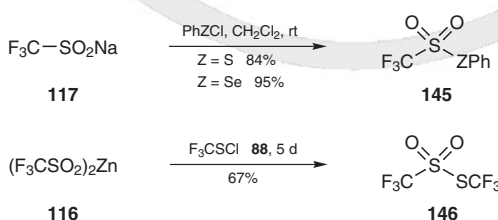
Scheme 70 Synthesis of Bromotris(trifluoromethylsulfonyl)methane and Chlorotris(trifluoromethylsulfonyl)methanes^[211,212]**Bis(trifluoromethylsulfonyl)methane (138):**^[210]

Trifluoromethanesulfonyl fluoride (**111**; 225 g, 1.48 mol) was bubbled into ice-cooled 2.5 M MeMgCl in THF (1200 mL) over 4–5 h. The temperature was not allowed to exceed 20°C. After addition of **111** was completed, further stirring of the suspension for approximately 1 h at 60°C was necessary to complete the reaction. The suspension was cooled to rt and 3 M HCl (50–60 mL) was added carefully, especially the first 3 mL. After evaporation of the solvent, the remaining solid was dissolved in 3 M HCl (1500 mL) and stirred for 4 h. The two-phase liquid was extracted with Et₂O (4 × 400 mL). After the Et₂O phases had been combined and the solvent had been removed, the remaining red oily liquid was distilled under reduced pressure. A colorless, waxy solid was obtained; yield: 160.0 g (77%); mp 36°C; bp 74–75°C/5 Torr; ¹H NMR (CDCl₃, δ): 4.98 (br s); ¹³C NMR (CCl₃D, δ): 118.7 (q), 64.0; ¹⁹F NMR (CDCl₃, δ): –75.1.^[211]

18.15.3.1.29

Method 29:**Esters of Trifluoromethanethiosulfonic S-Acid or Trifluoromethaneselenosulfonic Se-Acid from Metal Trifluoromethanesulfinates and Sulfenyl or Selenenyl Chlorides**

S-Phenyl trifluoromethanesulfonylthioate (**145**, Z = S) and Se-phenyl trifluoromethanesulfonylselenoate (**145**, Z = Se) are prepared in 84 and 95% yield, respectively, from sodium trifluoromethanesulfinate (**117**) and benzenesulfonyl chloride and benzeneselenenyl chloride, respectively (Scheme 71).^[213] S-Trifluoromethyl trifluoromethanesulfonylthioate (**146**) is prepared in 67% yield from zinc(II) trifluoromethanesulfinate (**116**) and trifluoromethanesulfonyl chloride (**88**) (Scheme 71).^[193]

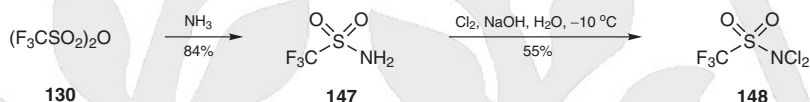
Scheme 71 Synthesis of Esters of Trifluoromethanethiosulfonic S-Acid or Trifluoromethaneselenosulfonic Se-Acid from Metal Trifluoromethanesulfinates and Sulfenyl or Selenenyl Chlorides^[193,213]

18.15.3.1.30

Method 30:**Difluorohalomethanesulfonamides and Difluorohalomethanesulfonyl Azides**

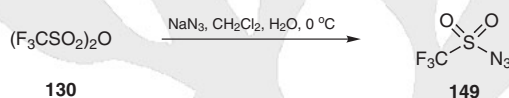
Trifluoromethanesulfonamide (**147**) is prepared from trifluoromethanesulfonic anhydride (**130**) and anhydrous ammonia (10% excess) or aqueous ammonium hydroxide (Scheme 72).^[183,198,205] *N,N*-Dichlorotrifluoromethanesulfonamide (**148**) is prepared in 55% yield from trifluoromethanesulfonamide (**147**) and chlorine in aqueous sodium hydroxide (Scheme 72).^[214]

Scheme 72 Synthesis of *N,N*-Dichlorotrifluoromethanesulfonamide from Chlorine and Trifluoromethanesulfonamide, Prepared from Trifluoromethanesulfonic Anhydride and Ammonia^[183,198,205,214]



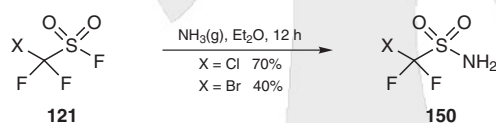
Trifluoromethanesulfonyl azide (**149**) is prepared from trifluoromethanesulfonic anhydride (**130**) and sodium azide (Scheme 73).^[215]

Scheme 73 Synthesis of Trifluoromethanesulfonyl Azide from Trifluoromethanesulfonic Anhydride and Sodium Azide^[215]



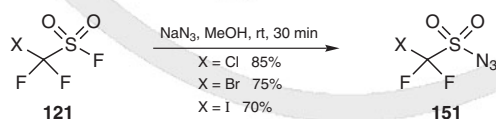
Bromo- and chlorodifluoromethanesulfonamide (**150**, $\text{X} = \text{Br}, \text{Cl}$) are prepared from bromo- and chlorodifluoromethanesulfonyl fluoride (**121**, $\text{X} = \text{Br}, \text{Cl}$), respectively, and ammonia (Scheme 74).^[187] In contrast, difluoroiodomethanesulfonamide (**150**, $\text{X} = \text{I}$) is prepared from difluoroiodomethanesulfonyl azide (**152**) (*vide infra*).

Scheme 74 Synthesis of Difluorohalomethanesulfonamides from the Corresponding Difluorohalomethanesulfonyl Fluorides and Ammonia^[187]

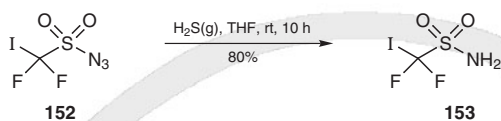


Difluorohalomethanesulfonyl azides **151** ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) are prepared in 70–85% yield from the corresponding difluorohalomethanesulfonyl fluorides **121** ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) and sodium azide in methanol (Scheme 75).^[187]

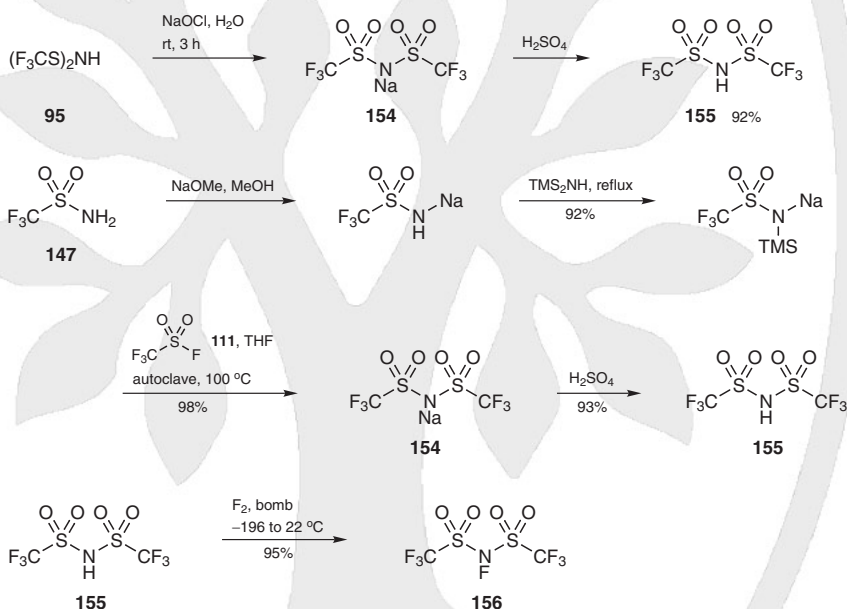
Scheme 75 Synthesis of Difluorohalomethanesulfonyl Azides from the Corresponding Difluorohalomethanesulfonyl Fluorides and Sodium Azide^[187]



Whereas chloro- and bromodifluoromethanesulfonamides (**150**, $\text{X} = \text{Cl}, \text{Br}$) can be prepared directly from the corresponding chloro- and bromodifluoromethanesulfonyl fluorides (**121**, $\text{X} = \text{Cl}, \text{Br}$) (see above), difluoroiodomethanesulfonamide (**153**) is obtained in 80% yield from difluoroiodomethanesulfonyl azide (**152**) and hydrogen sulfide (Scheme 76).^[187]

Scheme 76 Synthesis of Difluoroiodomethanesulfonamide from Difluoroiodomethanesulfonyl Azide and Hydrogen Sulfide^[187]

Bis(trifluoromethanesulfonyl)amine (155) is prepared from bis(trifluoromethylsulfanyl)amine (95) and sodium hypochlorite via sodium amide 154 in 92% yield (Scheme 77).^[216] Bis(trifluoromethanesulfonyl)amine (155) can be also prepared from trifluoromethanesulfonamide (147), hexamethyldisilazane, and trifluoromethanesulfonyl fluoride (111) (Scheme 77).^[217] N-Fluorobis(trifluoromethanesulfonyl)amine (156) is prepared in 95% yield by reaction of bis(trifluoromethanesulfonyl)amine (155) and fluorine (Scheme 77).^[217]

Scheme 77 Synthesis, Metalation, and Fluorination of Trifluoromethanesulfonamides^[216,217]

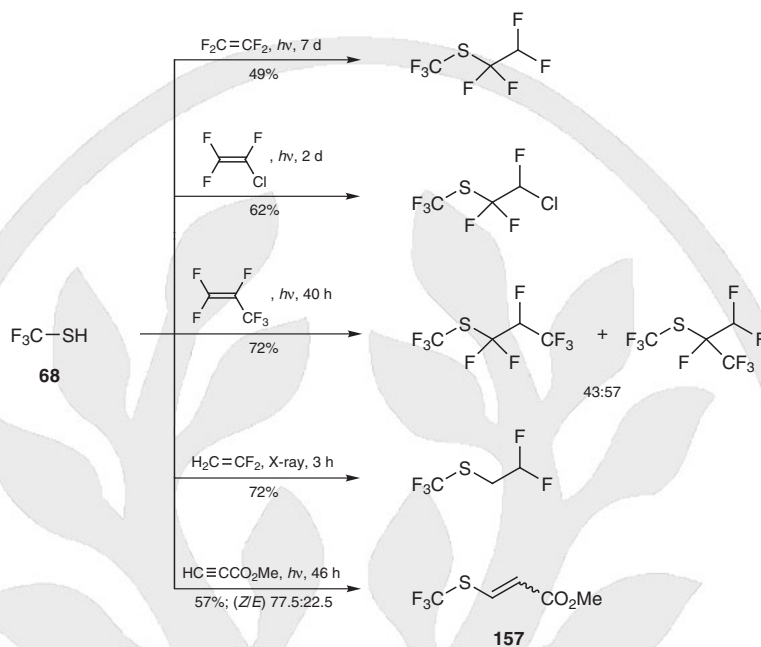
18.15.3.2

Applications of Product Subclass 3 in Organic Synthesis

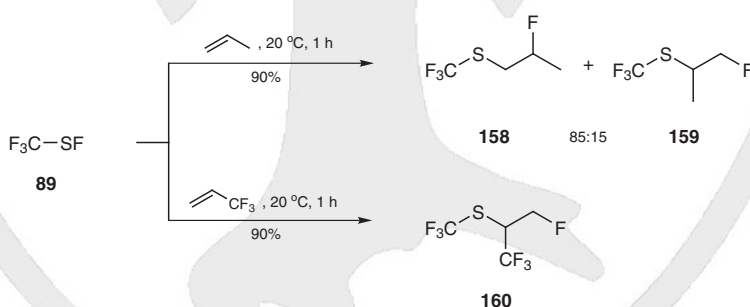
18.15.3.2.1

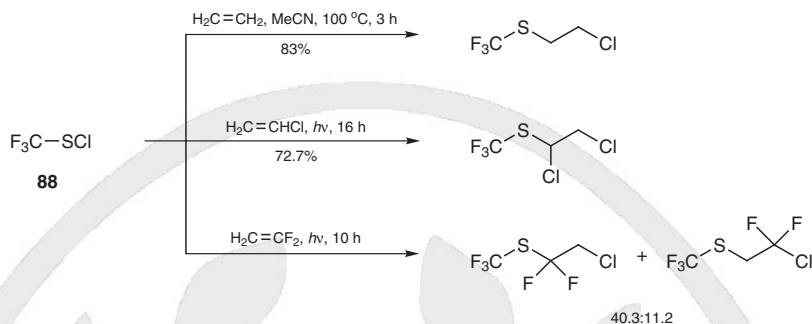
Method 1:**Addition of Trifluoromethanethiol or Trifluoromethanesulfonyl Fluoride or Chloride to Alkenes and Alkynes**

Trifluoromethanethiol (68) adds to tetrafluoroethene, chlorotrifluoroethene, hexafluoropropene, and 1,1-difluoroethene under ultraviolet or X-ray irradiation (Scheme 78).^[218] The addition of trifluoromethanethiol (68) to methyl propynoate gives a mixture of (*Z*)- and (*E*)-methyl 3-(trifluoromethylsulfanyl)acrylate (157) (Scheme 78).^[219]

Scheme 78 Addition of Trifluoromethanethiol to Alkenes and Alkynes^[218,219]

Trifluoromethanesulfonyl fluoride (**89**) adds to alkenes to form partially fluorinated sulfides (Scheme 79); with propene a mixture of fluoropropyl sulfide isomers **158** and **159** forms (**158/159** 85:15) (Scheme 79),^[220] whereas the addition to 3,3,3-trifluoropropene yields only one product, 1,1,1,3-tetrafluoro-2-(trifluoromethylsulfonyl)propane (**160**) (Scheme 79).^[220] Trifluoromethanesulfonyl chloride (**88**) adds to alkenes to form chloro(trifluoromethylsulfonyl)alkanes (Scheme 79).^[131,218,220]

Scheme 79 Addition of Trifluoromethanesulfonyl Fluoride or Chloride to Alkenes and Alkynes^[131,218,220,221]

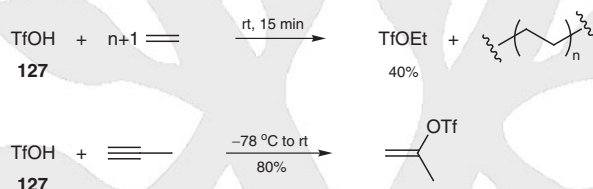


18.15.3.2.2

Method 2:
Applications of Trifluoromethanesulfonic Acid

Trifluoromethanesulfonic acid (**127**) adds to alkenes to give alkyl trifluoromethanesulfonates in good yields;^[222] however, with ethene at room temperature, ethyl trifluoromethanesulfonate and a low polymer of ethene rapidly form (Scheme 80).^[198]

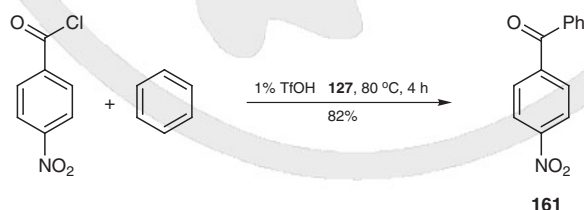
Scheme 80 Addition of Trifluoromethanesulfonic Acid to Ethene and Propyne^[198,222]

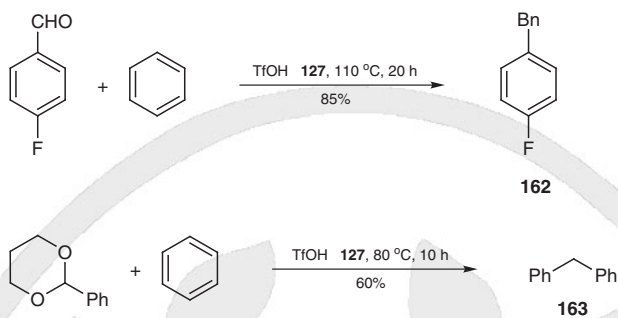


Trifluoromethanesulfonic acid (**127**) is an extremely powerful catalyst for Friedel–Crafts reactions.^[223–225] For example, in the presence of a catalytic amount of sulfonic acid **127**, benzene and 4-nitrobenzoyl chloride form 4-nitrobenzophenone (**161**),^[224] 4-fluorobenzaldehyde and benzene give 1-benzyl-4-fluorobenzene (**162**),^[225] and 2-phenyl-1,3-dioxane reacts with benzene to give diphenylmethane (**163**) (Scheme 81).^[225]

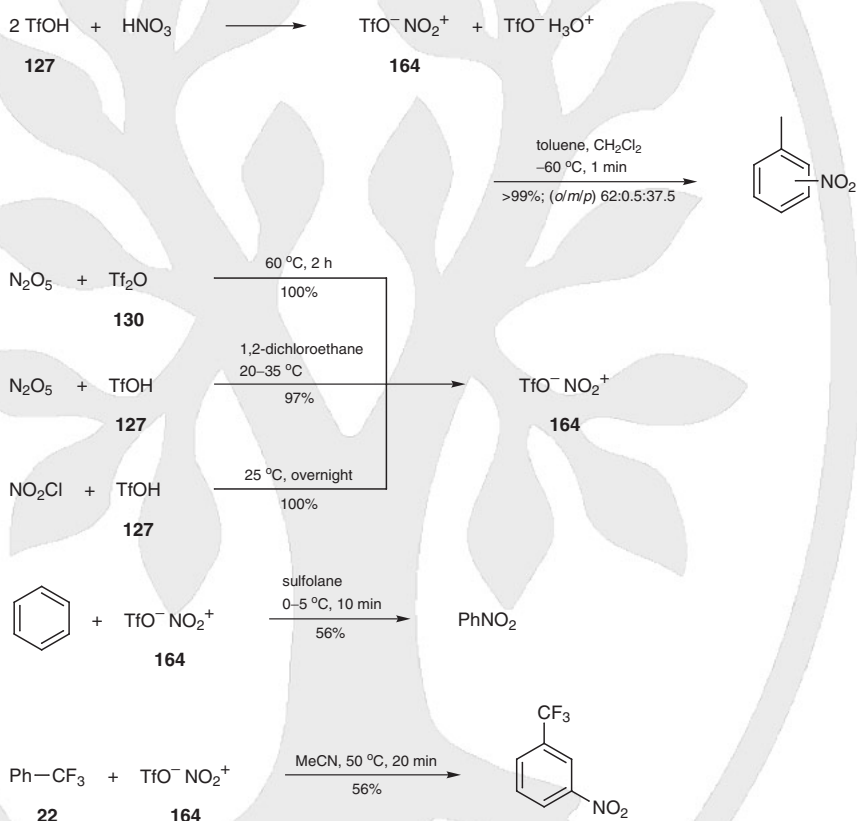
Trifluoromethanesulfonic acid (**127**) and 0.5 equivalents of anhydrous nitric acid combine to form a mixture of nitronium trifluoromethanesulfonate (**164**) and hydronium trifluoromethanesulfonate (Scheme 82).^[226] This mixture can be used for the nitration of arenes (Scheme 82).^[226] Nitronium trifluoromethanesulfonate (**164**) may also be prepared from trifluoromethanesulfonic anhydride (**130**) and dinitrogen pentoxide or from trifluoromethanesulfonic acid (**127**) and dinitrogen pentoxide or nitronium chloride (Scheme 82).^[226–229]

Scheme 81 Trifluoromethanesulfonic Acid as Catalyst for Friedel–Crafts Reactions^[223–225]





Scheme 82 Trifluoromethanesulfonic Acid in the Preparation of Nitronium Trifluoromethanesulfonate, Used for the Nitration of Arenes^[226–229]



18.15.3.2.3

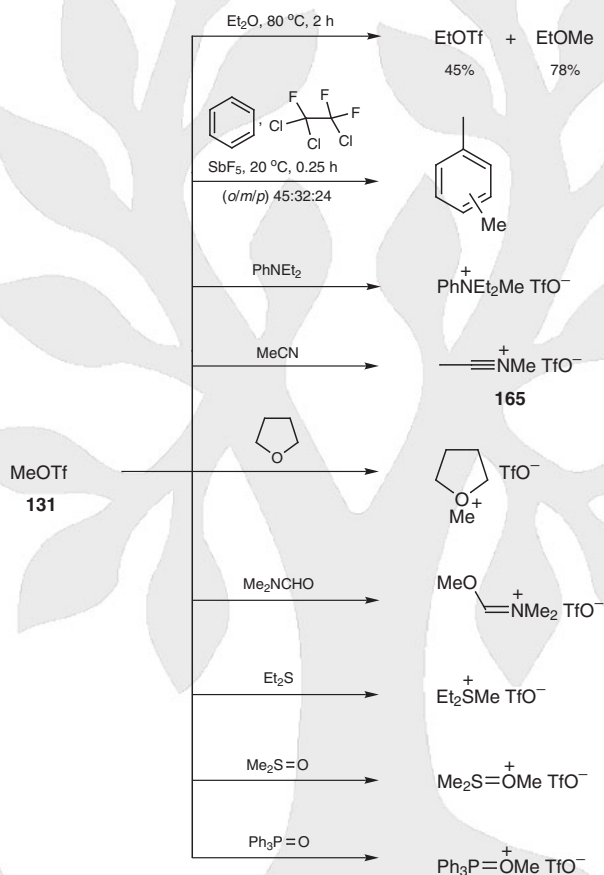
Method 3:**Applications of Alkyl Trifluoromethanesulfonates and Trifluoromethanesulfonic Anhydride**

Alkyl trifluoromethanesulfonates are powerful alkylating agents.^[230] Methyl trifluoromethanesulfonate (**131**) reacts with the majority of common functional groups containing lone-pair electrons. Methyl trifluoromethanesulfonate (**131**) also alkylates poor nucleophiles such as diethyl ether^[198] and benzene (Scheme 83).^[231] *N,N*-Diethylaniline easily undergoes quaternization with methyl trifluoromethanesulfonate (**131**) (Scheme 83).^[230] Nitriles which do not react with common methylating agents, e.g. iodomethane, readily form nitrilium ions, e.g. **165**, with methyl trifluoromethanesulfonate (**131**) (Scheme

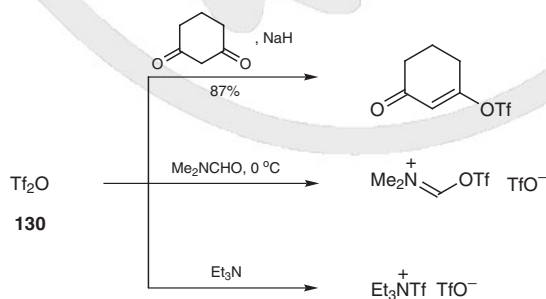
83).^[230] Tetrahydrofuran, dimethylformamide, diethyl sulfide, dimethyl sulfoxide, and triphenylphosphine oxide all undergo methylation with methyl trifluoromethanesulfonate (**131**) (Scheme 83).^[230] Methylations with methyl trifluoromethanesulfonate (**131**) are best carried out in nonnucleophilic, inert solvents such as dichloromethane, nitromethane, sulfolane, and dimethyl sulfate.^[230]

Trifluoromethanesulfonic anhydride (**130**) has found very broad application in synthetic organic chemistry.^[232] The main thrust of the synthetic use of anhydride **130** is reaction with oxygen nucleophiles, including carbonyl compounds, alcohols, and phenols, as well as oxides of phosphorus and sulfur. Examples are shown in Scheme 84.^[233–235]

Scheme 83 Application of Methyl Trifluoromethanesulfonate^[198,230,231]



Scheme 84 Application of Trifluoromethanesulfonic Anhydride^[233–235]

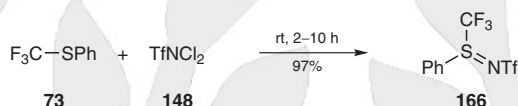


18.15.3.2.4

Method 4:**An *N*-(Trifluoromethylsulfonyl)sulfimide from *N,N*-Dichlorotrifluoromethanesulfonamide and (Trifluoromethylsulfonyl)benzene**

N,N-Dichlorotrifluoromethanesulfonamide (**148**) converts (trifluoromethylsulfonyl)benzene (**73**) into *S*-phenyl-*S*-(trifluoromethyl)-*N*-(trifluoromethylsulfonyl)sulfimide (**166**) (Scheme 85).^[236]

Scheme 85 Synthesis of a Fluorinated Sulfimide from *N,N*-Dichlorotrifluoromethanesulfonamide and (Trifluoromethylsulfonyl)benzene^[236]



18.15.4

Product Subclass 4:**Compounds with Carbon–Halogen and Carbon–Selenium Bonds**

18.15.4.1

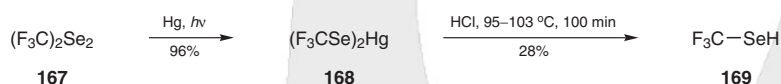
Synthesis of Product Subclass 4

18.15.4.1.1

Method 1:**Selenium(II) Compounds**

Trifluoromethaneselenol (**169**) is prepared from bis(trifluoromethylselanyl)mercury(II) (**168**) and anhydrous hydrogen chloride (Scheme 86).^[237] Bis(trifluoromethylselanyl)mercury(II) (**168**) is prepared from bis(trifluoromethyl) diselenide (**167**) and mercury under ultraviolet irradiation (Scheme 86).^[237] Bis(trifluoromethyl) diselenide (**167**) is prepared in 28% yield when silver(I) trifluoroacetate (**3**) and selenium are heated with an open flame (Scheme 87).^[238] (Trifluoromethylselanyl)copper(I) (**170**) is prepared in 99% yield from bis(trifluoromethyl) diselenide (**167**) and copper in dimethylformamide (Scheme 87).^[144,238,239]

Scheme 86 Synthesis of Trifluoromethaneselenol from Bis(trifluoromethylselanyl)mercury(II) and Hydrogen Chloride^[237]

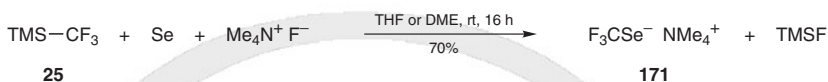


Scheme 87 Synthesis of (Trifluoromethylselanyl)copper(I) from Bis(trifluoromethyl) Diselenide and Copper^[144,238,239]



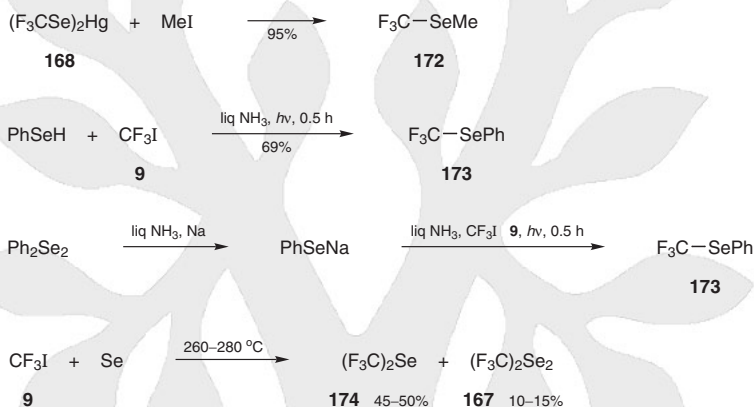
Tetramethylammonium trifluoromethylselenolate (**171**) is prepared in 70% yield from selenium, trimethyl(trifluoromethyl)silane (**25**), and tetramethylammonium fluoride (Scheme 88).^[240]

Scheme 88 Synthesis of Tetramethylammonium Trifluoromethylselenolate from Selenium, Trimethyl(trifluoromethyl)silane, and Tetramethylammonium Fluoride^[240]



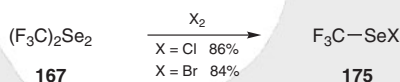
Trifluoro(methylselanyl)methane (**172**) is prepared in 95% yield from bis(trifluoromethylselanyl)mercury(II) (**168**) and iodomethane (Scheme 89).^[241,242] (Trifluoromethylselanyl)benzene (**173**) is prepared in 69% yield from benzeneselenol and trifluoroiodomethane (**9**) in liquid ammonia under ultraviolet irradiation (Scheme 89).^[243,244] (Trifluoromethylselanyl)benzene (**173**) can also be prepared in 55% yield from sodium benzeneselenolate and trifluoroiodomethane (**9**) in liquid ammonia under ultraviolet irradiation (Scheme 89).^[243] Bis(trifluoromethyl) selenide (**174**) is prepared when selenium and trifluoroiodomethane (**9**) are heated at 260–285 °C in a steel bottle (Scheme 89).^[1,237]

Scheme 89 Synthesis of Trifluoromethyl Selenides by Coupling of Selenolates with Alkyl Iodides or from Selenium and Trifluoroiodomethane^[237,241,243,244]



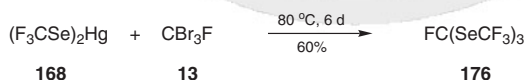
Trifluoromethaneselenenyl chloride and bromide (**175**, X = Cl, Br) are prepared from bis(trifluoromethyl) diselenide (**167**) and chlorine and bromine, respectively (Scheme 90).^[238]

Scheme 90 Synthesis of Trifluoromethaneselenenyl Chloride or Bromide from Bis(trifluoromethyl) Diselenide and the Corresponding Elemental Halogens^[238]



Fluorotris(trifluoromethylselanyl)methane (**176**) is prepared in 60% yield from bis(trifluoromethylselanyl)mercury(II) (**168**) and tribromofluoromethane (**13**) (Scheme 91).^[245]

Scheme 91 Synthesis of Fluorotris(trifluoromethylselanyl)methane from Bis(trifluoromethylselanyl)mercury(II) and Tribromofluoromethane^[245]

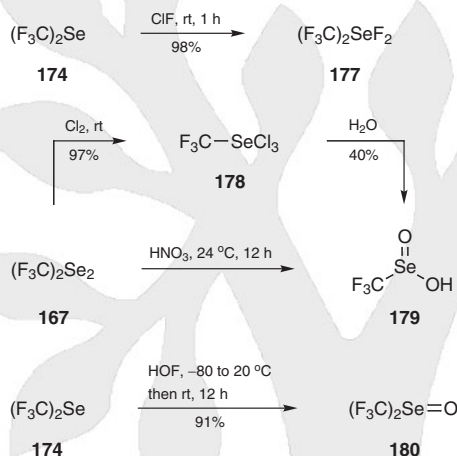


18.15.4.1.2

**Method 2:
Selenium(IV) Compounds**

Bis(trifluoromethyl) selenide (**174**) reacts quantitatively with chlorine monofluoride to give bis(trifluoromethyl)selenium difluoride (**177**) (Scheme 92).^[246] Bis(trifluoromethyl) diselenide (**167**) with an excess of chlorine at room temperature rapidly gives (trifluoromethyl)selenium trichloride (**178**) in 97% yield (Scheme 92).^[237] Bis(trifluoromethyl) diselenide (**167**) and concentrated nitric acid give trifluoromethaneseleninic acid (**179**) in high yield (Scheme 92).^[237] Trifluoromethaneseleninic acid (**179**) can also be obtained when (trifluoromethyl)selenium trichloride (**178**) is exposed to moist air for 36 hours and then dried over phosphorus pentoxide (Scheme 92).^[237] Bis(trifluoromethyl) selenoxide (**180**) is prepared in 91% yield from bis(trifluoromethyl) selenide (**174**) and hydrogen hypofluorite (Scheme 92).^[247]

Scheme 92 Synthesis of the (Trifluoromethyl)selenium(IV) Compounds
Bis(trifluoromethyl)selenium Difluoride, (Trifluoromethyl)selenium Trichloride,
Trifluoromethaneseleninic Acid, and Bis(trifluoromethyl) Selenoxide^[237,246,247]

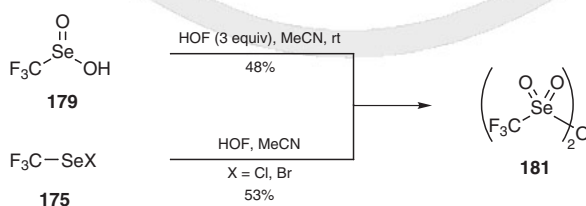


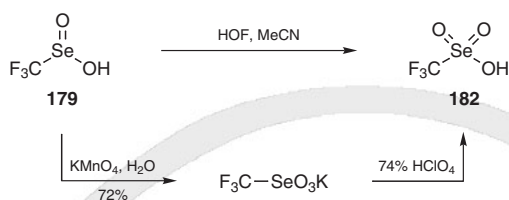
18.15.4.1.3

**Method 3:
Selenium(VI) Compounds**

Trifluoromethaneselenonic anhydride (**181**) is prepared in 48% yield from trifluoromethaneseleninic acid (**179**) and an excess of hydrogen hypofluorite,^[248] or in 53% yield from trifluoromethaneselenenyl chloride or bromide (**175**, X = Cl, Br) and hydrogen hypofluorite (Scheme 93).^[248] A concentrated solution of potassium permanganate oxidizes trifluoromethaneseleninic acid (**179**) in water to give potassium trifluoromethaneselenonate in good yield (Scheme 93). This is converted into free trifluoromethaneselenonic acid (**182**) by 74% perchloric acid (Scheme 93).^[249] The aqueous solution can be concentrated up to 90%, but above this concentration spontaneous decomposition occurs.^[249]

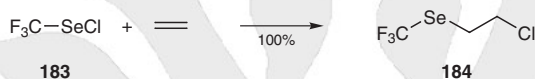
Scheme 93 Synthesis of Trifluoromethaneselenonic Acid and Anhydride^[248,249]



18.15.4.2 **Applications of Product Subclass 4 in Organic Synthesis**18.15.4.2.1 **Method 1:**
Addition of Trifluoromethaneselenenyl Chloride to Ethene

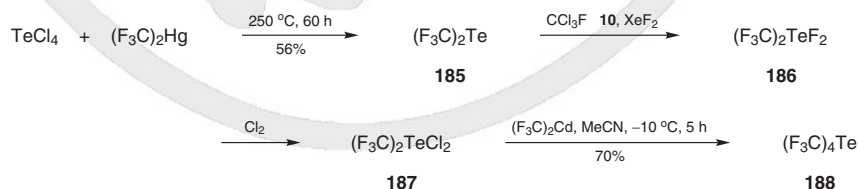
When ethene is passed through trifluoromethaneselenenyl chloride (**183**), 1-chloro-2-(trifluoromethylselanyl)ethane (**184**) forms in quantitative yield within a few minutes (Scheme 94).^[238]

Scheme 94 Synthesis of 1-Chloro-2-(trifluoromethylselanyl)ethane by Addition of Trifluoromethaneselenenyl Chloride to Ethene^[238]

18.15.5 **Product Subclass 5:**
Compounds with Carbon—Halogen and Carbon—Tellurium Bonds18.15.5.1 **Synthesis of Product Subclass 5**18.15.5.1.1 **Method 1:**
Bis(trifluoromethyl) Telluride, Bis(trifluoromethyl)tellurium Dihalides, and Tetrakis(trifluoromethyl)-λ⁴-tellane

Bis(trifluoromethyl) telluride (**185**), a pale yellow compound with a slight garlic odor and which is insensitive to hydrolysis, is prepared in 56% yield from tellurium tetrachloride and bis(trifluoromethyl)mercury(II) in an autoclave at 250 °C (Scheme 95).^[250,251] The reaction of bis(trifluoromethyl) telluride (**185**) and xenon difluoride in trichlorofluoromethane (**10**) gives bis(trifluoromethyl)tellurium difluoride (**186**),^[251] which reacts with chlorine to give bis(trifluoromethyl)tellurium dichloride (**187**) (Scheme 95).^[252] Tetrakis(trifluoromethyl)-λ⁴-tellane (**188**) forms from the reaction of bis(trifluoromethyl)tellurium dichloride (**187**) with bis(trifluoromethyl)cadmium(II) (Scheme 95).^[253]

Scheme 95 Syntheses of Bis(trifluoromethyl) Telluride, Bis(trifluoromethyl)tellurium Dihalides, and Tetrakis(trifluoromethyl)-λ⁴-tellane^[250–253]



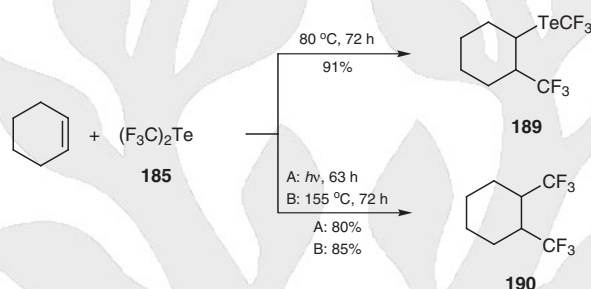
18.15.5.2 Applications of Product Subclass 5 in Organic Synthesis

18.15.5.2.1 Method 1:

Trifluoromethylations Using Bis(trifluoromethyl) Telluride

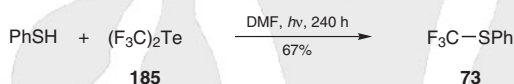
At 80 °C, bis(trifluoromethyl) telluride (**185**) adds to cyclohexene to give 1-trifluoromethyl-2-[(trifluoromethyl)tellanyl]cyclohexane (**189**) in 91% yield (Scheme 96).^[254] In contrast, ultraviolet irradiation or heating to 155 °C results in the formation of trifluoromethyl radicals from telluride **185**, and these add to cyclohexene to give 1,2-bis(trifluoromethyl)cyclohexane (**190**) in high yield (Scheme 96).^[254]

Scheme 96 Addition of Bis(trifluoromethyl) Telluride to Cyclohexene and Bis-trifluoromethylation of Cyclohexene by Bis(trifluoromethyl) Telluride^[254]



Ultraviolet irradiation of benzenethiol and bis(trifluoromethyl) telluride (**185**) over a long time gives (trifluoromethylsulfanyl)benzene (**73**) in 67% yield (Scheme 97).^[255]

Scheme 97 Trifluoromethylation of Benzenethiol by Bis(trifluoromethyl) Telluride^[255]



18.15.6 Product Subclass 6: Compounds with Carbon–Halogen and Carbon–Nitrogen Bonds

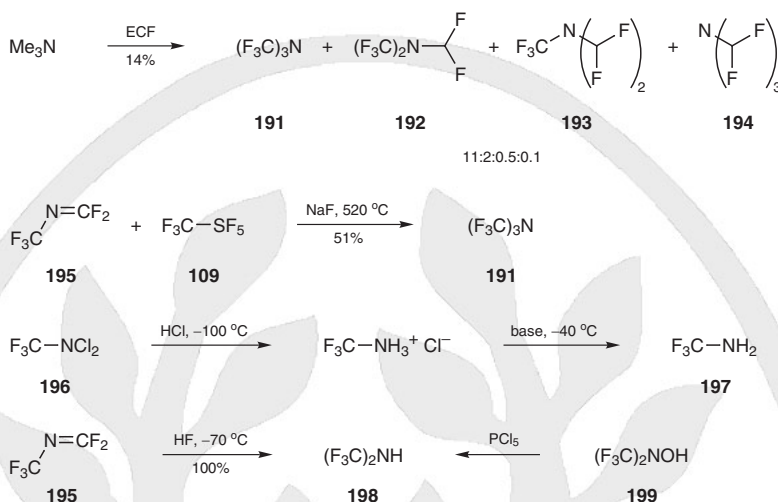
18.15.6.1 Synthesis of Product Subclass 6

18.15.6.1.1 Method 1:

Mono-, Bis-, and Tris(trifluoromethyl)amine

Electrochemical fluorination (ECF) of tertiary amines is perhaps the most effective process for producing perfluorinated tertiary amines.^[1] When trimethylamine undergoes electrochemical fluorination, tris(trifluoromethyl)amine (**191**)^[256] forms in 11% yield, together with smaller amounts of (difluoromethyl)amines **192–194** (Scheme 98).^[257] Tris(trifluoromethyl)amine (**191**) is obtained in better yield (51%) from perfluorinated imine **195**, (trifluoromethyl)sulfur pentafluoride (**109**), and sodium fluoride at 519 °C (Scheme 98).^[256] It is inert, showing none of the typical reactions of ordinary aliphatic amines, does not form salts with acids, is thermally stable, and is nontoxic.^[1]

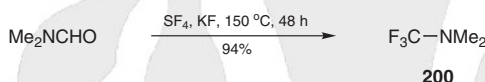
The reaction of dichloro(trifluoromethyl)amine (**196**) with hydrogen chloride followed with base (pyridine, trimethylamine) gives (trifluoromethyl)amine (**197**) (Scheme 98).^[258] Bis(trifluoromethyl)amine (**198**) is prepared in quantitative yield from perfluorinated imine **195** and hydrogen fluoride,^[259,260] or in high yield from *N,N*-bis(trifluoromethyl)hydroxylamine (**199**) and phosphorus pentachloride (Scheme 98).^[261,262]

Scheme 98 Synthesis of Mono-, Bis-, and Tris(trifluoromethyl)amine^[256–262]

18.15.6.1.2

Method 2:
Dimethyl(trifluoromethyl)amine from Dimethylformamide and Sulfur Tetrafluoride

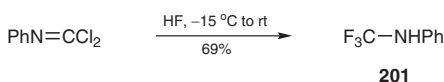
Dimethyl(trifluoromethyl)amine (**200**) forms in 94% yield when dimethylformamide and sulfur tetrafluoride react at 150 °C in the presence of potassium fluoride (Scheme 99).^[263]

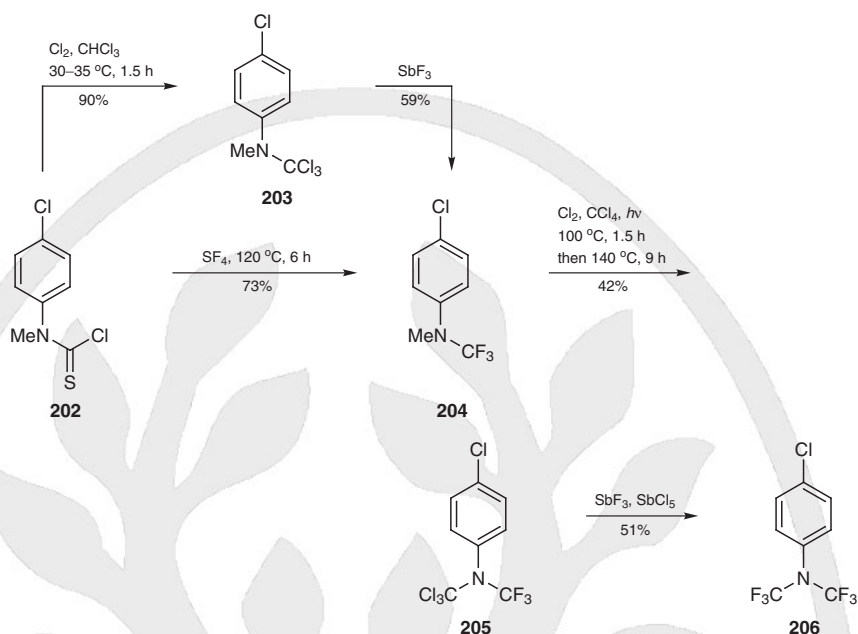
Scheme 99 Dimethyl(trifluoromethyl)amine from Dimethylformamide and Sulfur Tetrafluoride^[263]

18.15.6.1.3

Method 3:
***N*-(Trihalomethyl)anilines**

N-(Trifluoromethyl)aniline (**201**) is prepared in 69% yield from phenylcarbonimidic dichloride and hydrogen fluoride (Scheme 100).^[264] *N*-(Trichloromethyl)- and *N*-(trifluoromethyl)-substituted 4-chloroanilines **203–206** are accessible from 4-chloro-*N*-(chlorothiocarbonyl)aniline **202** (Scheme 100).^[265–267] Chlorination of *N*-(chlorothiocarbonyl)aniline **202** by chlorine in chloroform gives *N*-(trichloromethyl)aniline **203** in 90% yield,^[265] and fluorination of *N*-(chlorothiocarbonyl)aniline **202** by sulfur tetrafluoride gives, in 73% yield, *N*-(trifluoromethyl)aniline **204**,^[266] which may also be prepared in 59% yield from *N*-(trichloromethyl)aniline **203** and antimony(III) fluoride (Scheme 100).^[265,266] Ultraviolet radiation of *N*-methyl-*N*-(trifluoromethyl)aniline **204** and chlorine results in chlorination of the *N*-methyl group, giving 4-chloro-*N*-(trichloromethyl)-*N*-(trifluoromethyl)aniline (**205**),^[267] whose *N*-(trichloromethyl) group is fluorinated upon reaction with antimony(III) fluoride, to give 4-chloro-*N,N*-bis-(trifluoromethyl)aniline (**206**) (Scheme 100).^[267]

Scheme 100 Syntheses of *N*-(Trihalomethyl)anilines^[264–267]

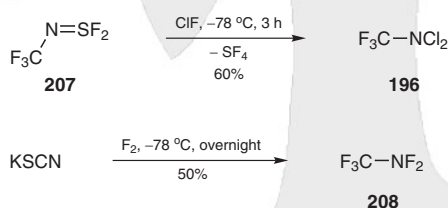


18.15.6.1.4

Method 4:
Dichloro- and Difluoro(trifluoromethyl)amine

Dichloro(trifluoromethyl)amine (**196**) is prepared from (trifluoromethyl)imidosulfurous difluoride (**207**) and chlorine monofluoride (Scheme 101).^[268] Difluoro(trifluoromethyl)amine (**208**) is prepared from potassium thiocyanate and fluorine (Scheme 101).^[269]

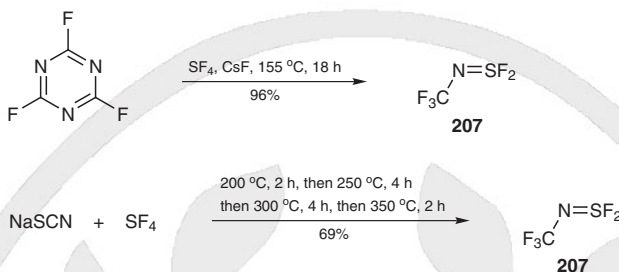
Scheme 101 Synthesis of Dichloro(trifluoromethyl)amine from (Trifluoromethyl)-imidosulfurous Difluoride and Chlorine Monofluoride and Synthesis of Difluoro(trifluoromethyl)amine from Potassium Thiocyanate and Fluorine^[268,269]



18.15.6.1.5

Method 5:
(Trifluoromethyl)imidosulfurous Difluoride from
Cyanuric Fluoride and Sulfur Tetrafluoride

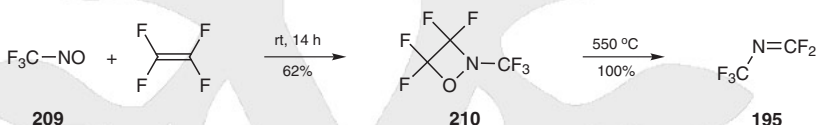
(Trifluoromethyl)imidosulfurous difluoride (**207**) may be prepared either in 96% yield by reaction of cyanuric fluoride with sulfur tetrafluoride in the presence of cesium fluoride,^[270] or in 69% yield from sodium thiocyanate and sulfur tetrafluoride (Scheme 102).^[271]

Scheme 102 Synthesis of (Trifluoromethyl)imidosulfurous Difluoride from Sulfur Tetrafluoride and Cyanuric Fluoride or Sodium Thiocyanate^[270,271]

18.15.6.1.6

Method 6:
(Difluoromethylene)(trifluoromethyl)amine from
Trifluoro(nitroso)methane and Tetrafluoroethene

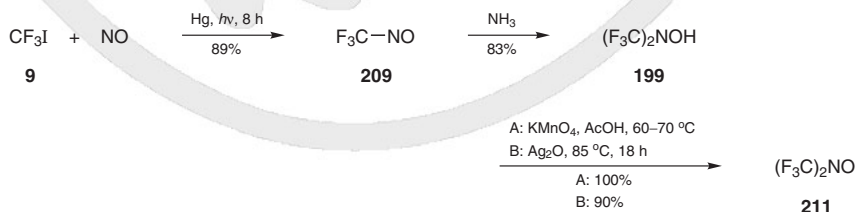
(Difluoromethylene)(trifluoromethyl)amine (**195**) forms when oxazetidine **210**, prepared by an addition reaction between trifluoro(nitroso)methane (**209**) and tetrafluoroethene, is pyrolyzed (Scheme 103).^[259,272]

Scheme 103 Synthesis of (Difluoromethylene)(trifluoromethyl)amine from Trifluoro(nitroso)methane and Tetrafluoroethene^[259,272]

18.15.6.1.7

Method 7:
Trifluoro(nitroso)methane, *N,N*-Bis(trifluoromethyl)hydroxylamine,
and the Bis(trifluoromethyl)nitroxide Radical

Trifluoro(nitroso)methane (**209**) forms in 89% yield when a mixture of trifluoro(iodo)methane (**9**) and nitric oxide are irradiated in the presence of mercury (Scheme 104).^[273] Trifluoro(nitroso)methane (**209**) is a gas with a magnificent deep-blue color, which on cooling yields a deep-blue liquid and purple solid. The reaction of trifluoro(nitroso)methane (**209**) with ammonia gives bis(trifluoromethyl)hydroxylamine (**199**),^[274,275] which forms the bis(trifluoromethyl)nitroxide radical (**211**), either by reaction with potassium permanganate in acetic acid,^[275] or by treatment with silver(I) oxide (Scheme 104).^[276]

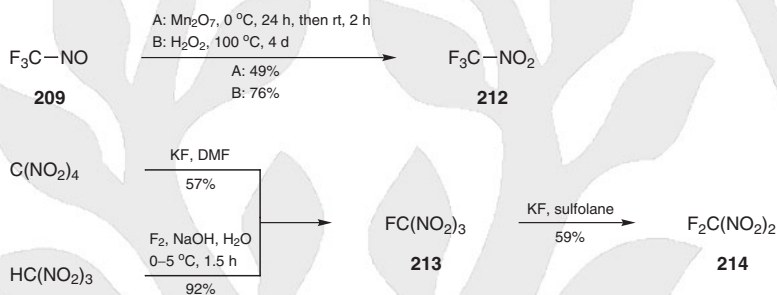
Scheme 104 Syntheses of Trifluoro(nitroso)methane, *N,N*-Bis(trifluoromethyl)hydroxylamine, and the Bis(trifluoromethyl)nitroxide Radical^[273–276]

18.15.6.1.8

Method 8:**Trifluoro(nitro)methane, Difluorodinitromethane, and Fluorotrinitromethane**

Trifluoro(nitro)methane (**212**) is prepared by oxidation of trifluoro(nitroso)methane (**209**) by manganese(VII) oxide^[277] or hydrogen peroxide^[273] (Scheme 105). Difluorodinitromethane (**214**) is prepared from fluorotrinitromethane (**213**) and potassium fluoride (Scheme 105).^[278] Fluorotrinitromethane (**213**) is prepared from trinitromethane and fluorine,^[278,279] or from tetranitromethane and potassium fluoride^[280] (Scheme 105).

Scheme 105 Syntheses of Trifluoro(nitro)methane, Difluorodinitromethane, and Fluorotrinitromethane^[273,277–280]



18.15.6.2

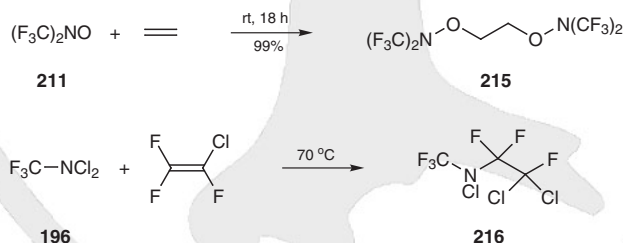
Applications of Product Subclass 6 in Organic Synthesis

18.15.6.2.1

Method 1:**Addition to Alkenes**

The bis(trifluoromethyl)nitroxide radical (**211**) adds to ethene to give *O,O'*-ethylene-*N,N,N',N'*-tetrakis(trifluoromethyl)di(hydroxylamine) (**215**) in 99% yield (Scheme 106).^[281] Dichloro(trifluoromethyl)amine (**196**) adds to chlorotrifluoroethene to give chloro(2,2-dichloro-1,1,2-trifluoroethyl)(trifluoromethyl)amine (**216**) (Scheme 106).^[282]

Scheme 106 Additions of Bis(trifluoromethyl)nitroxide and Dichloro(trifluoromethyl)amine to Alkenes^[281,282]



18.15.7

Product Subclass 7:**Compounds with Carbon—Halogen and Carbon—Phosphorus Bonds**

18.15.7.1

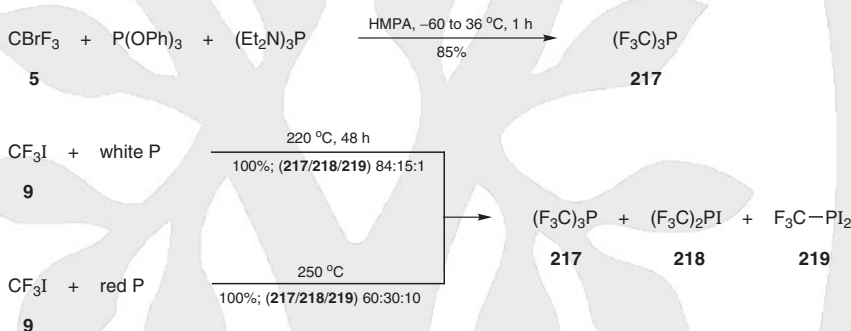
Synthesis of Product Subclass 7

18.15.7.1.1

Method 1:**Tris(trifluoromethyl)phosphine**

Tris(trifluoromethyl)phosphine (**217**), a colorless, spontaneously flammable liquid, can be prepared in 85% yield from bromotrifluoromethane (**5**), triphenyl phosphite, and tris(diethylamino)phosphine (Scheme 107).^[283] The reaction of white phosphorus and trifluoroiodomethane (**9**) yields mainly tris(trifluoromethyl)phosphine (**217**), but also iodobis(trifluoromethyl)phosphine (**218**) and diiodo(trifluoromethyl)phosphine (**219**) (**217/218/219** 84:15:1) (Scheme 107).^[284] A mixture of phosphines **217–219** also results from the reaction of red phosphorus and trifluoroiodomethane (**9**), with tris(trifluoromethyl)phosphine (**217**) as the major product, and higher yields of phosphines **218** and **219** than obtained from white phosphorus (**217/218/219** 60:30:10) (Scheme 107).^[285]

Scheme 107 Synthesis of Tris(trifluoromethyl)phosphine, Iodobis(trifluoromethyl)phosphine, and Diiodo(trifluoromethyl)phosphine^[283–285]



Tris(trifluoromethyl)phosphine (217**) from White Phosphorus and Trifluoro(iodo)methane (**9**):**^[284]

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

Commercial stick P (white phosphorus) was purified by being dipped into CS₂ until the outer oxide layer became detached. It was then transferred under a CO₂ atmosphere to the reaction vessel where it was dried under reduced pressure. In a typical experiment, CF₃I (**9**; 2.94 g, 15 mmol) was sealed under reduced pressure in a Carius tube containing the purified P (3 g, 97 mmol). There was no reaction after 24 h at 100 °C, but after 48 h at 220 °C, the tube contained a red solid and a liquid, which was less volatile than (F₃C)₃P (**217**). Fractionation gave unchanged CF₃I (30%), spontaneously flammable (F₃C)₃P (**217**); yield: 0.7 g (84%); (F₃C)₂PI (**218**); yield: 0.3 g (15%); bp 72–73 °C; and F₃CPI₂ (**219**); yield: 0.05 g (1%); bp 69 °C/29 Torr.

Tris(trifluoromethyl)phosphine (217) from Bromotrifluoromethane (5), Triphenyl Phosphite, and Tris(diethylamino)phosphine:^[283]

CAUTION: Hexamethylphosphoric triamide is a possible human carcinogen and an eye and skin irritant.

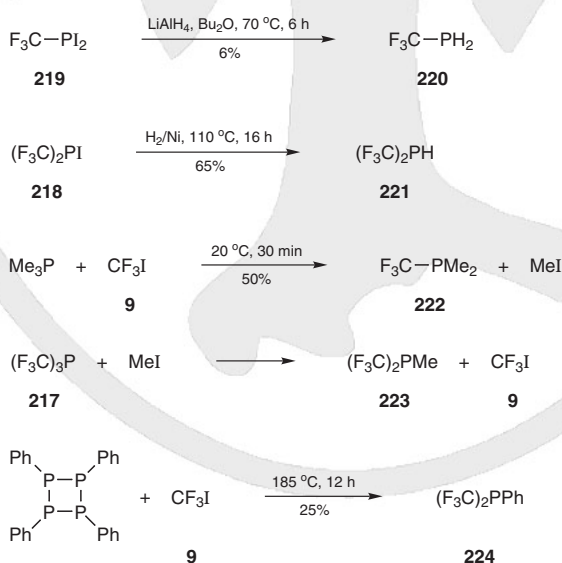
CBrF₃ (**5**; 32.2 g, 216 mmol) was condensed into a round-bottomed flask containing P(OPh)₃ (15.0 g, 48 mmol) dissolved in HMPA (30 mL); the mixture was kept at −60 °C for the whole reaction. (Et₂N)₃P (53.4 g, 216 mmol) was then added to the vigorously stirred mixture over 1 h. After reaching 36 °C, the mixture was stirred for an additional 1 h, turning dark brown in the process. All volatiles [CBrF₃, CHF₃, (F₃C)₃P] were removed under reduced pressure. Trap-to-trap condensation [−60 °C for CHF₃ and excess CBrF₃] permitted the isolation of (F₃C)₃P (**217**) as a colorless, spontaneously flammable liquid; yield: 9.7 g (85%); bp 17 °C; ¹⁹F NMR (benzene-*d*₆, δ): −51.2 (d, ²J_{F,F} = 85.4 Hz); ³¹P NMR (benzene-*d*₆, δ): 2.9 (dec).

18.15.7.1.2

Method 2:
Mono- and Bis(trifluoromethyl)phosphine, Dimethyl(trifluoromethyl)phosphine, Methylbis(trifluoromethyl)phosphine, and Phenylbis(trifluoromethyl)phosphine

(Trifluoromethyl)phosphine (**220**) and bis(trifluoromethyl)phosphine (**221**) are, respectively, prepared by hydrogenation of diiodo(trifluoromethyl)phosphine (**219**) by lithium aluminum hydride and of iodobis(trifluoromethyl)phosphine (**218**) by hydrogen/nickel (Scheme 108).^[285,286] Dimethyl(trifluoromethyl)phosphine (**222**) is prepared from trimethylphosphine and trifluoroiodomethane (**9**),^[287] and methylbis(trifluoromethyl)phosphine (**223**) is prepared from tris(trifluoromethyl)phosphine (**217**) and iodomethane^[285] (Scheme 108). Phenylbis(trifluoromethyl)phosphine (**224**) is prepared from tetraphenyltetraphosphetane and trifluoroiodomethane (**9**) (Scheme 108).^[288]

Scheme 108 Syntheses of Mono- and Bis(trifluoromethyl)phosphine, Dimethyl(trifluoromethyl)phosphine, Methylbis(trifluoromethyl)phosphine, and Phenylbis(trifluoromethyl)phosphine^[285–288]

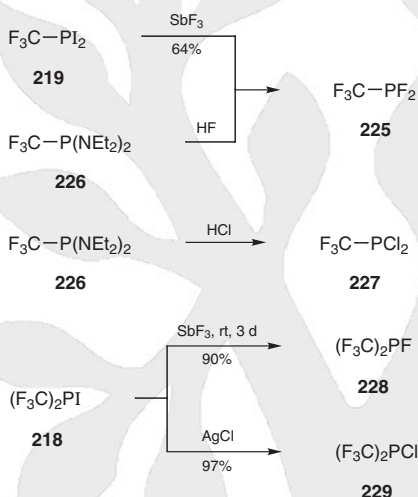


18.15.7.1.3

Method 3:**Mono- and Dihalo(trifluoromethyl)phosphines**

The halogen-exchange reaction of diiodo(trifluoromethyl)phosphine (**219**) with antimony(III) fluoride gives difluoro(trifluoromethyl)phosphine (**225**) (Scheme 109).^[289,290] Phosphine **225** is also prepared by reaction of hydrogen fluoride with bis(diethylamino)(trifluoromethyl)phosphine (**226**), which also reacts with hydrogen chloride to give dichloro(trifluoromethyl)phosphine (**227**) (Scheme 109).^[291] Fluorobis(trifluoromethyl)phosphine (**228**)^[292] and chlorobis(trifluoromethyl)phosphine (**229**)^[284] are prepared from iodo-bis(trifluoromethyl)phosphine (**218**) and antimony(III) fluoride or silver(I) chloride, respectively (Scheme 109).

Scheme 109 Syntheses of Difluoro(trifluoromethyl)phosphine, Dichloro(trifluoromethyl)phosphine, Fluorobis(trifluoromethyl)phosphine, and Chlorobis(trifluoromethyl)phosphine^[284,289–292]

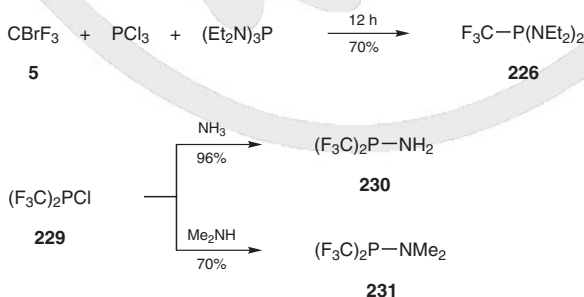


18.15.7.1.4

Method 4:**Amino(trifluoromethyl)phosphines**

Bis(diethylamino)(trifluoromethyl)phosphine (**226**) is prepared in 70% yield from tris(diethylamino)phosphine, phosphorus trichloride, and bromotrifluoromethane (**5**) (Scheme 110).^[291] The reactions of chlorobis(trifluoromethyl)phosphine (**229**) with ammonia and dimethylamine give aminobis(trifluoromethyl)phosphine (**230**) and (dimethylamino)bis(trifluoromethyl)phosphine (**231**), respectively (Scheme 110).^[293]

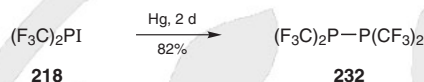
Scheme 110 Syntheses of Bis(diethylamino)(trifluoromethyl)phosphine, Aminobis(trifluoromethyl)phosphine, and (Dimethylamino)bis(trifluoromethyl)phosphine^[291,293]



18.15.7.1.5

Method 5:
Tetrakis(trifluoromethyl)diphosphine

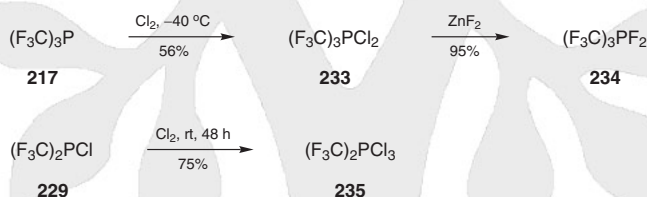
Tetrakis(trifluoromethyl)diphosphine (**232**) is prepared from iodobis(trifluoromethyl)phosphine (**218**) and mercury (Scheme 111).^[284]

Scheme 111 Synthesis of Tetrakis(trifluoromethyl)diphosphine^[284]

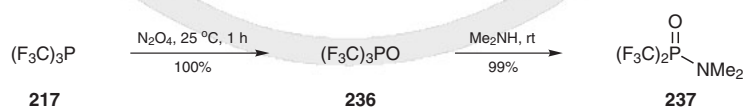
18.15.7.1.6

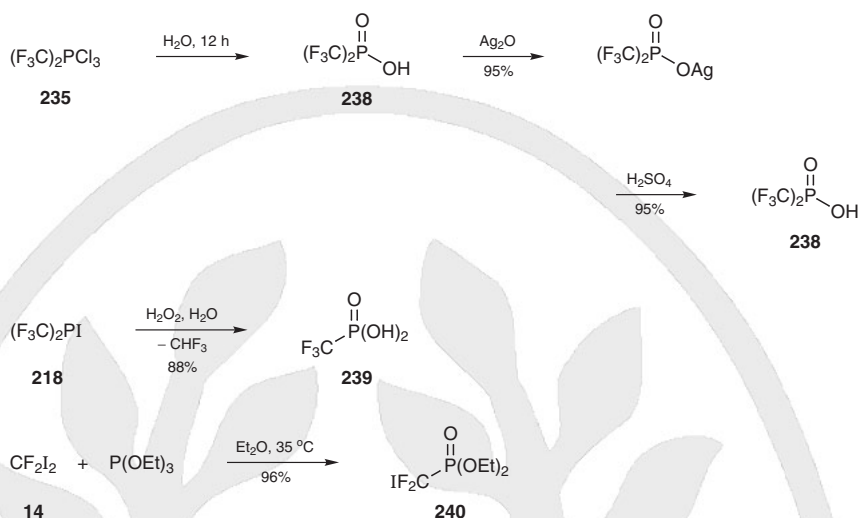
Method 6:
Halo(trifluoromethyl)phosphoranes, Tris(trifluoromethyl)phosphine Oxide, and (Trifluoromethyl)phosphonic and (Trifluoromethyl)phosphinic Acids and Derivatives

The reaction of tris(trifluoromethyl)phosphine (**217**) and chlorine gives dichlorotris(trifluoromethyl)phosphorane (**233**) (Scheme 112),^[284] which can react with zinc(II) fluoride to give difluorotris(trifluoromethyl)phosphorane (**234**) (Scheme 112).^[283] Trichlorobis(trifluoromethyl)phosphorane (**235**) is prepared from chlorobis(trifluoromethyl)phosphine (**229**) and chlorine (Scheme 112).^[288]

Scheme 112 Syntheses of Dichloro- and Difluorotris(trifluoromethyl)phosphorane and Trichlorobis(trifluoromethyl)phosphorane^[283,284,288]

Tris(trifluoromethyl)phosphine (**217**) is oxidized by dinitrogen tetroxide to give tris(trifluoromethyl)phosphine oxide (**236**) (Scheme 113),^[294] which reacts with dimethylamine at room temperature to give bis(trifluoromethyl)phosphinic dimethylamide (**237**) (Scheme 113).^[288] Bis(trifluoromethyl)phosphinic acid (**238**), a strong monobasic acid, is prepared from trichlorobis(trifluoromethyl)phosphorane (**235**) and purified via its silver salt (Scheme 113).^[288] Oxidation of iodobis(trifluoromethyl)phosphine (**218**) by hydrogen peroxide gives (trifluoromethyl)phosphonic acid (**239**) (Scheme 113).^[295] Diethyl (difluoroiodomethyl)phosphonate (**240**) is prepared from difluorodiodomethane (**14**) and triethyl phosphite (Scheme 113).^[296]

Scheme 113 Syntheses of Tris(trifluoromethyl)phosphine Oxide, Bis(trifluoromethyl)phosphinic Dimethylamide, Bis(trifluoromethyl)phosphinic Acid, (Trifluoromethyl)phosphonic Acid, and Diethyl [Difluoro(iodo)methyl]phosphonate^[288,294–296]

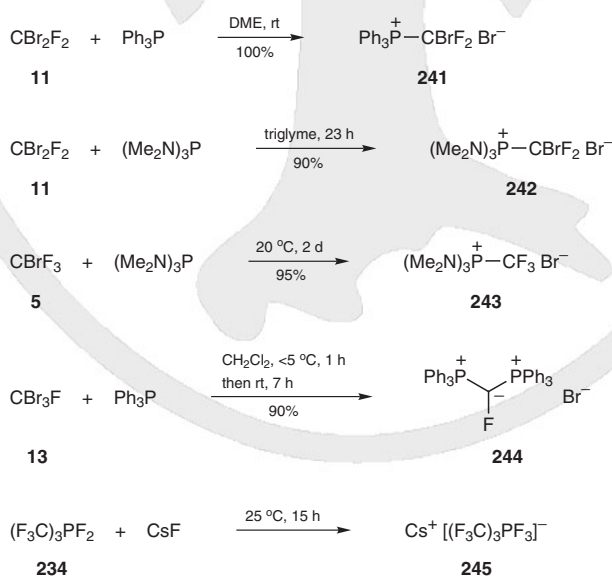


18.15.7.1.7

Method 7: (Halomethyl)phosphonium Bromides and Trifluorotris(trifluoromethyl)phosphate

(Bromodifluoromethyl)phosphonium bromides **241** and **242** are prepared from dibromodifluoromethane (**11**) and the corresponding phosphines (Scheme 114).^[297] The reaction of bromotrifluoromethane (**5**) and tris(dimethylamino)phosphine without a solvent gives (trifluoromethyl)tris(dimethylamino)phosphonium bromide (**243**) in 95% yield (Scheme 114).^[298] Bis(triphenylphosphonium) salt **244** is prepared from tribromofluoromethane (**13**) and triphenylphosphine at room temperature (Scheme 114).^[299] Cesium trifluorotris(trifluoromethyl)phosphate (**245**) is prepared from difluorotris(trifluoromethyl)phosphorane (**234**) and cesium fluoride (Scheme 114).^[300]

Scheme 114 Syntheses of (Halomethyl)phosphonium Bromides and Trifluorotris(trifluoromethyl)phosphate^[297–300]



18.15.7.2 Applications of Product Subclass 7 in Organic Synthesis

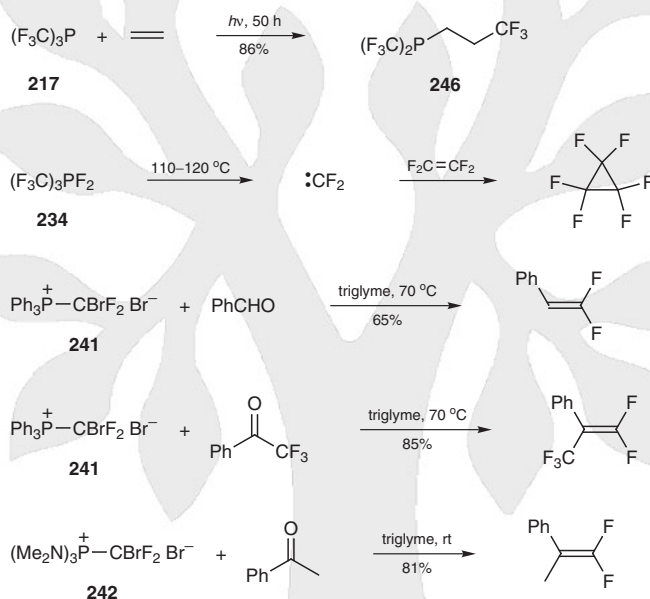
18.15.7.2.1

Method 1:

Additions of (Trifluoromethyl)phosphines and (Trifluoromethyl)-phosphoranes to Alkenes, and Wittig Reactions of (Halomethyl)-phosphonium Bromides with Aldehydes or Ketones

Tris(trifluoromethyl)phosphine (**217**) adds to ethene under ultraviolet irradiation to give bis(trifluoromethyl)(3,3,3-trifluoropropyl)phosphine (**246**) (Scheme 115).^[300] Difluorocarbene, generated from difluorotris(trifluoromethyl)phosphorane (**234**), adds to tetrafluoroethene to give hexafluorocyclopropane (Scheme 115).^[301] (Bromodifluoromethyl)-phosphonium bromides **241** and **242** are useful reagents for substitution of carbonyl oxygens by the difluoromethylene group to form difluoroalkenes (Scheme 115).^[297]

Scheme 115 Additions of (Trifluoromethyl)phosphines and (Trifluoromethyl)-phosphoranes to Alkenes, and Wittig Reactions of (Halomethyl)phosphonium Bromides with Aldehydes or Ketones^[297,300,301]



References

- [1] *Chemistry of Organic Fluorine Compounds II*, Hudlický, M.; Pavlath, A. E., Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, (1995).
- [2] Hudlický, M., *Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood: New York, London, (1976).
- [3] Chambers, R. D., *Fluorine in Organic Chemistry*, Wiley: New York, (1973).
- [4] Ishikawa, N.; Kobayashi, Y., *Fluorine Compounds*, Mir: Moscow, (1982).
- [5] Smart, B. E.; Fernandez, R. E., In *Concise Encyclopedia of Chemical Technology*, 4th ed., Wiley: New York, (1999); p 907.
- [6] Powell, R. L., In *Houben-Weyl*, (1999); Vol. E 10a, p 63.
- [7] Moissan, H., *C. R. Hebd. Seances Acad. Sci.*, (1890) **110**, 276.
- [8] Moissan, H., *C. R. Hebd. Seances Acad. Sci.*, (1890) **110**, 951.
- [9] Chabrière, C., *C. R. Hebd. Seances Acad. Sci.*, (1890) **110**, 279.
- [10] Chabrière, C., *C. R. Hebd. Seances Acad. Sci.*, (1890) **111**, 747.
- [11] Kwasnik, W., In *Handbook of Preparative Inorganic Chemistry*, 2nd Ed.; Brauer, G., Ed.; Academic: London, (1963); Vol. 1, p 203.
- [12] Simons, J. H.; Bond, R. L.; McArthur, R. E., *J. Am. Chem. Soc.*, (1940) **62**, 3477.
- [13] Yost, D. M., *Inorg. Synth.*, (1939) **1**, 34.
- [14] Simons, J. H.; Bloch, L. P., *J. Am. Chem. Soc.*, (1939) **61**, 2962.
- [15] Priest, H. F., *Inorg. Synth.*, (1950) **3**, 178.
- [16] Katamura, K.; Tomota, S.; Nakayama, H., JP 61 134 330, (1986); *Chem. Abstr.*, (1987) **106**, 17868.
- [17] Benning, A. F.; Park, J. D.; Krahler, S. E., US 2 458 551, (1949); *Chem. Abstr.*, (1949) **43**, 3437.
- [18] Miller, C. B.; Bratton, F. H., US 2 478 201, (1949); *Chem. Abstr.*, (1950) **44**, 5374.
- [19] Miller, C. B.; Bratton, F. H., US 2 478 932, (1949); *Chem. Abstr.*, (1950) **44**, 2006.
- [20] Whally, W. B., *J. Soc. Chem. Ind. (London)*, (1947) **66**, 427.
- [21] Haszeldine, R. N., *J. Chem. Soc.*, (1951), 584.
- [22] Schack, C. J.; Chrieste, K. O., *J. Fluorine Chem.*, (1980) **16**, 63.
- [23] Hauptschein, M.; Nodiff, E. A.; Grosse, A. V., *J. Am. Chem. Soc.*, (1952) **74**, 1347.
- [24] Clark, H. C.; Emeléus, H. J., *J. Chem. Soc.*, (1957), 2119.
- [25] Banks, R. E.; Emeléus, H. J.; Haszeldine, R. N.; Kerrigan, V., *J. Chem. Soc.*, (1948), 2188.
- [26] Henne, A. L.; Finnegan, W. G., *J. Am. Chem. Soc.*, (1950) **72**, 3806.
- [27] Crawford, G. H.; Simons, J. H., *J. Am. Chem. Soc.*, (1953) **75**, 5737.
- [28] Xu, H.; Zhai, H., *Huaxue Shiji*, (1989) **11**, 123; *Chem. Abstr.*, (1989) **111**, 194056.
- [29] Naumann, D.; Tyrre, W.; Kock, B.; Rudolph, W.; Wilkes, B., *J. Fluorine Chem.*, (1994) **67**, 91.
- [30] Su, D.-B.; Duan, J.-X.; Chen, Q.-Y., *J. Chem. Soc. Chem. Commun.*, (1992), 807.
- [31] Henne, A. L., *Org. React. (N. Y.)*, (1944) **2**, 49.
- [32] Jarkovský, L.; Pešata, V.; Hudlický, M., *Collect. Czech. Chem. Commun.*, (1957) **22**, 1827.
- [33] Haszeldine, R. N., *J. Chem. Soc.*, (1952), 4259.
- [34] Birchall, J. M.; Haszeldine, R. N., *J. Chem. Soc.*, (1959), 13.
- [35] Nutting, H. S.; Petrie, P. S., US 2 120 675, (1936); *Chem. Abstr.*, (1938) **32**, 5851.
- [36] Bolas, T.; Groves, C. E., *J. Chem. Soc.*, (1871), 773.
- [37] Soroos, H.; Hinkamp, J. B., *J. Am. Chem. Soc.*, (1945) **67**, 1642.
- [38] Burton, D. J.; Yang, Z.-Y., *Tetrahedron*, (1992) **48**, 189.
- [39] McBee, E. T.; Roberts, C. W.; Curtis, S. G., *J. Am. Chem. Soc.*, (1955) **77**, 6387.
- [40] Haszeldine, R. N., *J. Chem. Soc.*, (1954), 1273.
- [41] McBee, E. T.; Battershell, R. D.; Braendlin, H. P., *J. Org. Chem.*, (1963) **28**, 1131.
- [42] Lange, H.; Naumann, D., *J. Fluorine Chem.*, (1984) **26**, 435.
- [43] Burton, D. J.; Wiemers, D. M., *J. Am. Chem. Soc.*, (1985) **107**, 5014.
- [44] Dolbier, W. R.; Wojtowicz, H.; Burkholder, C. R., *J. Org. Chem.*, (1990) **55**, 5420.
- [45] Eugen, R., *Inorg. Synth.*, (1986) **24**, 52.
- [46] Krause, L. J.; Morrison, J. A., *J. Am. Chem. Soc.*, (1981) **103**, 2995.
- [47] Sanner, R. D.; Satcher, J. H.; Droege, M. W., *Organometallics*, (1989) **8**, 1498.
- [48] Nair, H. K.; Morrison, J. A., *J. Organomet. Chem.*, (1989) **376**, 149.
- [49] McLoughlin, V. C. R.; Thrower, J., *Tetrahedron*, (1969) **25**, 5921.
- [50] Chen, Q.-Y.; Yang, Z.-Y.; He, Y.-B., *J. Fluorine Chem.*, (1987) **37**, 171.
- [51] Dolbier, W. R., *Chem. Rev.*, (1996) **96**, 1557.
- [52] Haszeldine, R. N., *J. Chem. Soc.*, (1949), 2856.

- [53] Cullen, W. R.; Waldman, M. C., *Can. J. Chem.*, (1969) **47**, 3093.
- [54] Haszeldine, R. N.; Leedham, K., *J. Chem. Soc.*, (1954), 1261.
- [55] Haszeldine, R. N., *J. Chem. Soc.*, (1953), 3761.
- [56] Stefani, A. P.; Herk, L.; Szwarc, M., *J. Am. Chem. Soc.*, (1961) **83**, 4732.
- [57] Kharasch, M. S.; Jensen, E. V.; Urry, W. H., *Science*, (1945) **102**, 128.
- [58] Kharasch, M. S.; Jensen, E. V.; Urry, W. H., *J. Am. Chem. Soc.*, (1946) **68**, 154.
- [59] Kharasch, M. S.; Jensen, E. V.; Urry, W. H., *J. Am. Chem. Soc.*, (1947) **69**, 1100.
- [60] Kharasch, M. S.; Reinmuth, O.; Urry, W. H., *J. Am. Chem. Soc.*, (1947) **69**, 1105.
- [61] Wu, F.-H.; Huang, B.-N.; Lu, L.; Huang, W.-Y., *J. Fluorine Chem.*, (1996) **80**, 91.
- [62] Yagupolskii, L. M.; Il'chenko, A. Y., In *Soviet Scientific Reviews, Section B: Chemistry Reviews*, Vol'pin, M. E., Ed.; OPA: Amsterdam, (1984); Vol. 5, p 347.
- [63] Yagupolskii, L. M., *Aromatic and Heterocyclic Compounds with Fluorine-Containing Substituents*, Naukova Dumka: Kiev, (1988).
- [64] McClinton, M. A.; McClinton, D. A., *Tetrahedron*, (1992) **48**, 6555.
- [65] Kiselyov, A. S.; Streckowski, L., *Org. Prep. Proced. Int.*, (1996) **28**, 289.
- [66] Kobayashi, Y.; Kumadaki, I., *Tetrahedron Lett.*, (1969), 4095.
- [67] Kobayashi, Y.; Kumadaki, I.; Sato, S.; Hara, N.; Chikami, E., *Chem. Pharm. Bull.*, (1970) **18**, 2334.
- [68] Lukmanov, V. G.; Alexeyeva, L. A.; Yagupolskii, L. M., *Zh. Org. Khim.*, (1974) **10**, 2000; *Chem. Abstr.*, (1974) **81**, 151664.
- [69] Urata, H.; Kuchikami, T., *Tetrahedron Lett.*, (1991) **32**, 91.
- [70] Wiemers, D. M.; Burton, D. J., *J. Am. Chem. Soc.*, (1986) **108**, 832.
- [71] Birchall, J. M.; Irvin, G. P.; Boyson, R. A., *J. Chem. Soc., Perkin Trans. 2*, (1975), 435.
- [72] Huyser, E. S.; Bedard, E., *J. Org. Chem.*, (1964) **29**, 1588.
- [73] Cowell, A. B.; Tamborski, C., *J. Fluorine Chem.*, (1981) **17**, 345.
- [74] Kobayashi, Y.; Kumadaki, I.; Ohsawa, A.; Murakami, S.-I.; Nakano, T., *Chem. Pharm. Bull.*, (1978) **26**, 1247.
- [75] Hart, H.; Fish, R. W., *J. Am. Chem. Soc.*, (1961) **83**, 4460.
- [76] Yagupolskii, L. M.; Matyushecheva, G. I., *Zh. Obshch. Khim.*, (1965) **35**, 1422; *Chem. Abstr.*, (1965) **63**, 14730.
- [77] Marhold, A.; Klauke, E., *J. Fluorine Chem.*, (1981) **18**, 281.
- [78] Krishnamurti, R.; Bellew, D. R.; Prakash, G. K. S., *J. Org. Chem.*, (1991) **56**, 984.
- [79] Ruppert, I.; Schlich, K.; Vollbach, W., *Tetrahedron Lett.*, (1984) **25**, 2195.
- [80] Pawelke, G., *J. Fluorine Chem.*, (1989) **42**, 429.
- [81] Grobe, J.; Hegge, J., *Synlett*, (1995), 641.
- [82] Sheppard, W. A., *J. Org. Chem.*, (1964) **29**, 1.
- [83] Aldrich, P. E.; Sheppard, W. A., *J. Org. Chem.*, (1964) **29**, 11.
- [84] Seppelt, K., *Angew. Chem.*, (1977) **89**, 325; *Angew. Chem. Int. Ed. Engl.*, (1977) **16**, 322.
- [85] Louw, R.; Franken, P. W., *Chem. Ind. (London)*, (1977), 127.
- [86] Barber, H. J.; Fuller, R. F.; Green, M. B., *J. Appl. Chem.*, (1953) **3**, 409.
- [87] Yagupol'skii, L. M., *Dokl. Akad. Nauk SSSR*, (1955) **105**, 100; *Chem. Abstr.*, (1956) **50**, 11270.
- [88] Yarovenko, N. N.; Vasil'eva, A. S., *Zh. Obshch. Khim.*, (1958) **28**, 2502; *Chem. Abstr.*, (1959) **53**, 3116.
- [89] Yarovenko, N. N.; Vasil'eva, A. S., *Zh. Obshch. Khim.*, (1959) **29**, 3786; *J. Gen. Chem. USSR (Engl. Transl.)*, (1960) **29**, 3747.
- [90] Douglass, I. B.; Osborne, C. E., *J. Am. Chem. Soc.*, (1953) **75**, 4582.
- [91] Douglass, I. B.; Marascia, F. J., *J. Am. Chem. Soc.*, (1955) **77**, 1899.
- [92] Douglass, I. B.; Warner, G. H., *J. Am. Chem. Soc.*, (1956) **78**, 6070.
- [93] Kumai, S.; Shintani, S.; Seci, T., JP 04321638, (1992); *Chem. Abstr.*, (1993) **118**, 191330.
- [94] Feiring, A. E., *J. Org. Chem.*, (1979) **44**, 2907.
- [95] Fifolt, M. J.; Olczak, R. T.; Mundhenke, R. F.; Bieron, J. F., *J. Org. Chem.*, (1985) **50**, 4576.
- [96] Lustig, M.; Pitochelli, A. R.; Ruff, J. K., *J. Am. Chem. Soc.*, (1967) **89**, 2841.
- [97] Kellogg, K. B.; Cady, G. H., *J. Am. Chem. Soc.*, (1948) **70**, 3986.
- [98] Prager, J. H.; Thompson, P. G., *J. Am. Chem. Soc.*, (1965) **87**, 230.
- [99] Gould, D. E.; Anderson, L. R.; Young, D. E.; Fox, W. B., *J. Am. Chem. Soc.*, (1969) **91**, 1310.
- [100] Schack, C. J.; Maya, W., *J. Am. Chem. Soc.*, (1969) **91**, 2902.
- [101] Hohorst, F. A.; Shreeve, J. M., *J. Am. Chem. Soc.*, (1967) **89**, 1809.
- [102] Hohorst, F. A.; Shreeve, J. M., *Inorg. Synth.*, (1968) **11**, 143.
- [103] Cauble, R. L.; Cady, G. H., *J. Am. Chem. Soc.*, (1967) **89**, 1962.
- [104] Thompson, P. G., *J. Am. Chem. Soc.*, (1967) **89**, 1841.

- [105] Talbott, R. L., *J. Org. Chem.*, (1968) **33**, 2095.
- [106] Bernstein, P. A.; Hohorst, F. A.; DesMarteau, D. D., *J. Am. Chem. Soc.*, (1971) **93**, 3882.
- [107] Ratcliffe, C. T.; Hardin, C. V.; Anderson, L. R.; Fox, W. B., *J. Am. Chem. Soc.*, (1971) **93**, 3886.
- [108] Roberts, H. L., *J. Chem. Soc.*, (1964), 4538.
- [109] Ellingboe, E. K.; McClelland, A. L., US 3 202 718, (1965); *Chem. Abstr.*, (1965) **63**, 14 706.
- [110] Anderson, L. R.; Fox, W. B., *J. Am. Chem. Soc.*, (1967) **89**, 4313.
- [111] Thompson, P. G., *J. Am. Chem. Soc.*, (1967) **89**, 4316.
- [112] Allison, J. A. S.; Cady, G. H., *J. Am. Chem. Soc.*, (1959) **81**, 1089.
- [113] Sekiya, A.; Ueda, K., *Chem. Lett.*, (1990), 609.
- [114] Barton, D. H. R.; Hesse, R. H.; Jackman, G. P.; Ogunkaya, L.; Pechet, M. M., *J. Chem. Soc., Perkin Trans. 1*, (1974), 739.
- [115] Barton, D. H. R.; Danks, L. J.; Ganguly, A. K.; Hesse, R. H.; Tarzia, G.; Pechet, M. M., *J. Chem. Soc., Perkin Trans. 1*, (1976), 101.
- [116] Johri, K. K.; DesMarteau, D. D., *J. Org. Chem.*, (1983) **48**, 242.
- [117] Anderson, L. R.; Young, D. E.; Gould, D. E.; Juurik-Hogan, R.; Nuechterlein, D.; Fox, W. B., *J. Org. Chem.*, (1970) **35**, 3730.
- [118] Walker, N.; DesMarteau, D. D., *J. Am. Chem. Soc.*, (1975) **97**, 13.
- [119] Kollonitsch, J.; Barash, L.; Doldouras, G., *J. Am. Chem. Soc.*, (1970) **92**, 7494.
- [120] Barton, D. H. R.; Hesse, R. H.; Toh, H. T.; Pechet, M. M., *J. Org. Chem.*, (1972) **37**, 329.
- [121] Barton, D. H. R.; Hesse, R. H.; Markwell, R. E.; Pechet, M. M., *J. Am. Chem. Soc.*, (1976) **98**, 3034.
- [122] Middleton, W. J.; Bingham, E. M., *J. Am. Chem. Soc.*, (1980) **102**, 4845.
- [123] Ainsworth, C.; Chen, F.; Kuo, Y.-N., *J. Organomet. Chem.*, (1972) **42**, 59.
- [124] Pass, G.; Roberts, H. L., *Inorg. Chem.*, (1963) **2**, 1016.
- [125] Kitazume, T.; Shreeve, J. M., *J. Am. Chem. Soc.*, (1978) **100**, 492.
- [126] Hale, W. H.; Williamson, S. M., *Inorg. Chem.*, (1965) **4**, 1342.
- [127] Shreeve, J. M.; Duncan, L. C.; Cady, G. H., *Inorg. Chem.*, (1965) **4**, 1516.
- [128] Fox, W. B.; Franz, G.; Anderson, L. R., *Inorg. Chem.*, (1968) **7**, 382.
- [129] Hohorst, F. A.; DesMarteau, D. D.; Anderson, L. R.; Gould, D. E.; Fox, W. B., *J. Am. Chem. Soc.*, (1973) **95**, 3866.
- [130] Haszeldine, R. N.; Kidd, J. M., *J. Chem. Soc.*, (1953), 3219.
- [131] Harris, J. F., Jr., *J. Org. Chem.*, (1967) **32**, 2063.
- [132] Zack, N. R.; Shreeve, J. M., *Synth. Commun.*, (1974) **4**, 233.
- [133] Man, E. H.; Coffman, D. D.; Muetterties, E. L., *J. Am. Chem. Soc.*, (1959) **81**, 3575.
- [134] Truce, W. E.; Birum, G. H.; McBee, E. T., *J. Am. Chem. Soc.*, (1952) **74**, 3594.
- [135] Yagupolskii, L. M.; Marenets, M. S., *Zh. Obshch. Khim.*, (1954) **24**, 887; *Chem. Abstr.*, (1955) **49**, 8172.
- [136] Boiko, V. N.; Shchupak, G. M.; Yagupol'skii, L. M., *J. Org. Chem. USSR (Engl. Transl.)*, (1977) **13**, 972.
- [137] Popov, V. I.; Boiko, V. N.; Yagupolskii, L. M., *J. Fluorine Chem.*, (1982) **21**, 365.
- [138] Wakselman, C.; Tordeux, M., *J. Org. Chem.*, (1985) **50**, 4047.
- [139] Ignat'ev, N. V.; Boiko, V. N.; Yagupol'skii, L. M., *Zh. Org. Khim.*, (1985) **21**, 653; *Chem. Abstr.*, (1985) **103**, 141 549.
- [140] Rico, I.; Wakselman, C., *Tetrahedron Lett.*, (1981) **22**, 323.
- [141] Yagupolskii, L. M.; Kondratenko, N. V.; Sambur, V. P., *Synthesis*, (1975), 721.
- [142] Emel us, H. J.; MacDuffie, D. E., *J. Chem. Soc.*, (1961), 2597.
- [143] Clark, J. H.; Jones, C. W.; Kybett, A. P.; McClinton, M. A., *J. Fluorine Chem.*, (1990) **48**, 249.
- [144] Kondratenko, N. V.; Kolomeytsev, A. A.; Popov, V. I.; Yagupolskii, L. M., *Synthesis*, (1985), 667.
- [145] Yu, S.-L.; Sauer, D. T.; Shreeve, J. M., *Inorg. Chem.*, (1974) **13**, 484.
- [146] Munavalli, S.; Rossman, D. I.; Rohrbaugh, D. K.; Ferguson, C. P.; Durst, H. D., *J. Fluorine Chem.*, (1996) **76**, 7.
- [147] Boese, R.; Haas, A.; Kr ger, C.; M ller, G.; Waterfeld, A., *Chem. Ber.*, (1994) **127**, 597.
- [148] Tullock, C. W.; Coffman, D. D., *J. Org. Chem.*, (1960) **25**, 2016.
- [149] Seel, F.; Gombler, W., *Angew. Chem.*, (1969) **81**, 789; *Angew. Chem. Int. Ed. Engl.*, (1969) **8**, 773.
- [150] Gombler, W., *Angew. Chem.*, (1977) **89**, 740; *Angew. Chem. Int. Ed. Engl.*, (1977) **16**, 723.
- [151] K hle, E.; Klauke, E.; Grewe, F., *Angew. Chem.*, (1964) **76**, 807.
- [152] Dyson, G. M.; Whitmore, F. C.; Griswold, A. M., *Org. Synth., Coll. Vol. I*, (1941), 506.
- [153] Sosnovsky, G., *Chem. Rev.*, (1958) **58**, 509.
- [154] Kober, E., *J. Am. Chem. Soc.*, (1959) **81**, 4810.
- [155] Ospenson, J. N., US 2 824 136, (1958); *Chem. Abstr.*, (1958) **52**, 11 890.
- [156] Emel us, H. J.; Nabi, S. N., *J. Chem. Soc.*, (1960), 1103.

- [157] Brandt, G. A. R.; Emel  us, H. J.; Haszeldine, R. N., *J. Chem. Soc.*, (1952), 2198.
- [158] Sprenger, G. H.; Cowley, A. H., *J. Fluorine Chem.*, (1976) **7**, 333.
- [159] Ratcliffe, C. T.; Shreeve, J. M., *J. Am. Chem. Soc.*, (1968) **90**, 5403.
- [160] Sauer, D. T.; Shreeve, J. M., *J. Fluorine Chem.*, (1971/1972) **1**, 1.
- [161] Clifford, A. F.; El-Shamy, H. K.; Emel  us, H. J.; Haszeldine, R. N., *J. Chem. Soc.*, (1953), 2372.
- [162] Waterfeld, A.; Mews, R., *J. Fluorine Chem.*, (1984) **23**, 475.
- [163] Viets, D.; Mews, R.; Noltemeyer, M.; Schmidt, H. G.; Waterfeld, A., *Chem. Ber.*, (1991) **124**, 1353.
- [164] Viets, D.; Lork, E.; Behrens, U.; Mews, R.; Waterfeld, A., *J. Fluorine Chem.*, (1998) **89**, 55.
- [165] Burton, C. A.; Shreeve, J. M., *Inorg. Chem.*, (1977) **16**, 1039.
- [166] Yagupolskii, L. M.; Panteleimonov, A. G., *Zh. Org. Khim.*, (1965) **35**, 1120; *Chem. Abstr.*, (1965) **63**, 9800.
- [167] Yagupolskii, L. M.; Kolodyazhnyi, O. I.; Boiko, V. N., *Zh. Org. Khim.*, (1976) **12**, 2266; *Chem. Abstr.*, (1977) **86**, 54939.
- [168] Yagupol'skii, L. M.; Marenets, M. S.; Kondratenko, N. V., *Zh. Obshch. Khim.*, (1965) **35**, 377; *J. Gen. Chem. USSR (Engl. Transl.)*, (1965) **35**, 377.
- [169] Yagupolskii, Y. L.; Savina, T. I., *Zh. Org. Khim.*, (1979) **15**, 438; *Chem. Abstr.*, (1979) **90**, 203618.
- [170] Yang, J.-J.; Kirchmeier, R. L.; Shreeve, J. M., *J. Org. Chem.*, (1998) **63**, 2656.
- [171] Kondratenko, N. V.; Movchun, V. N.; Yagupolskii, Y. L., *Zh. Org. Khim.*, (1989) **25**, 1116; *Chem. Abstr.*, (1990) **112**, 55136.
- [172] Singh, R. P.; Cao, G.; Kirchmeier, R. L.; Shreeve, J. M., *J. Org. Chem.*, (1999) **64**, 2873.
- [173] Movchun, V. N.; Kolomeitsev, A. A.; Yagupolskii, Y. L., *J. Fluorine Chem.*, (1995) **70**, 255.
- [174] Wakselman, C.; Tordeux, M.; Freslon, C.; Saint-Jalmes, L., *Synlett*, (2001), 550.
- [175] Silver, G. A.; Cady, G. H., *J. Am. Chem. Soc.*, (1950) **72**, 3624.
- [176] Abe, T.; Shreeve, J. M., *J. Fluorine Chem.*, (1973) **3**, 187.
- [177] Harzdorf, C.; Meussdoerffer, J. N.; Niederpruem, H.; Wechsberg, M., *Justus Liebigs Ann. Chem.*, (1973), 33.
- [178] Hendrickson, J. B.; Giga, A.; Wareing, J., *J. Am. Chem. Soc.*, (1974) **96**, 2275.
- [179] Forat, G.; Mas, J.-M.; Saint-Jalmes, L., WO 98 05609, (1998); *Chem. Abstr.*, (1998) **128**, 166999.
- [180] Hendrickson, J. B.; Skipper, P. L., *Tetrahedron*, (1976) **32**, 1627.
- [181] Eugen, F.; Langlois, B.; Laurent, E., *J. Fluorine Chem.*, (1994) **66**, 301.
- [182] Wakselman, C.; Tordeux, M., *Bull. Soc. Chim. Fr.*, (1986), 868.
- [183] Gramstad, T.; Haszeldine, R. N., *J. Chem. Soc.*, (1956), 173.
- [184] Gramstad, T.; Haszeldine, R. N., *J. Chem. Soc.*, (1957), 2640.
- [185] Taylor, S. L.; Martin, J. C., *J. Org. Chem.*, (1987) **52**, 4147.
- [186] Volkov, N. D.; Nazaretyan, V. P.; Yagupol'skii, L. M., *Synthesis*, (1979), 972.
- [187] Volkov, N. D.; Nazaretyan, V. P.; Yagupol'skii, L. M., *Zh. Org. Khim.*, (1977) **13**, 1788; *Chem. Abstr.*, (1977) **87**, 167508.
- [188] Volkov, N. D.; Nazaretyan, V. P.; Yagupol'skii, L. M., *J. Fluorine Chem.*, (1997) **84**, 135.
- [189] Sartori, P.; J  schke, R., *J. Fluorine Chem.*, (1994) **69**, 157.
- [190] Kl  ter, G.; Pritzkow, H.; Seppelt, K., *Angew. Chem.*, (1980) **92**, 954; *Angew. Chem. Int. Ed. Engl.*, (1980) **19**, 942.
- [191] Tiers, G. V. D., *J. Org. Chem.*, (1963) **28**, 1244.
- [192] Benefice-Malouet, S.; Blancou, H.; Commeyras, A., *J. Fluorine Chem.*, (1985) **30**, 171.
- [193] Haszeldine, R. N.; Kidd, J. M., *J. Chem. Soc.*, (1955), 2901.
- [194] Schechter, M. S.; Haller, H. L., *J. Am. Chem. Soc.*, (1941) **63**, 1764.
- [195] Oudrhiri Hassani, M.; Germain, A.; Brunel, D.; Commeyras, A., *Tetrahedron Lett.*, (1981) **22**, 65.
- [196] Beard, C. D.; Baum, K.; Grakauskas, V., *J. Org. Chem.*, (1973) **38**, 3673.
- [197] Kobayashi, S.; Danda, H.; Saegusa, T., *Bull. Chem. Soc. Jpn.*, (1973) **46**, 3214.
- [198] Gramstad, T.; Haszeldine, R. N., *J. Chem. Soc.*, (1957), 4069.
- [199] Subramanian, L. R.; Hanack, M.; Chang, L. W. K.; Imhoff, M. A.; Schleyer, P. v. R.; Effenberger, F.; Kustz, W.; Stang, P. J.; Dueber, T. E., *J. Org. Chem.*, (1976) **41**, 4099.
- [200] Stang, P. J.; Anderson, A. G., *J. Org. Chem.*, (1976) **41**, 781.
- [201] Niederpruem, H.; Voss, P.; Beyl, V., *Justus Liebigs Ann. Chem.*, (1973), 20.
- [202] Haszeldine, R. N.; Kidd, J. M., *J. Chem. Soc.*, (1954), 4228.
- [203] Howells, R. D.; Mc Cown, J. D., *Chem. Rev.*, (1977) **77**, 69.
- [204] Hantzsch, A.; Langbein, W., *Z. Anorg. Allg. Chem.*, (1932) **204**, 193.
- [205] Burdon, J.; Farazmand, I.; Stacey, M.; Tatlow, J. C., *J. Chem. Soc.*, (1957), 2574.
- [206] Nakamura, T.; Tainaka, M.; Kida, Y., JP 9 227 498, (1997); *Chem. Abstr.*, (1997) **127**, 220392.

- [207] Nakamura, T.; Okabayashi, S.; Okamura, S., JP 10 114 734, (1998); *Chem. Abstr.*, (1998) **128**, 321 378.
- [208] Kolomeitsev, A. A.; Movchun, V. N.; Kondratenko, N. V.; Yagupolskii, Y. L., *Synthesis*, (1990), 1151.
- [209] Koshar, R. J.; Mitsch, R. A., *J. Org. Chem.*, (1973) **38**, 3358.
- [210] Jüschke, R.; Häsel, P.; Santory, P., *J. Fluorine Chem.*, (1998) **91**, 9.
- [211] Waller, F. J.; Barrett, A. G. M.; Braddock, D. C.; Ramprasad, D.; McKinnell, R. M.; White, A. J. P.; Williams, D. J.; Ducray, R., *J. Org. Chem.*, (1999) **64**, 2910.
- [212] Turowsky, L.; Seppelt, K., *Inorg. Chem.*, (1988) **27**, 2135.
- [213] Billard, T.; Langlois, B. R.; Large, S.; Anker, D.; Roidot, N.; Roure, P., *J. Org. Chem.*, (1996) **61**, 7545.
- [214] Nazaretyan, V. P.; Radchenko, O. A.; Yagupol'skii, L. M., *Zh. Org. Khim.*, (1974) **10**, 2460; *Chem. Abstr.*, (1975) **82**, 97 620.
- [215] Cavender, C. J.; Shiner, V. J., *J. Org. Chem.*, (1972) **37**, 3567.
- [216] Haas, A.; Klare, C., *Chimia*, (1986) **40**, 100.
- [217] Singh, S.; DesMarteau, D. D.; Zuberi, S. S.; Witz, M.; Huang, H.-N., *J. Am. Chem. Soc.*, (1987) **109**, 7194.
- [218] Harris, J. F., Jr., *J. Am. Chem. Soc.*, (1961) **83**, 840.
- [219] Harris, J. F., Jr., *J. Org. Chem.*, (1972) **37**, 1340.
- [220] Gombler, W.; Bollmann, G., *J. Fluorine Chem.*, (1987) **34**, 475.
- [221] Harris, J. F., Jr., *J. Am. Chem. Soc.*, (1962) **84**, 3148.
- [222] Stang, P. J.; Summerville, R. H., *J. Am. Chem. Soc.*, (1969) **91**, 4600.
- [223] Effenberger, F.; Epple, G., *Angew. Chem.*, (1972) **84**, 294; *Angew. Chem. Int. Ed. Engl.*, (1972) **11**, 299.
- [224] Effenberger, F.; Epple, G., *Angew. Chem.*, (1972) **84**, 295; *Angew. Chem. Int. Ed. Engl.*, (1972) **11**, 300.
- [225] Fukuzawa, S.; Tsuchimoto, T.; Hiyama, T., *J. Org. Chem.*, (1997) **62**, 151.
- [226] Coon, C. L.; Blucher, W. G.; Hill, M. E., *J. Org. Chem.*, (1973) **38**, 4243.
- [227] Yagupolskii, L. M.; Maletina, I. I.; Orda, V. V., *Zh. Org. Khim.*, (1974) **10**, 2226; *J. Org. Chem. USSR (Engl. Transl.)*, (1974) **10**, 2240.
- [228] Yarbrow, S. K.; Nofle, R. E., *J. Fluorine Chem.*, (1975) **6**, 187.
- [229] Effenberger, F.; Geke, G., *Synthesis*, (1975), 40.
- [230] Stang, P. J.; Hanak, M.; Subramanian, L. R., *Synthesis*, (1982), 85.
- [231] Olah, G. A.; Nishimura, J., *J. Am. Chem. Soc.*, (1974) **96**, 2214.
- [232] Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S., *Tetrahedron*, (2000) **56**, 3077.
- [233] Martinez, A. G.; Alvarez, R. M.; Casado, M. M.; Subramanian, L. R.; Hanack, M., *Tetrahedron*, (1987) **43**, 275.
- [234] Martinez, A. G.; Fernandez, A. H.; Jimenez, M. F.; Fraile, A. G.; Subramanian, L. R.; Hanack, M., *J. Org. Chem.*, (1992) **57**, 1627.
- [235] Nenajdenko, V. G.; Verteletzkiy, P. V.; Koldobskij, A. B.; Alabugin, I. V.; Balenkova, E. S., *J. Org. Chem.*, (1997) **62**, 2483.
- [236] Kondratenko, N. V.; Gavrilova, R. Y.; Yagupol'skii, L. M., *Zh. Org. Khim.*, (1988) **24**, 456; *Chem. Abstr.*, (1989) **110**, 7767.
- [237] Dale, J. W.; Emelús, H. J.; Haszeldine, R. N., *J. Chem. Soc.*, (1958), 2939.
- [238] Yarovenko, N. N.; Shemanina, V. N.; Gazieva, G. V., *Zh. Obshch. Khim.*, (1959) **29**, 942; *Chem. Abstr.*, (1960) **54**, 2158.
- [239] Yagupolskii, L. M., *J. Fluorine Chem.*, (1987) **36**, 1.
- [240] Tyrra, W.; Naumann, D.; Yagupolskii, Y. L., *J. Fluorine Chem.*, (2003) **123**, 183.
- [241] Emelús, H. J.; Weleman, N., *J. Chem. Soc.*, (1963), 1268.
- [242] Haas, A.; Lopusinski, A., *Chem. Ber.*, (1981) **114**, 3176.
- [243] Voloshchuk, V. G.; Boiko, V. N.; Yagupol'skii, L. M., *Zh. Org. Khim.*, (1977) **13**, 2008; *Chem. Abstr.*, (1977) **88**, 6483.
- [244] Yagupol'skii, L. M.; Voloshchuk, V. G., *Zh. Obshch. Khim.*, (1966) **36**, 165; *J. Gen. Chem. USSR (Engl. Transl.)*, (1966) **36**, 173.
- [245] Haas, A.; Möller, G., *Chem. Ber.*, (1996) **129**, 1383.
- [246] Hendrickson, J. B.; Bair, K. W., *J. Org. Chem.*, (1977) **42**, 3875.
- [247] Gockel, S.; Haas, A.; Probst, V.; Boese, R.; Müller, I., *J. Fluorine Chem.*, (2000) **102**, 301.
- [248] Dunkelberg, O.; Haas, A.; Klapdor, M. F.; Mootz, D.; Poll, W.; Appelman, E. H., *Chem. Ber.*, (1994) **127**, 1871.
- [249] Haas, A.; Weiler, H.-U., *Chem. Ber.*, (1985) **118**, 943.

- [250] Herberg, S.; Naumann, D., *Z. Anorg. Allg. Chem.*, (1982) **492**, 95.
- [251] Naumann, D.; Herberg, S., *J. Fluorine Chem.*, (1982) **19**, 205.
- [252] Herberg, S.; Naumann, D., *Z. Anorg. Allg. Chem.*, (1982) **494**, 151.
- [253] Naumann, D.; Wilkes, B., *J. Fluorine Chem.*, (1985) **27**, 115.
- [254] Naumann, D.; Wilkes, B.; Kischkewitz, J., *J. Fluorine Chem.*, (1985) **30**, 73.
- [255] Naumann, G. A.; Pazenok, S. V.; Tyrra, V., *Russ. J. Org. Chem. (Engl. Transl.)*, (1993) **29**, 128.
- [256] Dresdner, R. D., *J. Am. Chem. Soc.*, (1957) **79**, 69.
- [257] Bürger, H.; Niepel, H.; Pawelke, G.; Frohn, H. J.; Sartori, P., *J. Fluorine Chem.*, (1980) **15**, 231.
- [258] Klöter, G.; Lutz, W.; Seppelt, K.; Sundermeyer, W., *Angew. Chem.*, (1977) **89**, 754; *Angew. Chem. Int. Ed. Engl.*, (1977) **16**, 707.
- [259] Barr, D. A.; Haszeldine, R. N., *J. Chem. Soc.*, (1955), 1881.
- [260] Makarov, S. P.; Énglin, M. A.; Shpanskii, V. A.; Ermakova, I. V., *Zh. Obshch. Khim.*, (1968) **38**, 38; *J. Gen. Chem. USSR (Engl. Transl.)*, (1968) **38**, 37.
- [261] Haszeldine, R. N.; Mattinson, B. J. H., *J. Chem. Soc.*, (1955), 4172.
- [262] Haszeldine, R. N.; Mattinson, B. J. H., *Chem. Ind. (London)*, (1956), 81.
- [263] Dmowski, W.; Kaminski, M., *J. Fluorine Chem.*, (1983) **23**, 207.
- [264] Petrov, K. A.; Neĩmysheva, A. A., *Zh. Obshch. Khim.*, (1959) **29**, 2169; *Chem. Abstr.*, (1960) **54**, 10912.
- [265] Yagupol'skii, L. M.; Dronkina, M. I., *Zh. Obshch. Khim.*, (1966) **36**, 1309; *Chem. Abstr.*, (1966) **65**, 16885.
- [266] Dronkina, M. I.; Yagupol'skii, L. M., *Zh. Org. Khim.*, (1971) **7**, 2000; *Chem. Abstr.*, (1972) **76**, 13968.
- [267] Yagupol'skii, L. M.; Dronkina, M. I., *Zh. Obshch. Khim.*, (1966) **36**, 1343; *Chem. Abstr.*, (1966) **65**, 16885.
- [268] De Marco, R. A.; Shreeve, J. M., *J. Fluorine Chem.*, (1971/1972) **1**, 269.
- [269] Ruff, J. K., *J. Org. Chem.*, (1967) **32**, 1675.
- [270] Griffiths, J. E.; Sturman, D. F., *Spectrochim. Acta, Part A*, (1969) **25**, 1355.
- [271] Smith, W. C.; Tullock, C. W.; Smith, R. D.; Engelhardt, V. A., *J. Am. Chem. Soc.*, (1960) **82**, 551.
- [272] Ukharov, O. V.; Sizov, Yu. A.; Knunyants, I. L., *Zh. Vses. Khim. O-va. im. D. I. Mendeleeva*, (1982) **26**, 344; *Chem. Abstr.*, (1982) **97**, 181656.
- [273] Jander, J.; Haszeldine, R. N., *J. Chem. Soc.*, (1954), 912.
- [274] Banks, R. E.; Oppenheim, C., *J. Fluorine Chem.*, (1978) **12**, 27.
- [275] Makarov, S. P.; Yakubovich, A. Y.; Dubov, S. S.; Medvedev, A. N., *Dokl. Akad. Nauk SSSR*, (1965) **160**, 1319; *Chem. Abstr.*, (1965) **62**, 14481.
- [276] Blackley, W. D.; Reinhardt, R. R., *J. Am. Chem. Soc.*, (1965) **87**, 802.
- [277] Haszeldine, R. N., *J. Chem. Soc.*, (1953), 2075.
- [278] Kamlet, M.; Adolph, H. G., *J. Org. Chem.*, (1968) **33**, 3073.
- [279] Grakauskas, V.; Baum, K., *J. Org. Chem.*, (1968) **33**, 3080.
- [280] Khisamutdinov, G. K.; Slovet'skii, V. I.; L'vova, M. S.; Usyshkin, O. G.; Bespozvanni, M. A.; Fainzilberg, A. A., *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1970), 2553; *Chem. Abstr.*, (1971) **74**, 87266.
- [281] Banks, R. E.; Haszeldine, R. N.; Stevenson, M. J., *J. Chem. Soc. C*, (1966), 301.
- [282] Krumm, B.; Kirchmeier, R. L.; Shreeve, J. M., *Inorg. Chem.*, (1995) **34**, 3114.
- [283] Görg, M.; Röschenthaler, G.-V.; Kolomeitsev, A. A., *J. Fluorine Chem.*, (1996) **79**, 103.
- [284] Bennett, F. W.; Emel  us, H. J.; Haszeldine, R. N., *J. Chem. Soc.*, (1953), 1565.
- [285] Haszeldine, R. N., *Angew. Chem.*, (1954) **66**, 693.
- [286] Bennett, F. W.; Emel  us, H. J.; Haszeldine, R. N., *J. Chem. Soc.*, (1954), 3896.
- [287] Haszeldine, R. N.; West, B. O., *J. Chem. Soc.*, (1956), 3631.
- [288] Beg, M. A. A.; Clark, H. C., *Can. J. Chem.*, (1961) **39**, 564.
- [289] Kulakova, V. N.; Zinov'ev, J. M.; Soborovski  , L. Z., *Zh. Obshch. Khim.*, (1959) **29**, 3957; *Chem. Abstr.*, (1960) **54**, 20846.
- [290] Nixon, J. F.; Cavell, R. G., *J. Chem. Soc.*, (1964), 5983.
- [291] Volbach, W.; Ruppert, I., *Tetrahedron Lett.*, (1983) **24**, 5509.
- [292] Burg, A. B.; Brendel, G., *J. Am. Chem. Soc.*, (1958) **80**, 3198.
- [293] Harris, G. S., *J. Chem. Soc.*, (1958), 512.
- [294] Burg, A. B.; Sarkis, A. J., *J. Am. Chem. Soc.*, (1965) **87**, 238.
- [295] Bennett, F. W.; Emel  us, H. J.; Haszeldine, R. N., *J. Chem. Soc.*, (1954), 3598.
- [296] Li, A.-R.; Chen, Q.-Y., *Synthesis*, (1996), 606.
- [297] Burton, D. J., *J. Fluorine Chem.*, (1983) **23**, 339.
- [298] Chernega, A. N.; Kolomeitsev, A. A.; Yagupolskii, Y. L.; Gentzsch, A.; R  schenthaler, G.-V., *J. Fluorine Chem.*, (1995) **70**, 271.

- [299] Cox, D. G.; Burton, D. J., *J. Org. Chem.*, (1988) **53**, 366.
[300] Copper, P.; Fields, R.; Haszeldine, R. N.; Mitchel, G. H.; Nona, S. N., *J. Fluorine Chem.*, (1982) **21**, 317.
[301] Birchall, J. M.; Haszeldine, R. N.; Roberts, D. W., *Chem. Commun.*, (1967), 287.





Product Class 16: Other Tetraheterosubstituted Methanes

C. M. Diaper

General Introduction

The chemistry of this product class has been reviewed previously in *Houben–Weyl*, Vol. E 4, pp 625–725.

Most of the possible combinations of oxygen, sulfur, nitrogen, and phosphorus atoms around a central carbon have been synthesized. However, many of the oxidation state permutations for these heteroatoms remain to be isolated. The nomenclature used to describe these various heteroatom combinations around a central carbon varies greatly, and the terms used commonly in the literature are listed at the beginning of each product subclass. Derivatives of orthocarbonic acid are generally termed orthocarbonates. Carbamide acetal denotes derivatives with one or two amino and two or three alkoxy groups bonded to a central carbon. Examples of selenium-containing derivatives are scarce, whereas reports of the tetrahedral CTe₄ unit are limited to the carbide cubane cluster [Fe₃(CO)₉Te₄(μ₃-CTeBr₄)].^[1]

The development of synthetic methodology toward spirocyclic derivatives of orthocarbonic acid tetraesters and their sulfur and nitrogen analogues has been driven by their use as monomers in polymer chemistry.^[2–4] Toxicological data for derivatives of Product Class 16 are scarce, in part due to the low stability of simple alkyl derivatives toward hydrolysis or acidic conditions. The toxicity of some of the spirocyclic monomers, however, has been investigated because of their application in dental restoratives. Those tested were found to be nonmutagenic and display low cytotoxicity profiles.^[5,6]

Detailed spectroscopic analysis of a number of heterospirenes and -spirans have been carried out^[7–13] to investigate the effects of the different heteroatoms on the spiro conjugation of these systems.^[14]

Product Subclass 1: Orthocarbonic Acid Tetraesters (Tetraalkoxymethanes)

Although orthocarbonic acid and its ionic salts are unknown,^[15] the orthocarbonic acid tetraesters (generally referred to as tetraalkyl orthocarbonates) are readily synthesized and isolated. The acid-catalyzed hydrolysis of tetraethyl orthocarbonate played an important part in developing the Brønsted catalysis law.^[16] They are generally characterized by low toxicity;^[17] spiro orthocarbonate derivatives have been extensively studied as monomers in polymer chemistry, providing the main impetus for the development of synthetic approaches toward this functionality. *exo*-Methylene-substituted spiro orthocarbonates undergo ring opening polymerization with an expansion in volume.^[18] This important property resolves the problems arising from volume shrinkage such as cracking and bending during the curing of adhesive and molding materials.^[19] Epoxy resins formed from spiro orthocarbonates have been used as dental restoratives;^[4] as a result, the *in vitro* toxicity of a number of spiro orthocarbonate monomers has been studied.^[5] Other applications of spiro orthocarbonate-based polymers include the synthesis of environmentally friendly biodegradable plastics,^[20] drug delivery systems,^[21] and plastic lenses.^[22] Tetraalkyl and tetraaryl orthocarbonates are also useful materials and have been used in fuel cells^[23] and detergents as pro-fragrances.^[24]

Oxidation of trialkyl orthoformates with peroxide or molecular oxygen results in the formation of peroxyorthocarbonates.^[25,26] Their thermal decomposition proceeds via a radical mechanism, and their potential as initiators for radical processes has been explored.^[27] Their applicability for the epoxidation of alkenes has been investigated, but they were found to be poor reagents for this transformation.^[28]

Orthocarbonates are generally not compatible with silica gel chromatography and are usually purified by distillation or recrystallization. They are often moisture sensitive and simple derivatives such as tetramethyl orthocarbonate are flammable.^[29] In addition to the methods described herein, orthocarbonates have also been prepared successfully from chloroorthoformates^[30] and cyanic esters.^[31]

18.16.1.1 Synthesis of Product Subclass 1

18.16.1.1.1 Method 1: Substitution Reactions of Trichloromethane Derivatives with Alcohols or Alkoxides

A number of trichloromethane derivatives **1** have been used in the preparation of simple tetraalkyl and tetraaryl orthocarbonates **2** (Scheme 1). This approach was first described in 1864 by Basset, who prepared tetraethyl orthocarbonate by the reaction of sodium ethoxide with trichloronitromethane (chloropin).^[32] This methodology was extended to include the synthesis of a number of simple tetraalkyl orthocarbonates.^[33] Trichloromethanesulfonyl chloride can be used in place of the hazardous chloropin. It was found to give superior yields and was also compatible with simple sodium phenoxides to give the tetraaryl orthocarbonates.^[34] Trichloroacetonitrile was later used as another alternative reagent for this process, giving high yields on treatment with alkyl substrates.^[35,36] Another development was the use of trichloromethyl isocyanide dichloride (TMI, trichloromethylcarbonimidic dichloride),^[37] which on heating (170 °C) with either alkyl or aromatic alcohols led to the orthocarbonate in high yields. Treatment of catechols with the reagent results in the formation of symmetrical spiro orthocarbonates.

Scheme 1 Orthocarbonates from Trichloromethanes^[33–35,37–41]



X	R ¹	Y	Conditions	Yield (%)	Ref
NO ₂	alkyl, Bn	Na	R ¹ OH, 40–60 °C, 2 h	39–77	[33,40]
SCl	alkyl	Na	R ¹ OH, NaH, Et ₂ O, rt, 16 h	50–72	[34]
SCl	Ph	Na	R ¹ OH, NaH, Et ₂ O, rt, 16 h	78	[34]
CN	alkyl	Na	R ¹ OH, 30–80 °C, 3 h	75–80	[35]
N=CCl ₂	aryl	H	1,2-dichlorobenzene, 170 °C, 2 h	66–97	[37]
N=CCl ₂	CH ₂ CCl ₃	H	1,2-dichlorobenzene, 170 °C, 2 h	78	[37]
C(=NH)OEt	Et	Na	EtOH	85	[41]
Cl	aryl	Na	CuCl, MeCN, rt	50–60	[38]
Cl	CH ₂ R _f	H	FeCl ₃ , 76 °C, 6 h	30–40	[39]

The reaction of carbon tetrachloride with sodium alkoxides does not proceed in an analogous manner and instead leads to the formation of orthoformates.^[42] However, the reaction of copper(I) phenoxides with carbon tetrachloride does produce the corresponding tetraaryl orthocarbonates.^[38] Activation with iron(III) chloride in the presence of ex-

cess or stoichiometric quantities of carbon tetrachloride and trihydriyl perfluoro alcohols does lead to the formation of orthocarbonates in modest yield.^[39] Perfluoroalkyl orthocarbonates are not accessible via this route, as perfluorinated alcohols are unstable and degrade with loss of hydrogen fluoride.^[43] Instead, aerosol direct fluorination is required to convert alkyl orthocarbonates into their fully fluorinated derivatives.

Tetraalkoxymethanes 2; General Procedure:^[34]

NaH (0.2 mol) was added portionwise to a soln of the alcohol (0.1 mol) in anhyd Et₂O (200 mL) with cooling under an atmosphere of N₂. After the initial reaction was over, the temperature was raised and maintained at reflux for 30 min. The resulting mixture was stirred overnight and a soln of ClSCCl₃ (0.02 mol) in Et₂O (50 mL) was added dropwise to the cold soln. The mixture was then stirred overnight, further diluted with Et₂O, and filtered over Celite. The filtrate was dried (MgSO₄) and concentrated, and the residue distilled under reduced pressure to give the tetraalkyl orthocarbonate; yield: 50–72%.

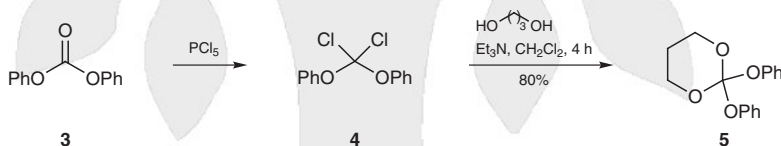
18.16.1.1.2

Method 2:

Substitution Reactions of Dichloroacetals

A common approach to the synthesis of unsymmetrical orthocarbonates such as **5** is nucleophilic displacement of dichloromethanes such as the dichloroacetal **4** under nonnucleophilic basic conditions with an alcohol (Scheme 2).^[44] The dichloroacetals are conveniently prepared from carbonates such as **3** by chlorination with phosphorus pentachloride.^[45] Symmetrical spiro orthocarbonates can also be synthesized from **5** by treating with excess diol.^[44] This is due to transesterification (Section 18.16.1.1.5) of orthocarbonate **5** with excess diol. Mixed polynitroalkyl orthocarbonates have also been synthesized from dichloromethanes by their reaction with nitro alcohols in the presence of iron(III) chloride.^[46]

Scheme 2 Orthocarbonates from Dichloroacetals^[47,48]



2,2-Diphenoxy-1,3-dioxane (5); Typical Procedure:^[48]

A soln of dichloroacetal **4** (3.54 g, 13.2 mmol) in CH₂Cl₂ (20 mL) was added dropwise to a soln of propane-1,3-diol (2.0 g, 26.3 mmol) and Et₃N (5.32 g, 52.6 mmol) in CH₂Cl₂ (20 mL). After the addition was complete, the mixture was stirred for a further 4 h. The organic extract was washed with 1 M NaOH (3 × 50 mL) and H₂O (50 mL). The organic layer was collected, dried (MgSO₄), and concentrated under reduced pressure to afford a pale red solid. Recrystallization (EtOH) yielded a crystalline white powder; yield: 2.88 g (80%); mp 95–96 °C; ¹H NMR (CDCl₃, δ): 4.18 (t, 4H, OCH₂, J = 5.6 Hz), 1.86 (quin, 2H, OCH₂CH₂, J = 5.6 Hz); ¹³C NMR (CDCl₃, δ): 63.3, 23.3.

18.16.1.1.3

Method 3:

Metal-Mediated Desulfurization of Carbon Disulfide with Alkoxides or Alcohols

Carbon disulfide represents an inexpensive and readily available starting material for symmetrical alkyl, aryl, and spiro orthocarbonates (Scheme 3). Desulfurization with thallium(I) alkoxides is initiated by insertion across the thallium(III)–oxygen bond,^[49] leading to a thiocarbonate intermediate which participates in a second insertion to form the de-

sired orthocarbonate **6** and thallium(I) sulfide.^[50] Similarly, refluxing carbon disulfide with dialkyltin dialkoxides also results in the formation of orthocarbonates in good yields. This process is driven by the formation of the more stable Sn—S—Sn system.^[51,52] A number of tetraaryl orthocarbonates have been prepared by the reaction of carbon disulfide with copper(I) phenoxides.^[53,54] This overcomes the limitations of the reaction of copper(I) phenoxide with carbon tetrachloride (Section 18.16.1.1.1), which cannot be used for aromatic substrates with substituents that are susceptible to radical attack. Another alternative procedure that avoids the use of toxic thallium(I) and stannyl reagents is silver-mediated desulfurization using silver(I) trifluoroacetate.^[55] This method can be applied to the synthesis of aliphatic, aromatic, and spiro orthocarbonates.

Scheme 3 Orthocarbonates from Carbon Disulfide by Desulfurization^[50,52,53,55]

$\text{R}^1\text{OX} \xrightarrow{\text{CS}_2} \text{C}(\text{OR}^1)_4 \quad \mathbf{6}$					
R ¹	X	Conditions	Yield (%)	Ref	
alkyl	Tl	CH ₂ Cl ₂ , rt, 4 h	55–72	[50]	
— ^a	Tl ^a	benzene, rt, 2 h	35–73	[50]	
alkyl	Sn(OR ¹)Bu ₂	100–120 °C, 5–20 h	49–95	[52]	
— ^b	Sn(OR ¹)Bu ₂ ^b	ClCH ₂ CH ₂ Cl, 100–110 °C, 2–10 h	0–92	[52]	
aryl	H	NaH, CuCl, MeCN, NaOH, rt	15–92	[53]	
Et	H	AgO ₂ CCF ₃ , Et ₃ N, rt, 16 h	61	[55]	
Ph	H	MeCN, AgO ₂ CCF ₃ , Et ₃ N, rt, 16 h	68	[55]	
— ^c	H	MeCN, AgO ₂ CCF ₃ , Et ₃ N, rt, 16 h	75	[55]	

^a R¹, R¹ = (CH₂)_n using TiO(CH₂)_nOTl as starting material.

^b R¹, R¹ = (CH₂)_n using Bu₂Sn(OR¹)₂ as starting material.

^c R¹OX = catechol.

Tetraethoxymethane (6, R¹ = Et); Typical Procedure:^[55]

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

AgO₂CCF₃ (9.05 g, 41 mmol) was added over 5 min to a soln of Et₃N (5.0 g, 50 mmol) and CS₂ (0.76 g, 10 mmol) in EtOH (10 mL) and stirred continuously for 5 h at rt. The solvent was then removed under reduced pressure and the resulting product was distilled; yield: 1.17 g (61%); bp 158–162 °C/760 Torr.

18.16.1.1.4

Method 4:

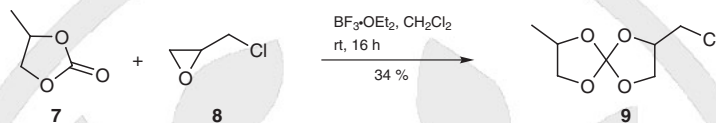
Spiro Orthocarbonates from Epoxides and Cyclic Carbonates by Addition

A number of approaches have been published for the synthesis of orthocarbonates from carbonates and thiocarbonates. Addition of alkoxide to electrophilic trialkoxycarbenium salts^[56] (which can be generated from carbonates by reaction with Meerwein's salt or dialkoxycarbenium salts) gives tetraalkyl orthocarbonates in good yield.^[57,58] Although carbonates are more widely used, spiro orthocarbonates can also be synthesized from *O,O*-dialkyl thiocarbonates. Pyrolysis of *O,O*-dialkyl thiocarbonates can result in dimerization with concomitant loss of carbon disulfide to give the symmetrical spiro orthocarbonate,^[59] whereas desulfurization with mercury(II) acetate in the presence of a diol results in the isolation of unsymmetrical spiro orthocarbonates in moderate yield.^[9]

Spiro orthocarbonates such as **9** can be synthesized by the acid-mediated addition of cyclic carbonates (e.g., **7**) to epoxides (e.g., **8**) (Scheme 4). Judicious choice of catalyst and

conditions are required to prevent ring opening and polymerization reactions from becoming dominant.^[60,61] Although the boron trifluoride–diethyl ether complex is most commonly used,^[44,62] *N*-benzylpyridinium salts have also been investigated, but their use results in low isolated yields of the desired product.^[63]

Scheme 4 Addition Reactions of Cyclic Carbonates and Epoxides^[62]



2-(Chloromethyl)-7-methyl-1,4,6,9-tetraoxaspiro[4.4]nonane (9):^[62]

A soln of 2-(chloromethyl)oxirane (**8**; 111 g, 1.2 mol) in anhyd CH_2Cl_2 (250 mL) was added dropwise to a soln of propylene carbonate (**7**; 102 g, 1.0 mol) and $\text{BF}_3 \cdot \text{OEt}_2$ (1 mL) in anhyd CH_2Cl_2 (250 mL) over a period of 1 h, maintaining a temperature of 24–26 °C. The stirring was continued over a period for 6 h and then the mixture was left to stand overnight. The catalyst was deactivated by addition of Me_3N (2 mL) followed by portions of 8% aq NaOH (500 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic extracts were washed with H_2O , dried (MgSO_4), and concentrated under reduced pressure. The residue was further purified by fractional distillation; yield: 66.2 g (34%); bp 110–115 °C/3 Torr.

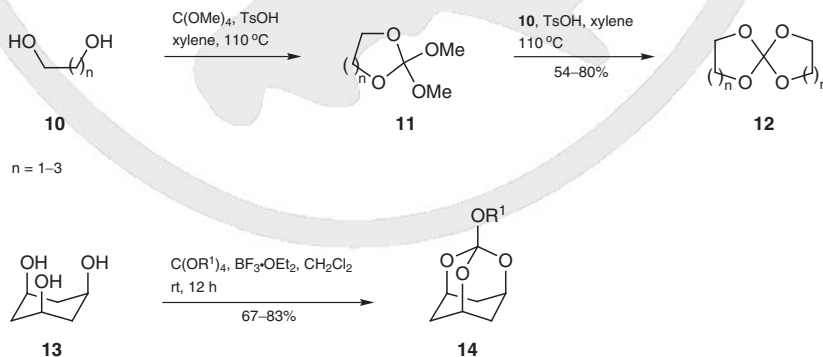
18.16.1.1.5

Method 5:

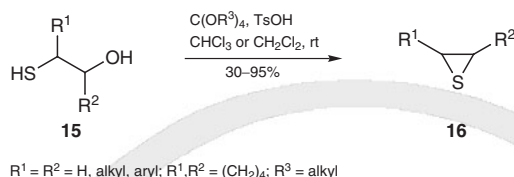
Transesterification of Orthocarbonic Acid Tetraesters with Alcohols

Transesterification reactions between alcohols and orthocarbonates are more difficult to drive to completion than the analogous reactions of orthoformates.^[64] However, several straight-chain alkyl orthocarbonates have been prepared by transesterification of tetramethyl orthocarbonate with the corresponding alcohol.^[65] This method does allow the facile synthesis of both unsymmetrical orthocarbonates **11** and symmetrical spiro orthocarbonates **12** by the sequential reaction of tetramethyl orthocarbonate with either one or two equivalents of diol **10** (Scheme 5).^[66] Diaryloxy acetals can be synthesized in good yield by heating an aromatic diol such as catechol with a stoichiometric quantity of tetraalkyl orthocarbonate.^[67] All-*cis*-cyclohexane-1,3,5-triol (**13**) undergoes transesterification under Lewis acid catalysis to form the rigid 3-alkoxy-2,4,10-trioxaadamantanes **14**.^[68] Analogous reactions of 2-sulfanyl alcohols **15** with tetraalkyl orthocarbonates under acidic conditions lead to the isolation of thiiranes **16** rather than the monothioorthocarbonates.^[69]

Scheme 5 Synthesis of Spiro Orthocarbonates, Trioxaadamantane Orthocarbonates, and Thiiranes^[66,68,69]



$\text{R}^1 = \text{alkyl, aryl}$



2,2-Dimethoxy-1,3-dioxane (11, n = 2); Typical Procedure:^[66]

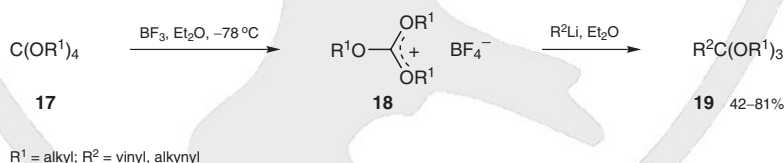
A soln of propane-1,3-diol (7.6 g, 0.1 mol), C(OMe)₄ (13.7 g, 0.1 mol), and TsOH (0.1 g) in *p*-xylene (200 mL) was heated at 110 °C for 3 h; the theoretical amount of MeOH was collected in a trap. Et₃N (0.6 mL) was added and the mixture was concentrated under reduced pressure. The residue was then distilled; yield: 8.9 g (60%); bp 71 °C/15 Torr; ¹H NMR (CDCl₃, δ): 1.7 (m, 2H), 3.31 (s, 6H), 3.84 (t, 4H).

18.16.1.2 Applications of Product Subclass 1 in Organic Synthesis

18.16.1.2.1 Method 1: Generation of Trialkoxycarbenium Salts

The highly stabilized trialkoxycarbenium salts **18**, first described by Meerwein,^[70] are a useful class of electrophilic reagents.^[35,71] They can be generated using several methods, including the reaction of tetraalkyl orthocarbonates **17** with Lewis acids such as boron trifluoride, antimony(V) chloride, or phosphorus pentafluoride.^[71] This method can be used to generate the trialkoxycarbenium salt catalytically in situ, or with excess boron trifluoride–diethyl ether complex to allow the isolation and characterization of the resultant salt.^[72] Treatment of these salts with alkoxides permits the interconversion of orthocarbonates,^[73] whereas attack with other heteroatom nucleophiles has been used to transform orthocarbonates into trialkoxy(phosphino)- and trialkoxy(phosphoryl)methanes (see Section 18.16.4.1). The reaction of salt **18** with alkynyl and vinylic organolithium reagents^[74] is another important application of this reagent. This results in the isolation of the alkyl orthoformate **19** or the carboxylic ester,^[75] depending on the conditions employed (Scheme 6). When the analogous Grignard reagents are used, the reactions often become complicated by the formation of ketals and ethers.^[74] These reactions can be improved by using a trialkoxyacetonitrile, which can be prepared from the orthocarbonate using cyanotrimethylsilane and a Lewis acid.^[76]

Scheme 6 Synthesis and Chemistry of Trialkoxycarbenium Tetrafluoroborates^[72,74]

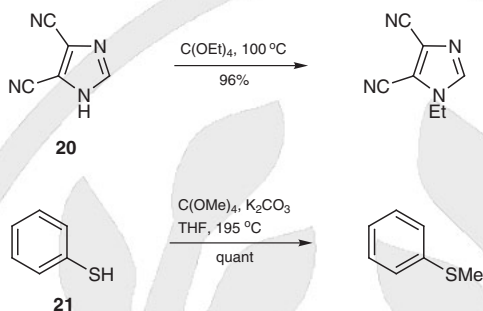


18.16.1.2.2 Method 2: Alkylation Reactions

Tetraalkyl orthocarbonates can be effective alkylating reagents, but have not found widespread use in this capacity. Nitrogen-containing heterocycles such as imidazole-4,5-carbonitriles **20** are N-alkylated upon heating with tetraethyl orthocarbonate (Scheme 7),^[77] whereas trimethoxycarbenium tetrafluoroborate (Section 18.16.1.2.1) has been used to N-methylate carbazole.^[78] The methylation of esters,^[79] phenols,^[80] and benzenethiol **21**^[80]

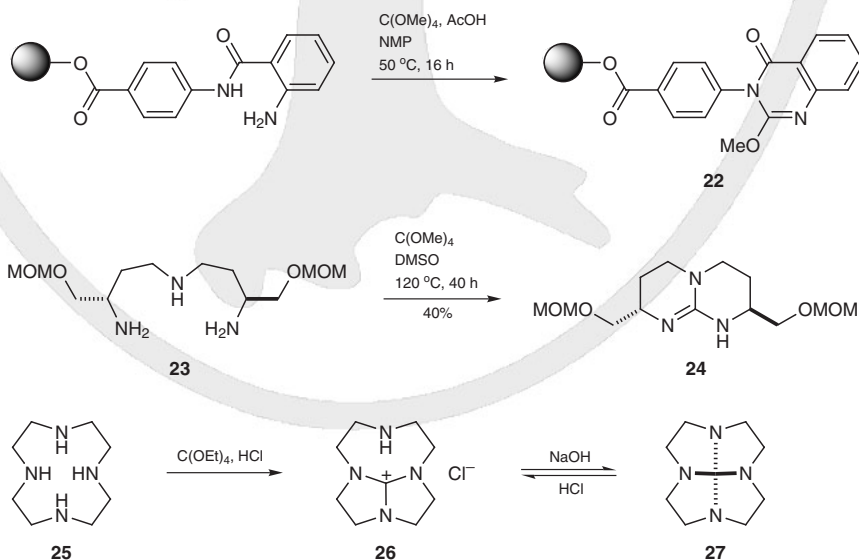
has been reported when they are heated with tetramethyl orthocarbonate at elevated temperatures.

Scheme 7 Tetraalkyl Orthocarbonates as Alkylating Reagents^[77,80]



The reaction of tetraalkyl orthocarbonates with furyl amines and sulfonamides results in the formation of imidocarbonates.^[81,82] Application of this methodology to polyamine substrates allows the synthesis of nitrogen heterocycles. Condensation of diamines with orthocarbonates results in ring annulation and has been utilized in the synthesis of alkoxy pyrimidines,^[83] alkoxy purines, and alkoxyimidazoles.^[84] These reaction conditions are sufficiently mild to be compatible with ester functionality, permitting the solid-phase synthesis of the 2-methoxyquinazolinone **22** using a hydroxymethyl phenoxy linker (Scheme 8).^[85] The bicyclic guanidine **24** is synthesized in a similar fashion by condensation of triamine **23** with tetramethyl orthocarbonate.^[86] Tetraethyl orthocarbonate reacts with both ammonia and aniline to form the corresponding guanidines rather than the tetraaminomethanes.^[87,88] However, in the case of 1,4,7,10-tetraazacyclododecane (**25**, cyclen), condensation with hydrochloric acid and tetraethyl orthocarbonate leads to the guanidinium hydrochloride **26**, which on extraction into benzene from basified aqueous solution gives the hygroscopic 1,4,7,10-tetraazatetracyclo[5.5.1.0^{4,13}.0^{10,13}]tridecane (**27**).^[89,90]

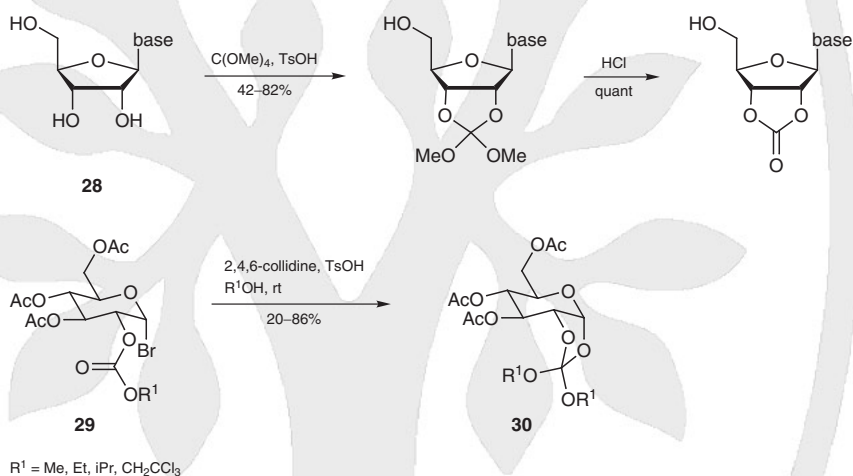
Scheme 8 Ring Annulation of Nitrogen Compounds by Condensation with Tetraalkyl Orthocarbonates^[85,86,89]



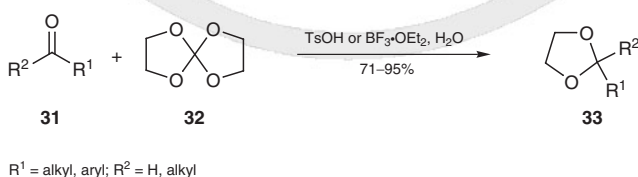
18.16.1.2.3

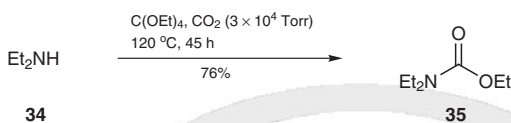
**Method 3:
Protecting Group Chemistry**

As discussed in Section 18.16.1.1.5, transesterification of polyols such as sugars with tetraalkyl orthocarbonates results in spiro orthocarbonates.^[91,92] These are stable toward basic conditions and have been used as protecting groups for di- and trihydroxy derivatives. Hydrolysis of these orthocarbonates under acidic conditions results in formation of the corresponding acid-stable cyclic carbonate.^[93,94] This strategy was demonstrated using ribonucleoside **28** (Scheme 9),^[95] and was utilized in the total synthesis of (+)-ryandol.^[96] Glucopyranosyl bromides **29** bearing a C2 alkoxy carbonyl group can be protected as the 2,3-orthocarbonate **30** by treatment with the appropriate alcohol under Koenigs–Knorr conditions.^[97] Orthocarbonates have also been introduced into sugars by the desulfurization of *O,O*-dialkyl thiocarbonates (frequently termed thionocarbonates) with methanolic silver(I) carbonate^[98] and of bis(*O*-thiocarbonyl) disulfides with pyridine.^[99] An orthocarbonate protection strategy has also been used in the solid-phase preparation of oligoribonucleotides.^[100]

Scheme 9 Protection of 1,2-Diols as Their Orthocarbonates^[95,97]

Orthocarbonates have also been used as reagents to introduce protecting groups on carbonyl and amine functionalities. The ethylene orthocarbonate **32** converts ketones and aldehydes **31** into their corresponding acetals **33** (Scheme 10).^[101] Simple aliphatic secondary amines such as **34** react with tetraalkyl orthocarbonates in the presence of carbon dioxide to form the corresponding alkyl carbamate **35**.^[102] This process involves two competing reactions: the esterification of the carbamic acid and the alkylation of the amine. The outcome of these reactions is dependent on the reactivities of the amine and the orthocarbonate and limits the generality of this approach.

Scheme 10 Protection of Ketones, Aldehydes, and Amines by Treatment with Tetraalkyl Orthocarbonates^[101,102]



18.16.2

Product Subclass 2:**Thioorthocarbonic Acid Tetraesters [Trialkoxy(alkylsulfanyl)methanes]**

Thioorthocarbonic acid tetraesters have not been widely reported in the literature. Only scattered reports dealing with their synthesis have been detailed, and the generality of these methods has not been explored extensively. Examples include the 1,3-dipolar cycloaddition of benzonitrile oxide with *O,O*-diphenyl thiocarbonate,^[103] and the oxidation of *O,O*-diorgano thiocarbonates with lead(IV) acetate, resulting in disulfide dimers.^[104,105]

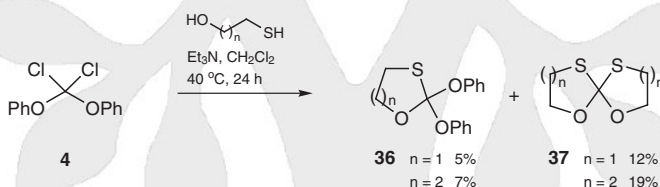
18.16.2.1

Synthesis of Product Subclass 2

18.16.2.1.1

Method 1:**Substitution Reaction of Dichloroacetals with 2-Sulfanylethanol**

The reaction of dichloroacetal **4** with sulfanyl alcohols in the presence of an amine base results in mixtures of the oxathiane **36** (*n* = 2) or oxathiolane **36** (*n* = 1) and the symmetrical spirans **37** (Scheme 11).^[48] The oxathiane/oxathiolane **36** can be recovered from the crude mixture by recrystallization, albeit in low isolated yields.

Scheme 11 Synthesis of Oxathianes or Oxathiolanes^[48]**2,2-Diphenoxy-1,3-oxathiane (36, *n* = 2); Typical Procedure:**^[48]

A soln of dichloroacetal **4** (1.46 g, 5.43 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 30 min to a stirred soln of 3-sulfanylpropan-1-ol (1.0 g, 10.9 mmol) and Et_3N (1.1 mL, 10.9 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at reflux for 24 h. The mixture was washed with 1 M NaOH (3 × 50 mL) and H_2O (50 mL). The organic layer was collected, dried (MgSO_4), and concentrated under reduced pressure to afford a creamy solid. The solid was extracted with hot hexane (4 × 50 mL) and the solvent was removed under reduced pressure to afford a white solid. This was sublimed (50 °C/0.2 Torr) to give the spiran **37** (*n* = 2) as fine white crystals; yield: 0.195 g (19%). The residual material was recrystallized (hexane) to give the 1,3-oxathiane as white crystals; yield: 0.10 g (7%); mp 101–102 °C.

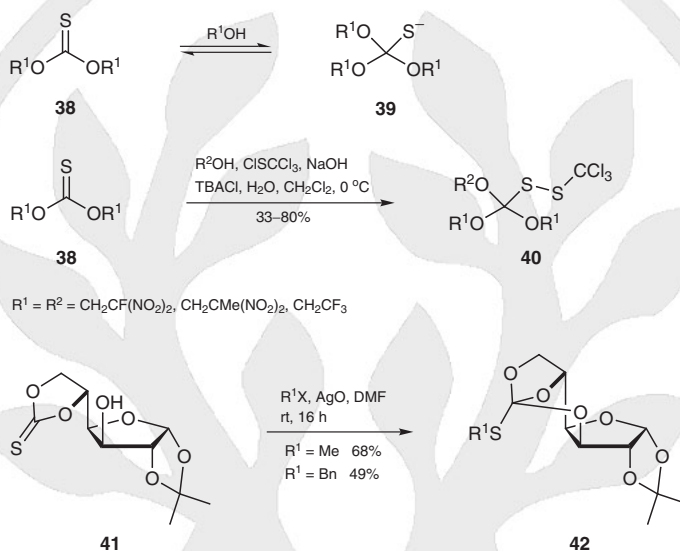
18.16.2.1.2

Method 2:**Nucleophilic Addition of Alcohols to *O,O*-Dialkyl Thiocarbonates**

Alkoxides form an unfavorable equilibrium with *O,O*-dialkyl thiocarbonates **38** which prevents the isolation of the trialkoxymethanethiolate **39** (Scheme 12). However, this thiolate can be trapped by trichloromethanesulfonyl chloride to form the disulfide **40** which can be isolated in good yield.^[106] The use of an alcohol that differs from the substituents on the *O,O*-dialkyl thiocarbonate results in mixed trialkoxy disulfides. Mixed trialkoxy disulfides can be converted by chlorination into chloroorthoformates, which can

then be used to synthesize mixed orthocarbonates.^[30] Attempts to methylate and benzylate the 3-position of glucufuranose **41** resulted in the unexpected formation of the thio-orthocarbonic acid tetraester **42**,^[107] due to internal nucleophilic attack by the 3'-hydroxy group followed by quenching of the resulting thiolate by the alkylating reagent.

Scheme 12 Trialkoxy Disulfides by Nucleophilic Addition to O,O-Dialkyl Thiocarbonates^[106,107]



Tris(2-fluoro-2,2-dinitroethoxy)[(trichloromethyl)disulfanyl]methane [40, R¹ = R² = CH₂CF(NO₂)₂]; Typical Procedure:^[106]

A well-stirred mixture of 2-fluoro-2,2-dinitroethanol (40 g, 0.26 mol) in CH₂Cl₂ (110 mL) and TBACl (2 g) in H₂O (100 mL) was cooled to 0 °C. A soln of 85% CSCI₂ in CCl₄ (6.06 g, 50 mmol) (**CAUTION: toxic**) and Cl₃CSCI (12.1 g, 65 mmol) in CH₂Cl₂ (30 mL) was added in a single portion, followed by dropwise addition of 50% aq NaOH (11.2 mL) over 30 min while maintaining the temperature at 0–4 °C. The reaction soln was kept slightly basic at 0 °C for 40 min by occasional addition of aq NaOH; the CH₂Cl₂ layer was then separated and dried and the volatiles were removed under reduced pressure to give an oily residue which was dissolved in CHCl₃ (60 mL). Cooling to –20 °C gave bis[tris(2-fluoro-2,2-dinitroethoxy)methyl] disulfide (1.55 g, 6%). Hexane was added to the CHCl₃ mother liquor until it began to cloud at rt. The soln was treated with charcoal and filtered through silica gel (CHCl₃/hexane 3:2). Addition of hexane to the filtrate followed by cooling to –78 °C gave white crystals. Recrystallization (CHCl₃/hexane) gave the product; yield: 21.2 g (65%); mp 55–57 °C; ¹H NMR (CDCl₃, δ): 4.84 (d).

18.16.3

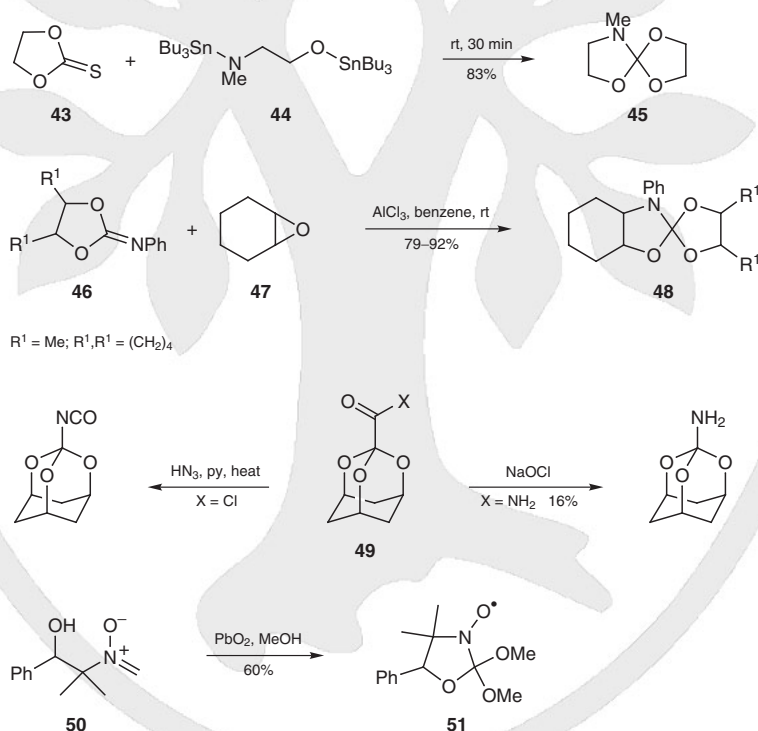
Product Subclass 3: Orthocarbamic Acid Triesters

Orthocarbamic acid triesters are generally referred to as carbamate acetals. Simple carbamate acetals and trioxazaspirans are acid sensitive. They are usually purified by distillation or recrystallization. This reactivity has led to research into their use as pro-drugs in drug delivery systems.^[108] Heterocyclic carbamate acetals such as 2,2-dialkoxy-substituted dihydrooxadiazoles and 2,5-dihydrooxazoles have been reported. They are generally more stable than the acyclic derivatives and can in some cases be purified by flash chromatography. Amide derivatives such as 3C₁₂-tris-C₁₀N⁺, however, are sufficiently stable to be used in the construction of synthetic bilayer membranes.^[109]

18.16.3.1

Synthesis of Product Subclass 3

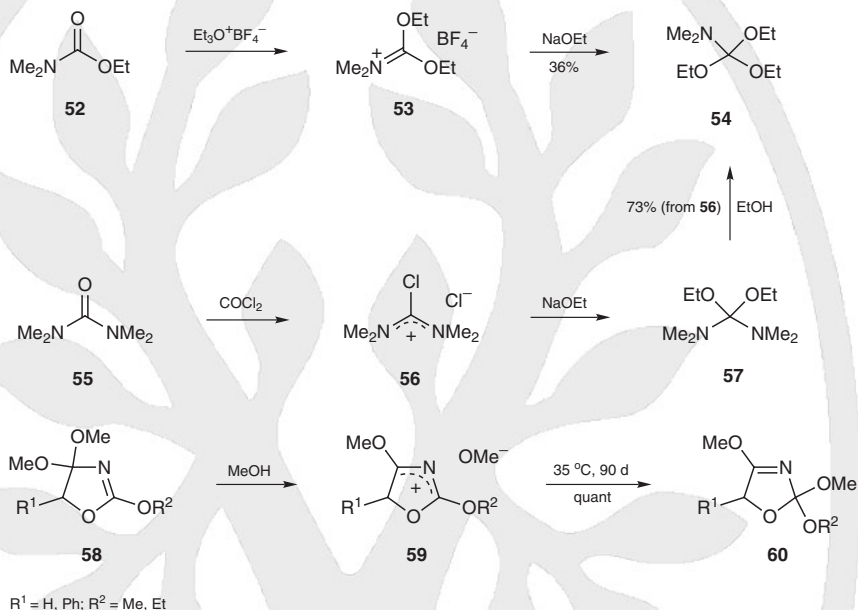
A number of approaches toward the synthesis of carbamate acetals have been reported, although the generality of these has not been thoroughly explored. Formation of the trioxaazaspiran **45** by desulfurization of 1,3-dioxolane-2-thione (**43**) with O,N-distannylated alkylamino alcohol **44** has been described (Scheme 13) and is an analogous process to that described for the synthesis of spiro orthocarbonates (Section 18.16.1.1.3).^[110,111] Secondary amines are required for this transformation. When O,N-distannylated primary amino alcohols are used, oxazolidinones are formed.^[111] The Lewis acid catalyzed addition of dioxolanamines **46** to epoxides such as **47** generally results in the formation of polymers or oxazolidin-2-ones via trioxaazaspiran intermediates. However, a number of factors influence the product distribution of these reactions. Both the stoichiometry and the configuration of the substrates are influential, and the conditions can be modified to favor the formation of 1:1 spiran adducts such as **48**.^[112] Other specific examples of carbamate acetal formation include Hofmann and Curtius rearrangements of the trioxaadamantane derivatives **49**^[68] and the oxidative cyclization of acyclic hydroxyarylnitrone **50** to give the stable oxazolidine nitroso radical **51**.^[113] Pentafluoroguanidine forms adducts with electrophilic reagents, and this has been utilized in the synthesis of {fluoro[(fluorosulfonyl)-oxy]amino}methanetriyl trifluoridosulfate [(FO₂SO)₃CNFOSO₂F] by its reaction with bis(fluorosulfonyl) peroxide [(FO₂SO)₂].^[114]

Scheme 13 Synthesis of Carbamate Acetals^[68,110,112,113]

18.16.3.1.1

Method 1:**Addition of Alkoxides to Dialkoxyaminocarbenium and Chloroformamidinium Salts**

The dialkoxy(amino)carbenium salt **53** (generated from carbamate **52** by addition of Meerwein's salt) reacts with alkoxides to give simple aliphatic carbamate acetals such as **54** in modest yields (Scheme 14).^[56]

Scheme 14 Synthesis of Carbamate Acetals^[56,115,116]

When the addition of alkoxide to chloroformamidinium salt **56** (generated from tetraalkylurea **55** by reaction with phosgene) is carried out in alcoholic media, the aliphatic carbamate acetals (e.g., **54**) are isolated in moderate to good yields.^[115] This is due to the facile nucleophilic substitution of one of the amino substituents by the alcohol in the urea acetal intermediate **57**.^[35] In the absence of alcohol, the urea acetal **57** is recovered. Analogous results are observed when ureas are treated with dimethyl sulfate in the presence of alkoxide.^[117] 4,5-Dihydrooxazole **58** slowly isomerizes to 2,5-dihydrooxazole **60** on gentle heating in alcoholic media via the carbenium intermediate **59**.^[116]

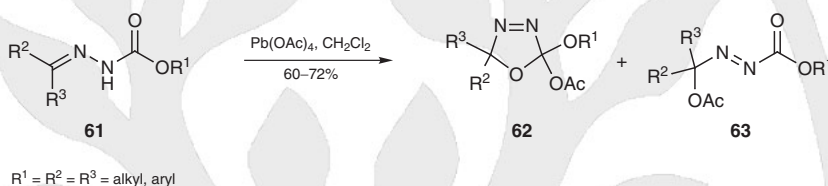
Dimethyl(triethoxymethyl)amine (54):^[115]

Chloroformamidinium salt **56** (171 g, 1.0 mol) was added to a soln of NaOEt [prepared by addition of Na (65.0 g, 2.8 mol) to abs EtOH (800 mL)] at 10–20 °C. The solvent was removed under reduced pressure and the residue was dissolved in H_2O (1 L). The soln was extracted with Et_2O , and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Vacuum distillation of the residue gave **54** as a colorless oil; yield: 140 g (73%); bp 63 °C/14 Torr.

18.16.3.1.2

Method 2:**2,5-Dihydro-1,3,4-oxadiazoles from Ketone Hydrazones by Oxidative Cyclization**

2,5-Dihydro-1,3,4-oxadiazoles **62** (commonly referred to as Δ^3 -1,3,4-oxadiazolines) are routinely prepared in good yield from ketone hydrazones **61** by oxidative cyclization with lead(IV) acetate, resulting in mixtures of **62** and the acyclic isomer **63**; the latter can be removed by vacuum distillation (Scheme 15).^[118] Alternative procedures for this transformation are the use of phenyliodonium acetate^[119] or electrochemical oxidation.^[120] Both alkoxy and phenoxy substituents can be tolerated. In the latter case, however, the resulting dihydrooxadiazole is less stable, resulting in problems with purification and handling.^[121] Aldehyde hydrazones ($R^3 = H$) are not compatible with this chemistry.^[122]

Scheme 15 Dihydrooxadiazoles from Ketone Hydrazones by Oxidative Cyclization^[118]

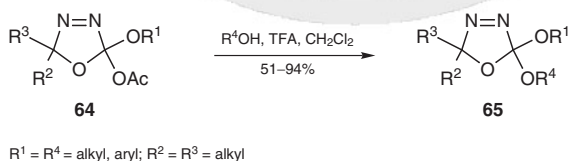
5,5-Dimethyl-2-phenoxy-2,5-dihydro-1,3,4-oxadiazol-2-yl Acetate (62**, $R^1 = Ph$; $R^2 = R^3 = Me$); Typical Procedure:**^[123]

A soln of the hydrazone **61** ($R^1 = Ph$; $R^2 = R^3 = Me$; 5 g, 20 mmol) in CH_2Cl_2 (60 mL) under dry N_2 was added dropwise over 1 h to a stirred soln of $Pb(OAc)_4$ (10.6 g, 24 mmol) at 0 °C. After the addition, the soln was kept in an ice bath for 2 h and then at rt overnight. The soln was washed with 10% aq $NaHCO_3$ (4×50 mL) and the organic layer was dried ($MgSO_4$). Filtration and concentration under reduced pressure left a yellow oil containing the desired product (ca. 70%) and an acyclic isomer **63** ($R^1 = Ph$; $R^2 = R^3 = Me$; ca. 30%). Purification by flash chromatography (silica gel, EtOAc/hexane 1:19) gave the dihydrooxadiazole; yield: 3.37 g (72%); 1H NMR ($CDCl_3$, δ): 1.35 (s, 3H), 1.66 (s, 3H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, δ): 21.2, 22.6, 23.9.

18.16.3.1.3

Method 3:**2,2-Diaryloxy- and 2,2-Dialkoxydihydrooxadiazoles from 2-Acetoxy-2-aryloxydihydrooxadiazoles**

Commonly, the products **64** of oxidative cyclization of ketone hydrazones (see Section 18.16.3.1.2) are not isolated from the crude product mixtures but converted directly into the dialkoxy derivatives **65** by nucleophilic substitution with an alcohol under acidic conditions (Scheme 16).^[118] The remaining acyclic byproduct **63** (see Scheme 15) can then be removed by selective hydrolysis with aqueous base. Although dialkoxydihydrooxadiazoles decompose on exposure to silica, the bis(aryloxy) analogues are sufficiently stable to be purified by flash chromatography.^[123]

Scheme 16 Synthesis of 2,2-Diaryloxy- and 2,2-Dialkoxydihydrooxadiazoles^[122]

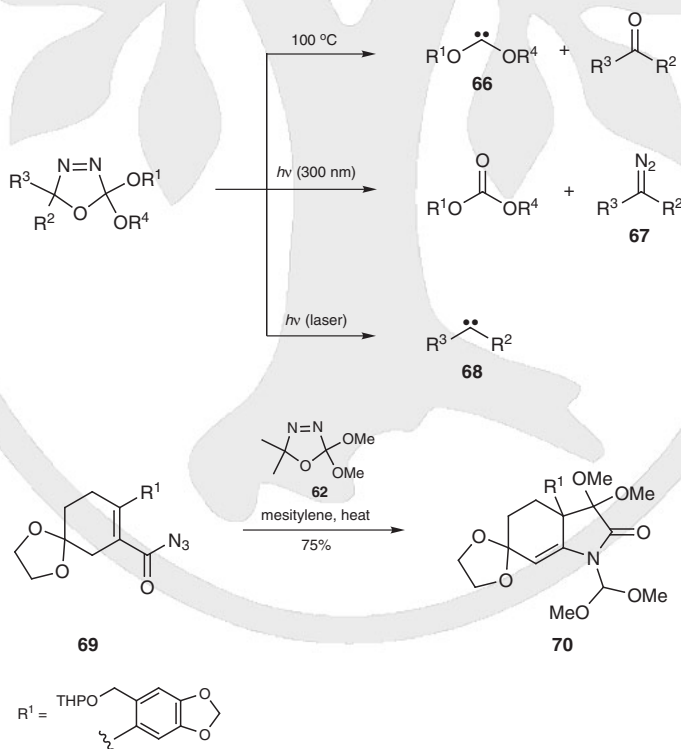
5,5-Bis(aryloxy)-2,5-dihydro-2,2-dimethyl-1,3,4-oxadiazoles 65 ($R^2 = R^3 = \text{Me}$);**General Procedure:**^[123]

A soln of a dihydrooxadiazole **64** ($R^2 = R^3 = \text{Me}$; 6 mmol) and a substituted phenol (18 mmol) in CH_2Cl_2 (40 mL) was acidified with catalytic TFA. After refluxing for 16 h, the soln was washed with 10% NaOH ($3 \times 30 \text{ mL}$). The organic layer was separated, dried (MgSO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography afforded the oxadiazole; yield: 51–94%.

18.16.3.2 Applications of Product Subclass 3 in Organic Synthesis**18.16.3.2.1****Method 1:****Dihydrooxadiazoles as Precursors of Dialkoxycarbenes**

Dihydrooxadiazoles can be used to generate a number of synthetically important reactive intermediates (Scheme 17). A detailed account of their chemistry is beyond the scope of this work, but has been reviewed in detail elsewhere.^[122,124,125] Extensive studies have focused on their thermolytic decomposition to generate synthetically useful dialkoxycarbenes **66**. An example of the successful application of this methodology in total synthesis is the reaction of dimethoxycarbene with the vinyl isocyanate generated in situ from the acyl azide **69** to give the hydroindolone **70**, a key intermediate in the synthesis of tazettine.^[126] Steady-state photolysis of dihydrooxadiazoles produces diazo compounds **67** that have been trapped with dipolarophiles. Laser flash photolysis generates dialkylcarbenes **68** and diazo compounds which are suitable for the study of the kinetics of fast reactions such as carbene rearrangements and diazo protonations.^[122]

Scheme 17 Generation and Reaction of Reactive Intermediates Using Dihydrooxadiazoles^[122,126]



18.16.4

Product Subclass 4:**Trialkoxy(phosphino)methanes and Trialkoxy(phosphoryl)methanes**

Reports of trialkoxy(phosphino)methanes and trialkoxy(phosphoryl)methanes are scarce. Trialkoxy(phosphino)methanes are also called dialkyl(trialkoxymethyl)phosphines (IUPAC), whereas trialkoxy(phosphoryl)methanes have been referred to as ortho esters of dialkoxyposphinylformic acid, phosphorylated formic acid, phosphorylated trialkyl orthoformates, and (trialkoxymethyl)phosphonates. Little is known about their chemistry, but heating trialkoxy(phosphoryl)methanes with dialkyl chloridophosphates is known to cleave the C–P bond, resulting in the isolation of tetraalkyl pyrophosphites.^[127]

18.16.4.1

Synthesis of Product Subclass 4

18.16.4.1.1

Method 1:**Addition to Trialkoxycarbenium Salts**

The reaction of electrophilic trialkoxycarbenium ions (Section 18.16.1.2.1) with metalated phosphorus nucleophiles provides facile and direct access to both trialkoxy(phosphino)methanes and trialkoxy(phosphoryl)methanes. The latter can also be prepared by the reaction of tetraalkyl pyrophosphates with tetraalkyl orthocarbonates in the presence of catalytic boron trifluoride–diethyl ether complex, which generates the trialkoxycarbenium salt in situ.^[127] Alternatively, the same reaction can be achieved without a catalyst by heating the two reagents at elevated temperatures.^[128]

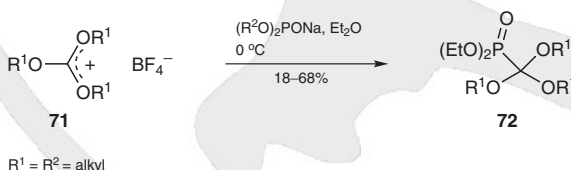
An alternative preparation of trialkoxy(phosphoryl)methanes is the anodic electrolysis of dialkoxyl(phosphoryl)methanes in a carbon dioxide saturated methanolic solution of sodium methoxide.^[129]

18.16.4.1.1.1

Variation 1:**Trialkoxy(phosphoryl)methanes by Addition of Sodium Dialkyl Phosphites**

Sodium dialkyl phosphites react smoothly with trialkoxycarbenium salts **71** to give trialkoxy(phosphoryl)methanes **72** in moderate yields (Scheme 18).^[130] Attempts to purify the product by distillation are complicated by decomposition to trialkyl phosphates and dialkyl carbonates unless excess boron trifluoride is removed by addition of excess sodium dialkyl phosphite.

Scheme 18 Reaction of Sodium Dialkyl Phosphites and Trialkoxycarbenium Salts To Give Trialkoxy(phosphoryl)methanes^[130,131]

**Diethyl Triethoxymethylphosphonate (72, R¹ = R² = Et); Typical Procedure:**^[130]

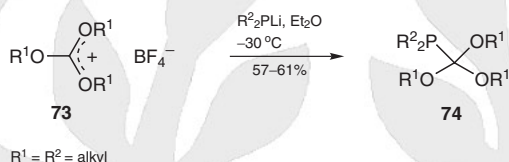
A soln of (EtO)₂PONa [prepared by boiling a mixture of Na (1.3 g, 57 mmol) and (EtO)₂P(O)H (7.6 g, 62 mmol)] in Et₂O (50 mL) was rapidly added to a suspension of triethoxycarbenium tetrafluoroborate [prepared by addition of BF₃•OEt₂ (9.6 g, 85 mmol) to a soln of C(OEt)₄ (9.6 g, 50 mmol) in Et₂O (50 mL)] at 0 °C and stirred for 30 min. Hexane (100 mL) was then added and the resulting precipitate removed by centrifugation. The solvent was removed under reduced pressure and the residue was distilled to give the product; yield: 8.5 g (60%); bp 85 °C/1 Torr; ¹³C NMR (δ): 111.6 (d, J = 259.7 Hz); ³¹P NMR (δ): 8.1.

18.16.4.1.1.2

Variation 2:**Trialkoxy(phosphino)methanes by Addition of Lithium Dialkylphosphides**

Trialkoxycarbenium ions **73** react rapidly with lithium dialkylphosphides to give trialkoxy(phosphino)methanes **74** (Scheme 19).^[132] Purification of these derivatives by distillation can be problematic since they are thermally unstable and condense on heating unless bulky substituents are present.

Scheme 19 Reaction of Lithium Dialkylphosphides with Trialkoxycarbenium Salts^[132]



Diisopropyl(triethoxymethyl)phosphine (74, R¹ = Et; R² = iPr); Typical Procedure:^[132]

A soln of iPr_2PLi [prepared by addition of a 1.4 M soln of BuLi in pentane (57 mL, 80 mmol) to a soln of iPr_2PH (9.5 g, 80 mmol) in THF (100 mL)] was added to a suspension of triethoxycarbenium tetrafluoroborate [prepared from $\text{C}(\text{OEt})_4$ (11.8 g, 80 mmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (15.1 g, 0.1 mol) in Et_2O (100 mL), with stirring, at -30°C]. The mixture was stirred for 30 min and then brought to rt, the solvent was concentrated under reduced pressure, hexane (150 mL) was added to the residue, and the oily precipitate was separated on a centrifuge. The hexane was removed under reduced pressure and the residue was distilled to give the product; yield: 16.3 g (61%); bp $72^\circ\text{C}/2\text{ Torr}$.

18.16.5

Product Subclass 5:**Dithioorthocarbonic Acid Tetraesters [Dialkoxybis(alkylsulfanyl)methanes]**

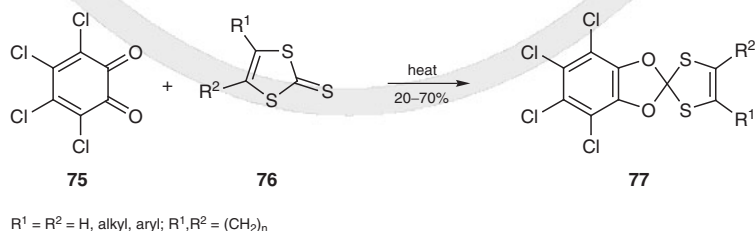
The chemistry of dithioorthocarbonic acid esters has received little attention. Spirocyclic dithioorthocarbonic acid esters have been used as monomers for tandem double ring-opening polymerizations.^[3] Derivatives containing tri- and tetracoordinate sulfur have not been reported, but have been proposed as possible intermediates in the rearrangement reactions of disulfonylcarbenes.^[133]

18.16.5.1

Synthesis of Product Subclass 5

Published methods for synthesizing dithioorthocarbonic acid esters are limited. The thermolysis of tetrachlorobenzo-1,2-quinone (**75**) with 1,3-dithiole-2-thiones **76**, however, is a useful method for constructing the spirocyclic dithioorthocarbonic acid esters **77** (Scheme 20).^[134]

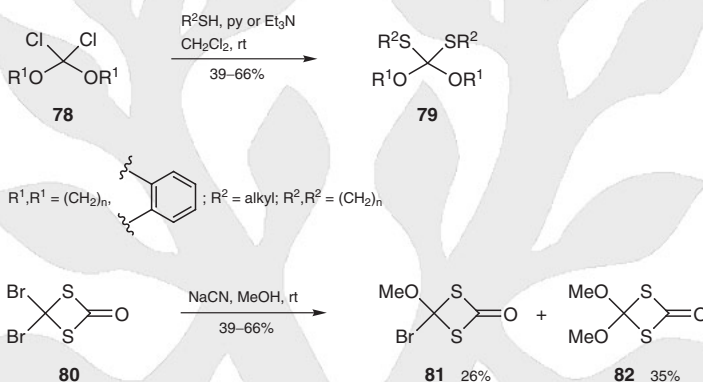
Scheme 20 Addition of Dithiolethiones to Tetrachlorobenzo-1,2-quinone^[134]



18.16.5.1.1

Method 1:**Substitution Reactions of Dihaloacetals and Dihalothioacetals**

Nucleophilic displacement of dichloroacetals **78** by thiols^[67] or dithiols^[48] in the presence of an amine base such as triethylamine or pyridine results in the formation of dithioorthocarbonic acid esters **79** in moderate to good yields (Scheme 21). The displacement of halogen with alcohol rather than thiol nucleophiles has also been reported in the case of 4,4-dibromo-1,3-dithietan-2-one (**80**).^[135] Nucleophilic displacement with methanol does not reach completion even with extended reaction periods and both mono- and disubstituted products **81** and **82** are isolated. Both are stable toward chromatography but polymerize on standing at room temperature. All the examples of this methodology are limited to heterocyclic substrates.

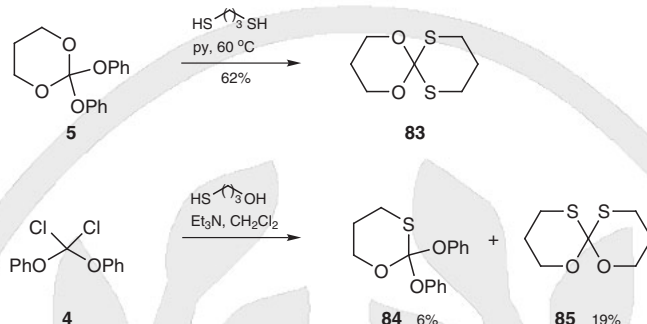
Scheme 21 Dithioorthocarbonic Acid Esters by Nucleophilic Substitutions^[48,135]**2,2-Diphenoxy-1,3-dithiane [79, $\text{R}^1 = \text{Ph}$; $\text{R}^2, \text{R}^{2'} = (\text{CH}_2)_3$]; Typical Procedure:**^[48]

A soln of the dichloroacetal **78** ($\text{R}^1 = \text{Ph}$; 10.0 g, 37.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 30 min to a stirred soln of propane-1,3-dithiol (4.02 g, 37.0 mmol) and pyridine (5.85 g, 74.0 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at rt for 20 h. The organic extract was washed with 1 M NaOH (3×50 mL) and H_2O (50 mL). The organic layer was collected, dried (MgSO_4), and concentrated under reduced pressure to afford a yellow solid. Recrystallization ($\text{CH}_2\text{Cl}_2/\text{EtOH}$) afforded off-white crystals; yield: 7.43 g (66%); mp 110–112 °C; ^1H NMR (CDCl_3 , δ): 3.04–3.02 (m, 4H, SCH_2), 2.14–2.08 (m, 2H, SCH_2CH_2); ^{13}C NMR (CDCl_3 , δ): 30.3, 24.8.

18.16.5.1.2

Method 2:**Transesterification of Orthocarbonates with Dithiols**

Refluxing diphenoxy acetals such as **5** with dithiols under nonnucleophilic basic conditions produces symmetrical spirocyclic dithioorthocarbonates, e.g. **83** (Scheme 22).^[48] Analogous transesterification of the diphenoxy thioacetals with diols also leads to **83**, albeit in a much lower yield (37%). Direct conversion of dichloro acetal **4** into the six-membered spirocyclic dithioorthocarbonate **85** by treatment with two equivalents 1-sulfanylpentan-3-ol under these conditions has been reported, although this process is accompanied by the competing formation of oxathiane **84**. Attempts to reproduce this chemistry with the five-membered system were unsuccessful owing to the instability of the final spirocyclic dithioorthocarbonates.

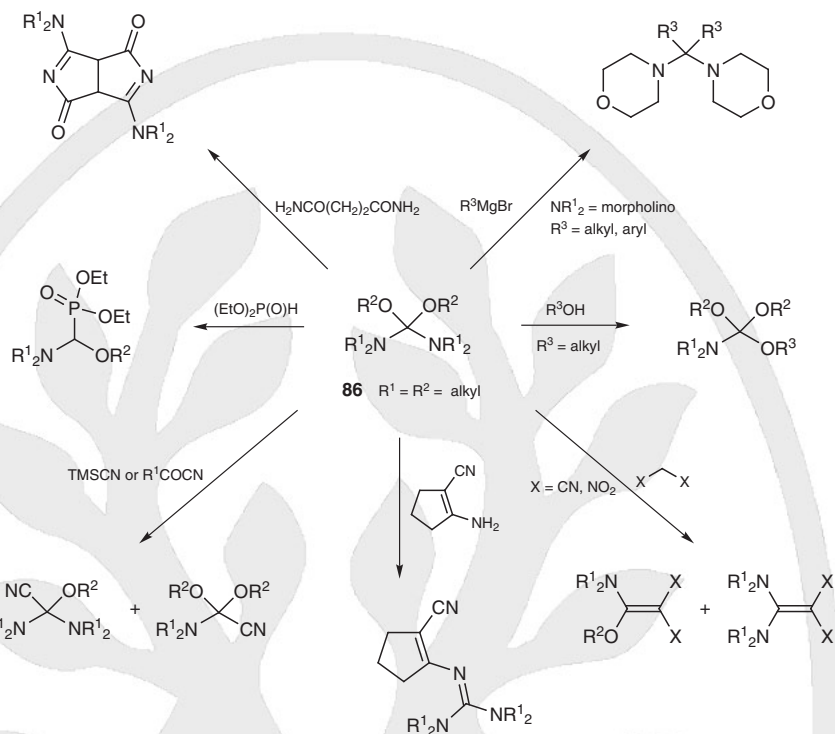
Scheme 22 Transesterification of Orthocarbonates with Dithiols under Basic Conditions^[48]**1,5-Dioxo-7,11-dithiaspiro[5.5]undecane (**83**):**^[48]

A soln of 2,2-diphenoxy-1,3-dioxane (**5**; 10.0 g, 36.8 mmol), propane-1,3-dithiol (4.38 g, 40.5 mmol), and pyridine (8.9 mL, 0.11 mol) was stirred at 60 °C for 36 h. The organic extract was washed with 1 M NaOH (3 × 50 mL) and H₂O (50 mL). The organic layer was collected, dried (MgSO₄), and concentrated under reduced pressure. The residue was extracted with hot hexane (3 × 50 mL) and the solvent was removed under reduced pressure to afford an off-white solid. This material was sublimed (50 °C/0.05 Torr) to yield white crystals; yield: 4.36 g (62%); mp 60–62 °C; ¹H NMR (CDCl₃, δ): 4.15 (t, 4H, *J* = 5.6 Hz, OCH₂), 3.00–2.97 (m, 4H, SCH₂), 2.08–2.03 (m, 2H, SCH₂CH₂), 1.85 (quin, 2H, *J* = 5.6 Hz, OCH₂CH₂); ¹³C NMR (CDCl₃, δ): 110.5, 61.8, 29.5, 25.8, 24.6.

18.16.6

Product Subclass 6:
Orthocarbonic Acid Diester Diamides (Dialkoxydiaminomethanes)

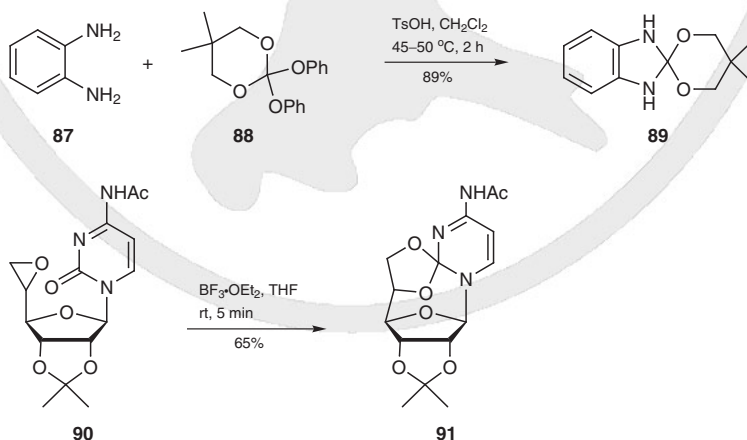
Orthocarbonic acid diester diamides are carbamide acetals, a term which denotes an orthocarbonic acid derivative with one or two amino and two or three alkoxy groups bonded to a central carbon.^[136] Orthocarbonic acid diester diamides are commonly referred to as tetraalkylurea dialkyl acetals, or more often simply urea acetals.^[35] The chemistry of simple alkyl and aryl urea acetals **86** has been examined in detail (Scheme 23). Alcohols,^[35] trimethylsilyl cyanide,^[137] acyl cyanides,^[41] and Grignard reagents^[138] displace one or both of the amino groups, whereas active methylene compounds,^[35] amines,^[139] amides,^[140] and phosphites^[141] participate in condensation reactions when treated with the urea acetals **86**.

Scheme 23 The Chemistry of Urea Acetals^[35,41,56,137–141]

18.16.6.1

Synthesis of Product Subclass 6

In addition to the methods described (*vide infra*), specific approaches to spirocyclic urea acetals have been reported. Transesterification of the benzene-1,2-diamine (**87**) with orthocarbonate **88** under acidic conditions gives the symmetrical dioxadiazaspiran **89**.^[44] Intramolecular acetalization has been used to form the anhydro nucleoside **91** containing two oxygen bridges within the molecule from epoxide **90** (Scheme 24).^[142,143]

Scheme 24 Symmetrical Dioxadiazaspirans by Esterification and Intramolecular Acetalization of Nucleoside Epoxides^[44,143]

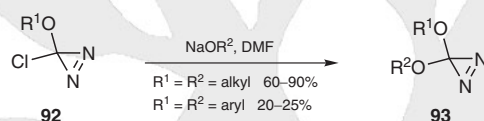
18.16.6.1.1 Method 1:
Substitution Reactions of Halomethanes

The nucleophilic displacement of halomethanes by amines or alcohols has been used as a synthetic approach toward urea acetals, although examples using this methodology have been limited to cyclic substrates such as the halogenated diazirines, benzodioxoles, and imidazolidines.

18.16.6.1.1.1 Variation 1:
Substitution Reactions of 3-Alkoxy-3-chlorodiazirines with Alkoxides

Dialkoxydiazirines **93** are synthetically useful precursors of dialkoxycarbenes (Section 18.16.6.2.1).^[144] Their synthesis is achieved by the nucleophilic displacement of 3-alkoxy-3-halodiazirines **92** with sodium alkoxide in dimethylformamide (Scheme 25).^[145] Both symmetrical and nonsymmetrical diazirines can be synthesized in this manner with alkoxy,^[145] fluorinated alkoxy,^[146,147] and phenoxy substituents.^[148] The diazirines are unstable at room temperature, decomposing rapidly to the carbenes. However, they can be generated at low temperatures (−50 to −30 °C) and be purified prior to their use by passage through short silica gel columns.

Scheme 25 Synthesis of Dialkoxydiazirines^[148,149]



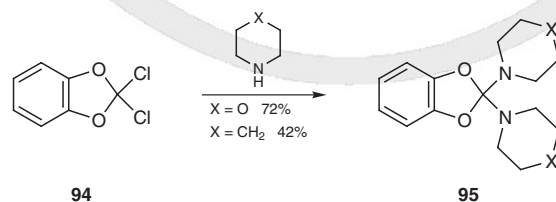
3,3-Dimethoxy-3H-diazirine (93, R¹ = R² = Me); Typical Procedure:^[149]

A cold (0 °C) soln of 3-chloro-3-methoxydiazirine^[149] in anhyd DMF was added to NaOMe (4.5 g, 83 mmol) in anhyd DMF (30 mL) and cooled to −40 °C so as to maintain a temperature of below −20 °C. Stirring was continued at −50 to −30 °C for 30 min after the addition. The mixture was then diluted with crushed ice/H₂O (30 mL) and then extracted with cold pentane (3 × 15 mL). The pentane extract was back-washed with ice water and then dried (CaCl₂) at −20 °C for 20 min. The pentane soln was then filtered through silica gel to give the product as a ca. 0.07 M pentane soln; yield: ca. 60%.

18.16.6.1.1.2 Variation 2:
Unsymmetrical Dioxadiazaspirans by Substitution Reactions of 2,2-Dihaloacetals with Amines

Nucleophilic displacement of 2,2-dichloro-1,3-benzodioxole (**94**) with cyclic amines such as piperidine^[67] or morpholine^[138] gives 1,3-benzodioxole-2,2-diamines **95** in moderate to good yields (Scheme 26).

Scheme 26 Synthesis of 1,3-Benzodioxole-2,2-diamines^[67,138]



2,2-Dimorpholino-1,3-benzodioxole (95, X = O):^[138]

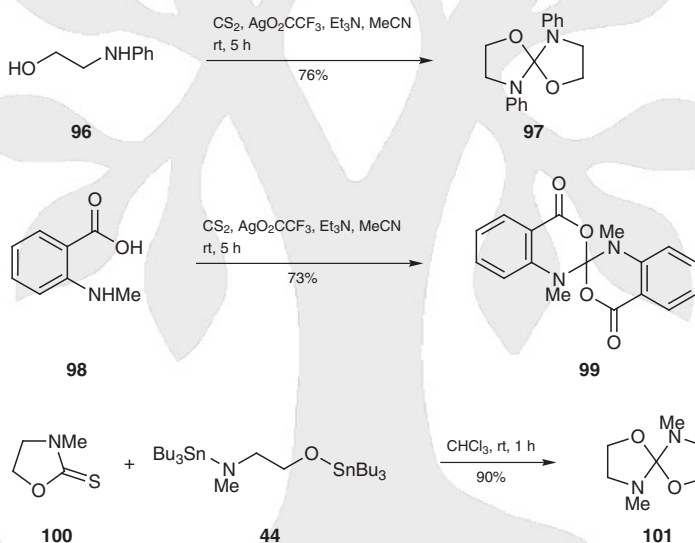
A soln of morpholine (10.4 g, 119 mmol) in Et₂O (10 mL) was added to a soln of 2,2-dichloro-1,3-benzodioxole (5.0 g, 26 mmol) in Et₂O (18 mL), with stirring, at 0 °C. The mixture was allowed to stand at rt for 2 h and then the organic layer was washed many times with H₂O and then dried (CaCl₂). The Et₂O was removed under reduced pressure and the residue was recrystallized (EtOH); yield: 5.5 g (72%); mp 120–122 °C; ¹H NMR (CDCl₃, δ): 2.75 (m, 8H, NCH₂), 3.60 (m, 8H, OCH₂), 6.68 (m, 4H, C₆H₄).

18.16.6.1.2

Method 2:**Symmetrical Dioxadiazaspirans by Desulfurization of Carbon Disulfide or *N*-Alkylthiocarbamates with Amino Alcohols**

Carbon disulfide is a useful material in the synthesis of a number of orthocarbonates (Section 18.16.1.1.3) and can also be used analogously in the synthesis of symmetrical dioxadiazaspirans. Although the generality of this method has yet to be explored fully, the silver-mediated desulfurization of carbon disulfide with 2-anilinoethanol (**96**) yields the dioxadiazaspiran **97** in high yield (Scheme 27).^[55] This methodology also tolerates carboxylic acids in place of the alcohols. This is successfully demonstrated using *N*-methylantranilic acid (**98**), which is used in the synthesis of the spiran **99**.

Scheme 27 Synthesis of Symmetrical Dioxadiazaspirans by Desulfurization of Carbon Disulfide or *N*-Alkylthiocarbamates^[55,111]



An alternate method for synthesizing dioxadiazaspirans such as **101** involves the desulfurization of *N*-alkylthiocarbamates (e.g., **100**) with distannylated alkylamino alcohols (e.g., **44**) (Scheme 27).^[111] This process is analogous to that described for the synthesis of orthocarbonates from *O,O*-dialkyl thiocarbonates (Section 18.16.1.1.4). Attempts to synthesize the unsymmetrical dioxadiazaspirans from dioxolane-2-thiones and distannylated diamines resulted instead in the formation of imidazolidine-2-thiones.^[111]

4,9-Diphenyl-1,6-dioxo-4,9-diazaspiro[4.4]nonane (97); Typical Procedure:^[55]

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

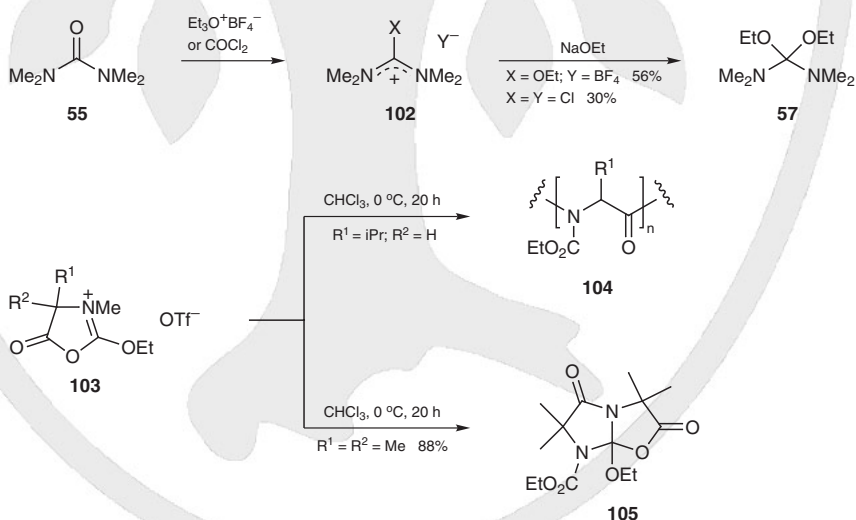
AgO₂CCF₃ (1.10 g, 5 mmol) was added portionwise over 3 min to a soln of CS₂ (76 mg, 1 mmol), 2-anilinoethanol (330 mg, 2.4 mmol), and Et₃N (710 mg, 7.0 mmol) in MeCN (5 mL) at 0 °C. The mixture was then stirred continuously for 5 h at rt. The mixture was concentrated under reduced pressure, EtOAc was added, and the Ag₂S was removed by filtration. Column chromatography (silica gel, hexane/EtOAc 1:1) gave the product as a colorless powder; yield: 215 mg (76%); mp 110 °C; ¹H NMR (CDCl₃, δ): 3.86 (m, 4H), 4.25 (m, 4H); ¹³C NMR (CDCl₃, δ): 45.1, 46.4, 61.2, 62.4.

18.16.6.1.3

Method 3:**Addition of Alkoxides to Uronium and Formamidine Salts**

The reaction of tetramethylurea (**55**) with Meerwein's salt generates the uronium tetrafluoroborate **102** (X = OEt; Y = BF₄⁻), which can be converted into the urea acetal **57** by addition of sodium ethoxide (Scheme 28).^[56] Phosgene can be used to generate the tetramethyl chloroformamidine chloride **102** (X = Y = Cl), which is similarly converted into the urea acetal **57**.^[115] Care must be taken to exclude ethanol from the reaction to avoid the facile nucleophilic displacement of one of the amino groups by ethanol to give the carbamate acetal **54** (see Section 18.16.3.1.1, Scheme 14). The reactions of **102** (X = OEt; Y = BF₄⁻) with sodium hydride, amines, and trimethyl borate have been studied. These result in complex mixtures and are not a viable route toward these derivatives.^[150] Addition of methyl trifluoromethanesulfonate to 2-alkoxyoxazolones generates the salts **103**, which undergo cationic ring-opening polymerization to **104** or dimerization pathways to **105**, depending on the substitution at the 4-position.^[151]

Scheme 28 Synthesis of Urea Acetals from Uronium and Formamidine Salts^[56,115,151]

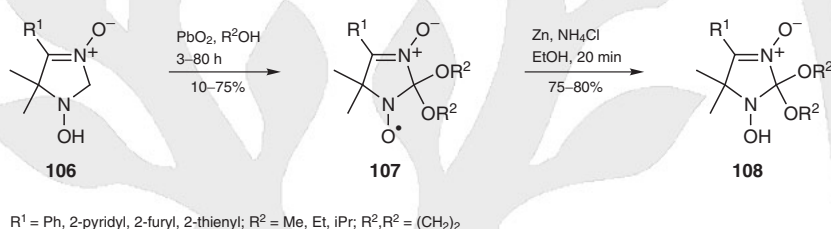
**Diethoxy-*N,N,N',N'*-tetramethylmethanediamine (57):**^[115]

A soln of *N,N,N',N'*-tetramethylchloroformamidine chloride (**102**, X = Y = Cl; 170 g, 1.0 mol) in MeCN (400 mL) was added dropwise to a suspension of NaOEt (136 g, 2.0 mol) in MeCN (300 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and the solid was then removed by filtration. The solvent was removed by distillation (50 °C/760 Torr) and the residue purified by fractional distillation; yield: 58.0 g (30%); bp 61–65 °C/18 Torr.

18.16.6.1.4

Method 4:
Oxidation of Dihydroimidazole *N*-Oxides

A series of 2,2-dialkoxydihydroimidazole nitroxyl radicals **107** have been synthesized as part of nuclear magnetic resonance,^[152] photoelectron,^[153] and electron paramagnetic resonance^[154] spectroscopic studies investigating the effects of different substituents at the 2- and 4-positions of these stable species (Scheme 29). They are generated from *N*-hydroxydihydroimidazoles **106** by oxidation in the presence of an alcoholic solvent.^[155] The radicals **107** are typically red or brown and are sufficiently stable to be purified by flash chromatography. Although a range of aromatic substituents can be tolerated at the 4-position, increasing the steric bulk of the alcohol strongly retards the reaction. Thus when propan-2-ol is used the reaction proceeds slowly (80 hours), but no reaction is observed when butanol is used.^[156] Moreover, as the size of the alcohol increases, the stability of the resulting nitroxyl radical **107** decreases.^[157] Manganese(IV) oxide is the oxidant of choice when ethylene glycol is used as the solvent.^[156]

Scheme 29 Oxidative Alkoxylation of 4*H*-Imidazole *N*-Oxides^[155,156]


Reduction of the radical **107** with zinc in the presence of ammonium chloride results in the corresponding *N*-hydroxy-4*H*-imidazoles **108** (Scheme 29). This process is concomitant with the onset of a blue coloration of the mixture.

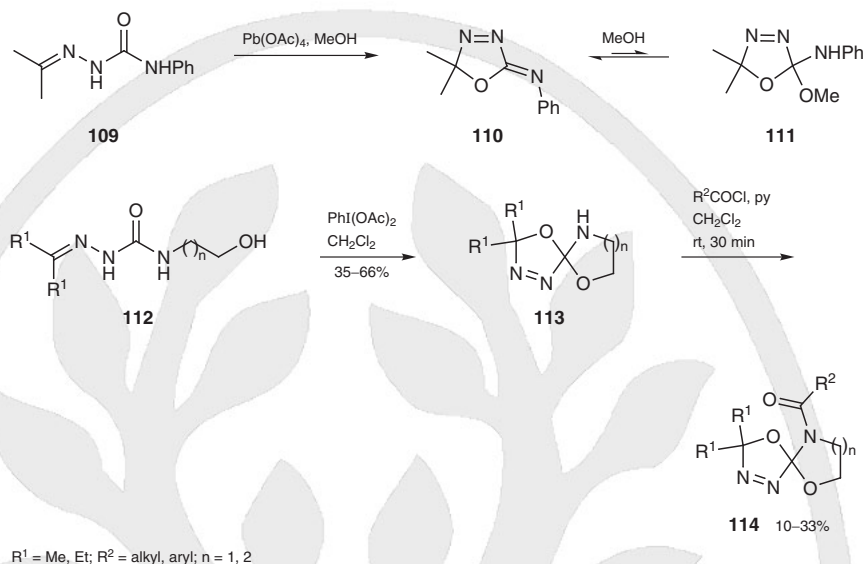
2,2-Dimethoxy-5,5-dimethyl-4-(2-pyridyl)-2,5-dihydro-1*H*-imidazol-1-oxyl 3-Oxide (107, R¹ = 2-Pyridyl; R² = Me); Typical Procedure:^[155]

PbO₂ (11.47 g, 48.0 mmol) was added to a soln of 5,5-dimethyl-4-(2-pyridyl)-2,5-dihydro-1*H*-imidazol-1-ol 3-oxide (1.0 g, 4.8 mmol) in MeOH (80 mL) and the mixture was stirred for 8 h. Then the oxidant was filtered off, the filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (silica gel, CHCl₃) to give the product as a solid; yield: 0.96 g (75%); mp 101–102 °C.

18.16.6.1.5

Method 5:
Oxidation of Acetone Semicarbazones

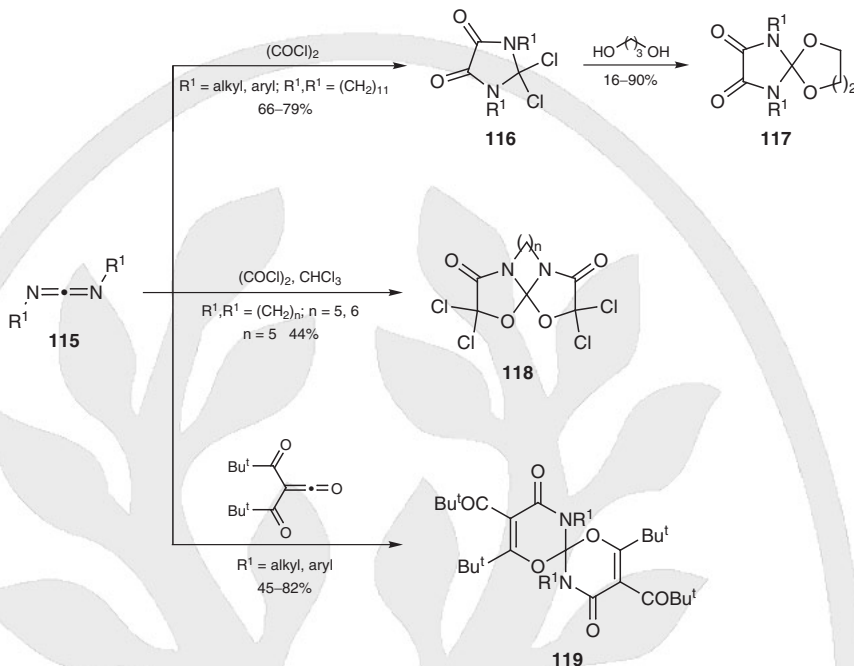
Spiroamino(oxy)dihydrooxazoles [usually termed spiroamino(oxy)-Δ³-1,3,4-oxadiazolines] **113** are useful precursors of amino(oxy)carbenes.^[158,159] Attempts to synthesize these derivatives by nucleophilic displacement of acetoxy groups in an analogous manner to that described previously for 2,2-dialkoxydihydrooxazoles (Section 18.16.3.1.3) results in poor yields of the desired products.^[160] The oxidation of semicarbazone **109** with lead(IV) acetate in methanol forms a mixture of **110** and **111** which cannot be separated, owing to the instability of the dihydrooxazole **111** (Scheme 30). However, the tethered intramolecular variant of this reaction with **112** does result in a stable spiran **113** which is sufficiently robust that it can be isolated by chromatography. *N*-Sulfonates and acetyl derivatives **114** can subsequently be synthesized under standard conditions. The nature of the *N*-substituent has been shown to effect the rate of carbene generation during thermolysis.

Scheme 30 Spirocyclic Amino(oxy)dihydrooxazoles from Acetone Semicarbazones by Oxidation^[160]**3,3-Dimethyl-4,6-dioxo-1,2,9-triazaspiro[4.4]non-1-ene (113, R¹ = Me; n = 2);****Typical Procedure:**^[160]

Under anhyd N₂, a soln of PhI(OAc)₂ (7.47 g, 23 mmol) in CH₂Cl₂ (150 mL) was added dropwise over 1–2 h to a stirred soln of semicarbazone **112** (R¹ = Me; n = 2; 3.50 g, 22 mmol) in CH₂Cl₂ (200 mL) at 0 °C. After the addition was complete, the soln was kept in the ice bath for another 2 h before it was allowed to warm to rt overnight. After about half the solvent had been removed under reduced pressure, the soln was washed with 5% aq NaHCO₃ (4 × 30 mL), followed by brine (30 mL). Drying (MgSO₄), filtration by gravity, and evaporation of the solvent afforded an oil (ca. 6 g) containing a mixture of **113** and PhI, which were separated by radial chromatography (silica gel, EtOAc/hexane 1:10 to 3:2). This typically gave slightly impure **113**; yield: 1.63 g (47%). Further purification by bulb-to-bulb distillation gave pure **113** as a colorless oil; bp 30–40 °C/2 Torr; ¹H NMR (CDCl₃, δ): 1.48 (s, 3H, CH₃), 1.53 (s, 3H, CH₃), 2.87 (br s, 1H, NH), 3.44–3.54 (m, 2H, NCH₂), 4.14–4.33 (m, 2H, OCH₂); ¹³C NMR (CDCl₃, δ): 24.5, 24.6, 44.7, 67.9, 117.7, 139.2.

18.16.6.1.6**Method 6:****Symmetrical Dioxadiazaspirans from Dialkylcarbodiimides**

Symmetrical 2,2-dichloro-1,3-dialkylimidazolidine-4,5-diones **116** are generated from dialkylcarbodiimides **115** by addition of oxalyl chloride (Scheme 31).^[161] These undergo substitution reactions with simple aliphatic diols to give the spirans **117**,^[161,162] whereas treatment with water results in hydrolysis to give the corresponding trione.^[163] The outcome of the imidazolidine formation step, however, is dependent on the structure of the carbodiimide used. Cyclic carbodiimides have been shown to react with two equivalents of oxalyl chloride to form the dimers **118**. However, in larger ring systems the reaction can proceed in the standard fashion to form the corresponding dihalide **116**.^[164] Dipivaloylketene adds to carbodiimides in a 2:1 ratio, resulting in the formation of symmetrical spirocyclic dimers **119** in high yields.^[165]

Scheme 31 Symmetrical Dioxadiazaspirans from Carbodiimides^[161–165]

2,8-Di-*tert*-butyl-3,9-bis(2,2-dimethylpropanoyl)-5,11-diisopropyl-1,7-dioxo-5,11-diaza-spiro[5.5]undeca-2,8-diene-4,10-dione (119, $R^1 = \text{iPr}$):^[165]

Diisopropylcarbodiimide (**115**, $R^1 = \text{iPr}$; 130 mg, 1.0 mmol) was added to dipivaloylketene (420 mg, 2.0 mmol). After the strongly exothermic reaction ceased, the resulting solid was treated with hexane and then removed by filtration. Recrystallization (toluene) gave the product; yield: 450 mg (82%); mp 200–202 °C; ^1H NMR (CDCl_3 , δ): 1.18 and 1.28 (s, 36H, *t*-Bu), 1.47 and 1.56 [d, $J = 6$ Hz, 12H, $\text{CH}(\text{CH}_3)_2$], 3.82 [hept, $J = 6$, 2 Hz, 4H, $\text{CH}(\text{CH}_3)_2$]; ^{13}C NMR (CDCl_3 , δ): 19.0, 21.2, 28.8, 29.0, 37.0, 45.3, 50.1, 113.2, 115.5, 162.5, 164.2, 210.2.

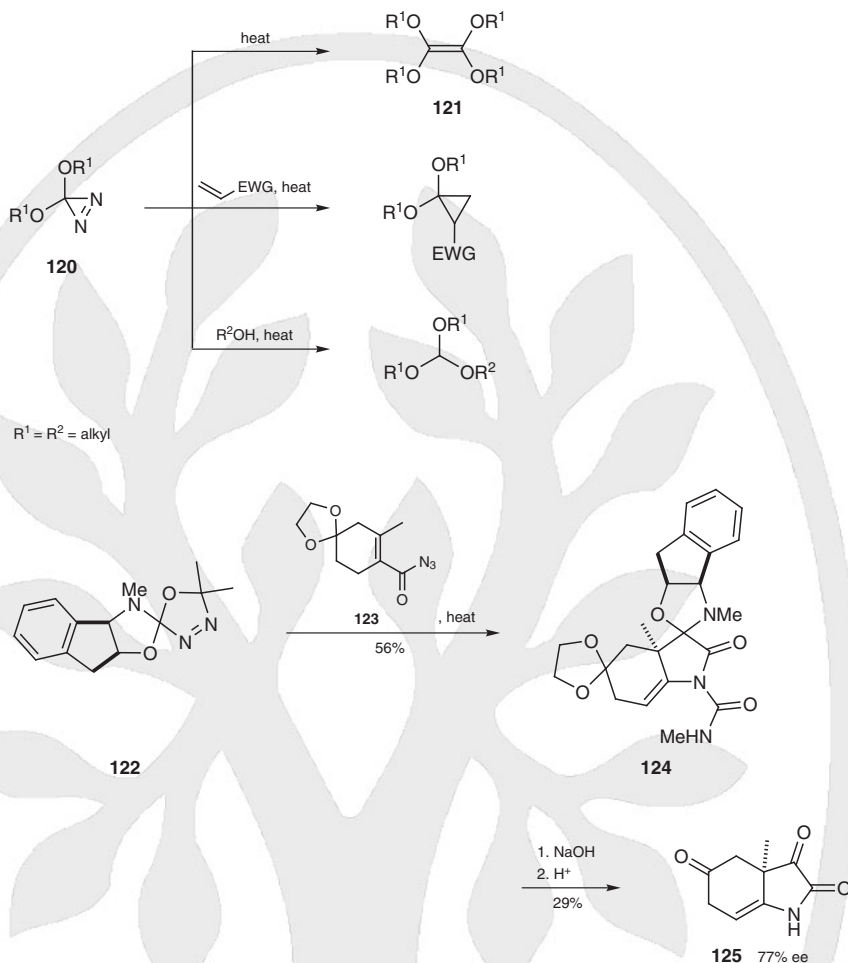
18.16.6.2 Applications of Product Subclass 6 in Organic Synthesis

18.16.6.2.1

Method 1:

Dialkoxydiazirines and Amino(oxy)dihydrooxazoles as Dialkoxycarbene Precursors

The use of diazirines and dihydrooxazoles as carbene precursors has been extensively reviewed.^[122,124,144] Dialkoxydiazirines **120** have been used to generate a series of dialkoxy-carbenes which have been trapped by insertion into alcoholic^[149,166] and acrylic substrates (Scheme 32).^[145,167] In the absence of a trapping agent, dimers **121** are isolated. Diaryl-oxydiazirines have been studied and their thermolysis affords the expected carbenes, whereas photolysis results in both carbene and aryloxy radicals.^[148]

Scheme 32 Synthetic Applications of Thermolytically Generated Diheterocarbenes^[167,168]

Spiro amino(oxy)dihydrooxazoles decompose at 90 °C in benzene to generate amino(oxy)-carbenes, which have been trapped by phenols and isocyanates.^[158] Chirality can be incorporated into these precursors and into the resulting carbene. Asymmetric induction using this methodology has been demonstrated in the synthesis of (–)-hydroisatin **125**. The reaction of the chiral amino(oxy)dihydrooxazole **122** with a vinyl isocyanate (generated in situ from acyl azide **123**) was shown to give the advanced intermediate **124**, which on de-protection produces (–)-hydroisatin (**125**) in 77% ee (Scheme 32).^[168]

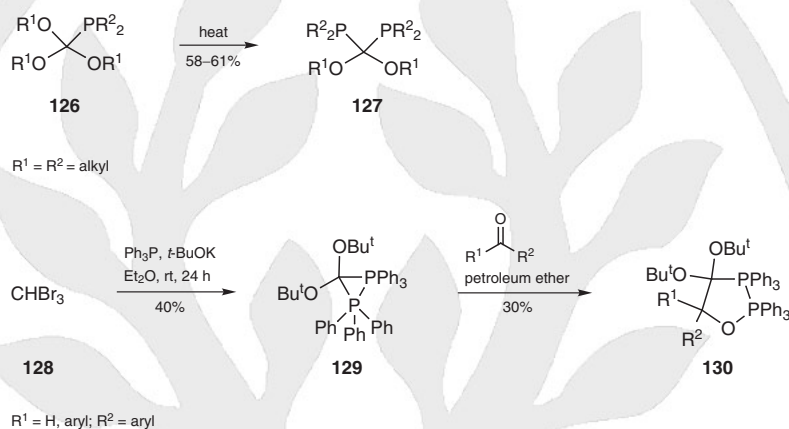
18.16.7

Product Subclass 7:
Dialkoxybis(phosphino)methanes and Dialkoxybis(phosphoryl)methanes

Dialkoxybis(phosphoryl)methanes (formerly also termed dialkoxymethylene bisphosphonic acids/phosphonates or tetraalkylcarbonyl diphosphate acetals) in common with the other bis(phosphoryl)methanes have been shown to have interesting complexation chemistry^[169] and biological activity. Their specific affinity for bone has led to their use in treating conditions such as Paget's disease and osteoporosis.^[170]

18.16.7.1 Synthesis of Product Subclass 7

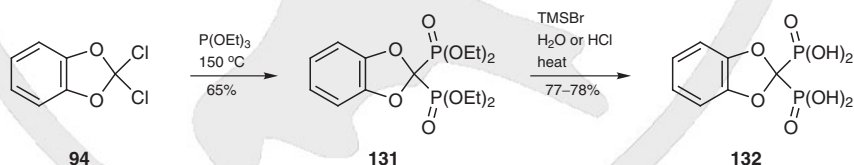
Dialkoxybis(phosphino)methanes **127** are formed by the thermolysis of trialkoxy(phosphino)methanes **126** (Scheme 33).^[132] In a deviation from the standard Wittig reaction, the diphosphirane **129** is formed by treatment of bromoform (**128**) with potassium *tert*-butoxide and triphenylphosphine.^[171] The addition of ketones to the diphosphirane **129** results in the isolation of the oxadiphospholane **130**.

Scheme 33 Synthesis of Dialkoxybis(phosphino)methanes^[132,172]

18.16.7.1.1

Method 1: Substitution Reactions of Dichloroacetals with Trialkyl Phosphites

The Arbuzov reaction of phosgene and trimethyl phosphite was originally reported to form a carbonyldiphosphate, which formed a hydrate with water.^[173] Further studies, however, demonstrated that the reaction is a chlorination of the trialkyl phosphite.^[174] Arbuzov reactions of 2,2-dichlorobenzodioxoles **94** are found to be effective methods of synthesizing bis(phosphoryl)benzodioxoles **131** in good yields (Scheme 34).^[175] Hydrolysis of the phosphonates **131** is achieved directly with hydrochloric acid, or indirectly via the trimethylsilyl ester.^[176] The aromatic ring of the diphosphonic acid **132** can undergo electrophilic substitution with bromine to give dibrominated benzodioxoles.

Scheme 34 Dialkoxybis(phosphoryl)methanes by the Arbuzov Reaction^[176]

Diethyl [2-(Diethoxyphosphoryl)-1,3-benzodioxol-2-yl]phosphonate (**131**):^[176]

A mixture of 2,2-dichloro-1,3-benzodioxole (19.1 g, 0.1 mol) and P(OEt)_3 (35.6 g, 0.215 mol) was heated for 5 h at 150–160 °C. The byproducts were then removed by distillation under reduced pressure (bp 155–158 °C/0.01 Torr) to give the ester; yield: 25.4 g (65%).

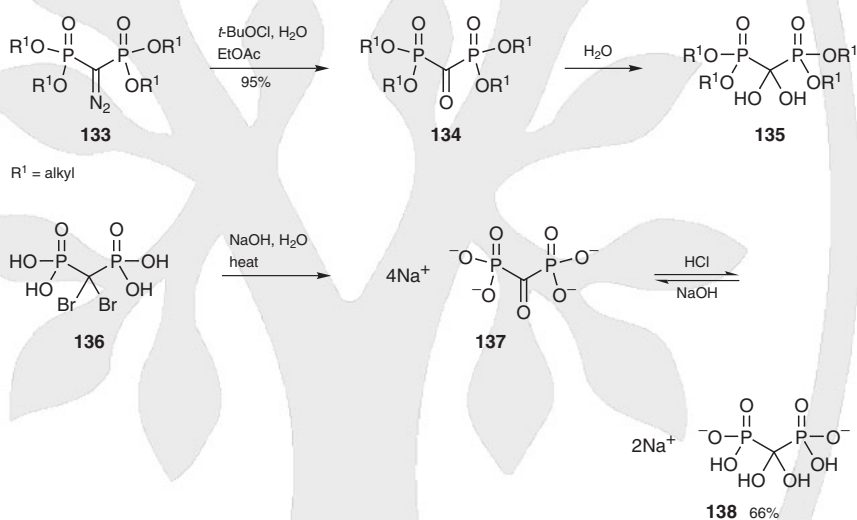
18.16.7.1.2

Method 2:
Hydrates of Carbonyldiphosphonates

The ability of carbonyldiphosphonates and diphosphonic acids to form stable hydrates under mildly acidic conditions can be compared to the behavior of oxomalononic acid. Oxomalononic acid exists as the hydrate but its esters can be in either the keto or hydrate form.^[177]

It has been shown that in the synthesis of carbonyldiphosphonates **134** from diazodiphosphonates **133** the addition of several equivalents of water leads to the crystalline hydrates **135** in quantitative yield (Scheme 35).^[178] Tetrasodium carbonyldiphosphonate (**137**), prepared from the dibromo compound **136**, can be converted into the visible (yellow) chromophore disodium hydrate **138** by titration with hydrochloric acid to pH 4.5.^[177] This process is pH dependent, and adjusting the solution to pH 11 with sodium hydroxide results in a return to the carbonyl form **137**. ³¹P NMR studies on carbonyldiphosphonates demonstrate how the equilibrium between the keto and dihydroxy forms varies with the pH and that the addition of magnesium can alter the apparent pK of this equilibrium.^[179]

Scheme 35 Synthesis of Carbonyldiphosphonates and Their Hydrates^[177,178]


Disodium Dihydroxymethylenediphosphonate (138):^[177]

NaOH (640 g, 16 mol) was added to a soln of dibromide **136** (715 g, 2.14 mol) in a minimum quantity of H₂O and the resulting soln was heated at reflux for 1 h. The crude hydrate (500 g) was precipitated by the addition of MeOH. This was dissolved in H₂O (2 L) and the pH was adjusted to 4.5 by addition of HCl. The bright yellow color of the basic soln faded to a pale yellow during the pH change. On standing, a white solid precipitated; a second crop was also recovered; yield: 356 g (66%); ³¹P NMR (δ): −14.5.

18.16.8

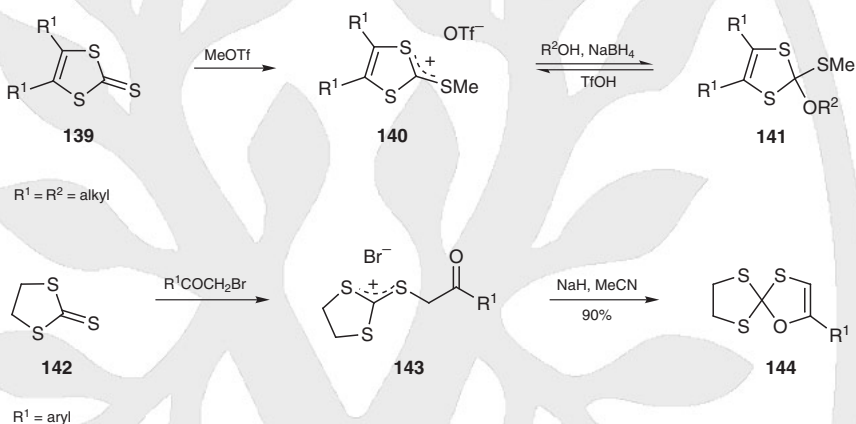
Product Subclass 8:
Trithioorthocarbonic Acid Tetraesters [Alkoxytris(organosulfanyl)methanes]

Examples of trithioorthocarbonic acid tetraesters (or trithioorthocarbonates) in the literature are scarce and are limited to heterocyclic derivatives, including 1,4,2-oxathiazolium salts^[180] and oxathiazines.^[181] Purification of trithioorthocarbonates is often achieved by recrystallization or distillation, but a number of derivatives are sufficiently stable to be purified by flash chromatography on silica gel.

18.16.8.1 Synthesis of Product Subclass 8

18.16.8.1.1 Method 1:
Addition of Alkoxide to Sulfanylcarbenium Salts

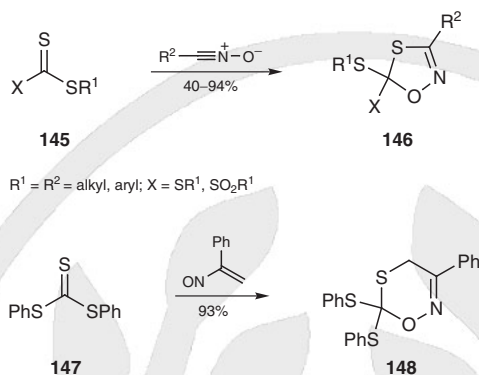
Trithioorthocarbonates **141** are synthesized by the reaction of alkoxide with sulfanylcarbenium halide^[182] or trifluoromethanesulfonate salts **140** (Scheme 36).^[183] These salts are prepared by the addition of trifluoromethanesulfonic acid to trithioorthocarbonates or by the alkylation of trithiocarbonates such as **139** and **142**. When α -haloacetophenones are used as the alkylating agent, the resulting salt **143** can be deprotonated by strong base to form the enolate, which undergoes ring closure to form the oxatrithiaspiroan **144**.^[184]

Scheme 36 Addition of Alkoxide to Sulfanylcarbenium Salts^[183,184]**2-(4-Bromophenyl)-1-oxa-4,6,9-trithiaspiro[4.4]non-2-ene (144, $R^1 = 4\text{-BrC}_6\text{H}_4$);****Typical Procedure:**^[184]

50% NaH (0.2 g) was added to a suspension of sulfanylcarbenium salt **143** (1.24 g, 3.0 mmol) in MeCN (40 mL). The mixture turned a reddish brown color and was stirred at rt for 3 h and then poured into H_2O (500 mL) with stirring. The resulting precipitate was removed by filtration and recrystallized (hexane/ Et_2O); yield: 0.90 g (90%); mp $85\text{--}86^\circ\text{C}$ (dec); $^1\text{H NMR}$ (CCl_4 , δ): 3.34 (s, 4H, SCH_2), 6.03 (s, 1H, SCH), 7.35 (m, 4H, C_6H_4).

18.16.8.1.2 Method 2:
Cycloaddition of Thiocarbonyl Compounds

Alkyl and aryl nitrile oxides readily undergo 1,3-dipolar cycloaddition with trithiocarbonates **145** ($\text{X} = \text{SR}^1$) to give 1,4,2-oxathiazoles **146** ($\text{X} = \text{SR}^1$) in high yield (Scheme 37).^[103] Heating ($80\text{--}140^\circ\text{C}$) the resulting oxathiazoles leads to their decomposition, whereas treatment with strong acid in the presence of an acyl anhydride allows synthetic access to 1,4,2-oxathiazolium salts.^[180] Trithiocarbonate *S,S*-dioxides **145** ($\text{X} = \text{SO}_2\text{R}^1$) also participate in cycloaddition reactions with nitrile oxides to yield the corresponding oxathiazoles **146** ($\text{X} = \text{SO}_2\text{R}^1$).^[185]

Scheme 37 Cycloaddition Reactions of Trithiocarbonates^[180,181,185]

α -Nitrosoalkenes (generated in situ from α -bromoketoximes) undergo [4+2]-cycloaddition reactions with diphenyl trithiocarbonate (**147**) to give oxathiazines such as **148** in high yield (Scheme 37).^[181]

5,5-Bis(alkylsulfanyl)-1,4,2-oxathiazoles **146** ($\text{X} = \text{SR}^1$); General Procedure:^[180]

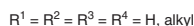
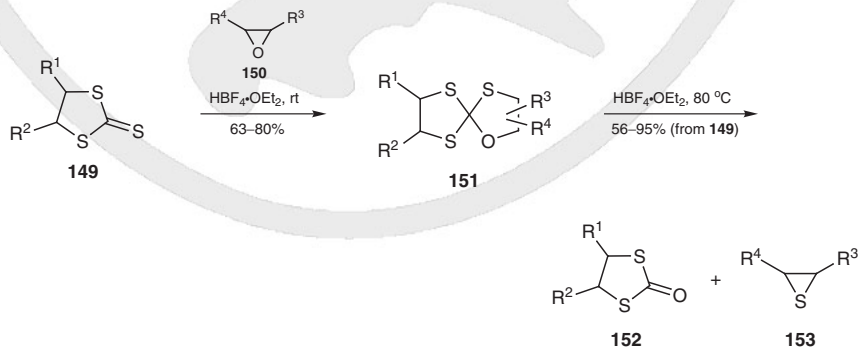
A soln of Et_3N (5 mmol) in Et_2O (10 mL) was added dropwise to a soln of the dialkyl trithiocarbonate (5 mmol) and acetonitrile *N*-oxide (5 mmol) in Et_2O (60 mL), with stirring, at rt until the orange color disappeared. The resulting mixture was washed with H_2O and concentrated under reduced pressure ($<40^\circ\text{C}$); chromatography of the residue (silica gel, CH_2Cl_2 /petroleum ether 1:1) gave the oxathiazole; yield: 40–94%.

18.16.8.1.3

Method 3:

Oxatrithiaspirans by Addition of Epoxides to 1,3-Dithiolane-2-thiones

The reaction of 1,3-dithiolane-2-thione (**149**) with epoxides **150** in the presence of the boron trifluoride–diethyl ether complex at 170 – 180°C results in the formation of the 1,3-dithiolan-2-one **152** and thiirane **153**.^[186] Subsequent studies into this reaction using various Lewis acids in 1,2-dichloroethane at -20°C demonstrated that the reaction could be stopped at the oxatrithiaspiran **151**, albeit in poor isolated yields.^[187] These conditions were further modified to permit selective synthesis of either the oxatrithiaspiran **151** or the 1,3-dithiolane-2-thione **152** and thiirane **153** by controlling the reaction temperature and the stoichiometry of the tetrafluoroboric acid–diethyl ether catalyst used (Scheme 38).^[188]

Scheme 38 Lewis Acid Mediated Addition of Epoxides to 1,3-Dithiolane-2-thione^[188]

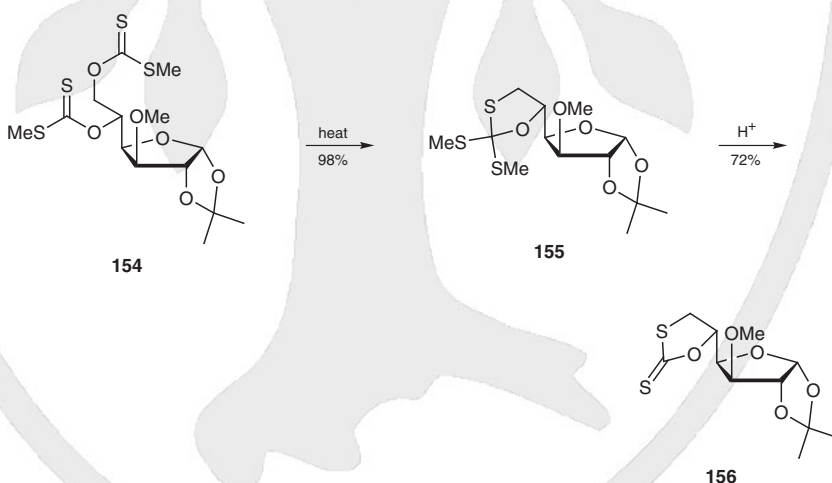
1-Oxa-4,6,9-trithiaspiro[4.4]nonane (151, $R^1 = R^2 = R^3 = R^4 = H$); Typical Procedure:^[188]

A 54% soln of $\text{HBF}_4 \cdot \text{OEt}_2$ in Et_2O (0.02 mL, 0.015 mmol) was added to a soln of 1,3-dithiolane-2-thione (1.36 g, 10 mmol) in anhyd chlorobenzene (20 mL) at 0–5 °C. After the mixture had been stirred for 5 min, a soln of oxirane (0.48 g, 11 mmol) in chlorobenzene (20 mL) was added dropwise over ca. 1 h at such a rate that the temperature was maintained at 0–5 °C. After the addition was complete, the mixture was allowed to warm to rt and was stirred until the thione had disappeared (TLC). The mixture was then treated with 5% aq NaHCO_3 (50 mL), after which the layers were separated and extracted with CH_2Cl_2 (3×50 mL). The combined extracts were washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (silica gel, petroleum ether/ Et_2O 4:1) gave the product; yield: 1.18 g (66%); mp 71–72 °C; ^1H NMR (CDCl_3 , δ): 3.17 (t, 2H, $J=6.0$ Hz, SCH_2), 3.47 [br s, 4H, $\text{S}(\text{CH}_2)_2$], 4.27 (t, 2H, $J=6.0$ Hz, OCH_2); ^{13}C NMR (CDCl_3 , δ): 34.3, 41.3, 71.4, 100.1.

18.16.8.1.4

**Method 4:
Thermal Decomposition of Bisdithiocarbonates**

The thermolysis of aliphatic dithiocarbonates (xanthates) results in a Chugaev elimination to give alkenes.^[189] Alkenes can also be obtained from bis-xanthates by radically induced dideoxygenation.^[190] However, thermolysis of 1,2- or 1,3-bis-xanthates such as **154** results in the formation of the trithioorthocarbonates **155** in moderate to high yields.^[191,192] In certain cases, thermolysis favors the formation of double Freudenberg rearrangement products. This methodology has been applied to the synthesis of thiosugars by treatment of the trithioorthocarbonate **155** with acid. This gives the cyclic dithiocarbonate **156** (Scheme 39), which is further elaborated to thiosugars using established chemistry.^[193–195]

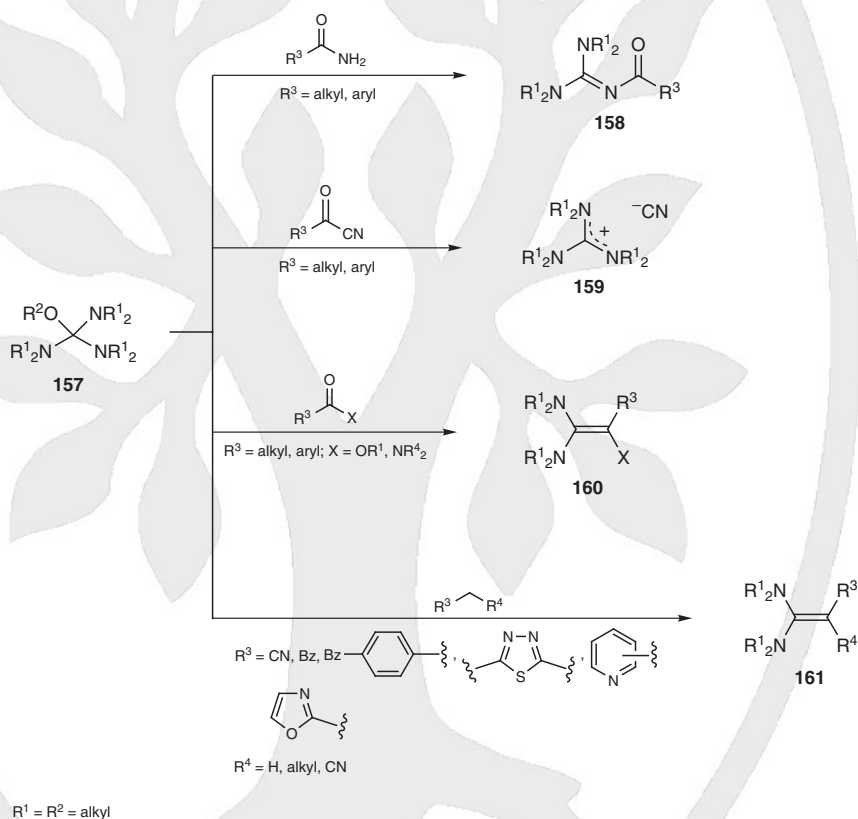
Scheme 39 Synthesis of Trithioorthocarbonates by Thermolysis of Bis-xanthates^[193]**1,2-O-Isopropylidene-3-O-methyl-6-thio- α -D-glucofuranose 5,6-O,S-(S,S-Dimethyltrithioorthocarbonate) (155):**^[193]

The bis-xanthate **154** (3.0 g, 7.25 mmol) was heated under reduced pressure at 230 °C/2 Torr for 30 min. The product crystallized on cooling and was washed with cold petroleum ether and the solvent was removed by suction. Drying and recrystallization (Et_2O /hexane) gave the pure product; yield: 2.5 g (98%); mp 70–73 °C.

18.16.9

Product Subclass 9:
Alkoxytriaminomethanes and Alkoxytrinitromethanes

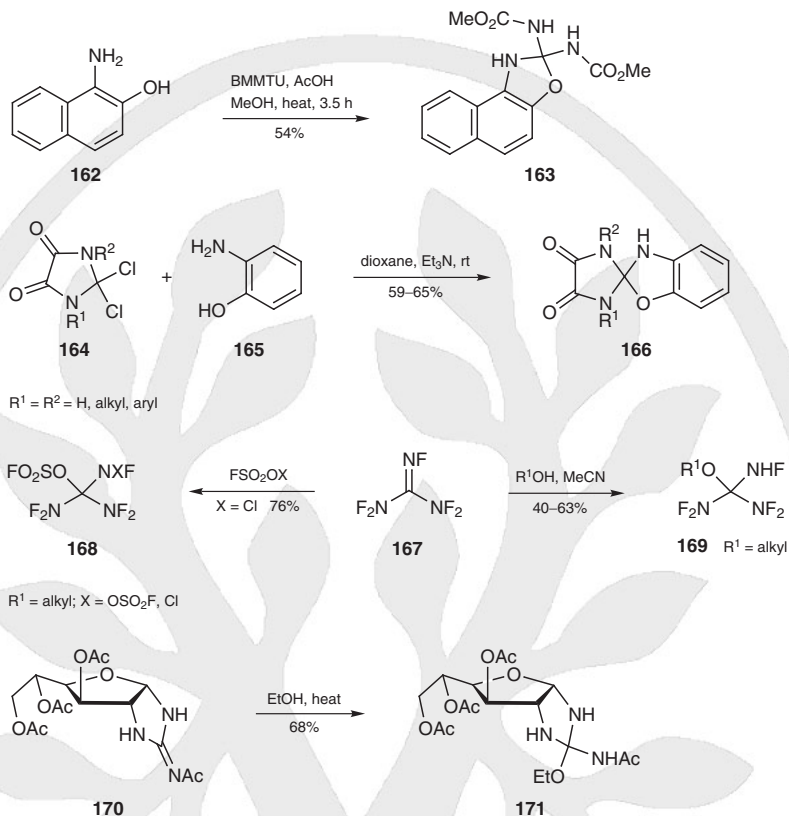
The chemistry and properties of alkoxytriaminomethanes **157** have been investigated. 4,4-Dimethyloxazolidine derivatives have been used as thermal and UV stabilizers in linear low-density polyethylene (LLDPE) films by acting as radical scavengers.^[196] 2,2-Diamino-2*H*-oxazolones have been identified as oxidation products of the base 2'-deoxyguanosine and have been used in the study of the oxidative damage to DNA.^[197] Alkoxytriaminomethanes condense with a range of active methylene compounds to form 1,1-diaminoalkenes **161** (Scheme 40).^[139,198] They react with esters and *N,N*-dialkylamides to form tetrasubstituted alkenes **160**,^[35] but react with free amides to give *N*-acylureas **158** and with acyl cyanides to form guanidinium cyanides **159**.^[41]

Scheme 40 The Chemistry of Alkoxytriaminomethanes^[35,41,139,198]


18.16.9.1

Synthesis of Product Subclass 9

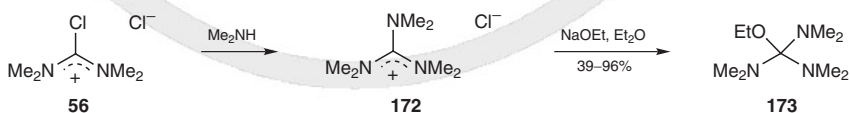
The reaction of 1-amino-2-naphthol (**162**) with 1,3-bis(methoxycarbonyl)-2-methylisothiourea (BMMTU; a reagent generally used to prepare carbamates) leads to isolation of the alkoxytriaminomethane **163** (Scheme 41).^[199] The amino alcohol **165** reacts with 2,2-dichloroimidazolidines **164** to give oxatriazaspirans **166** in an analogous reaction to the synthesis of spirocyclic orthocarbamides (Section 18.16.6.1.6).^[200,201] Although guanidines are generally unreactive toward heteroatomic nucleophiles, they react in certain cases. The reactive pentafluoroguanidine (**167**) reacts with fluorosulfates and alcohols to give **168** and **169**, respectively.^[114,202,203] Heating the imidazolidinimine **170** with ethanol is reported to give the alkoxytriaminomethane **171**.^[204]

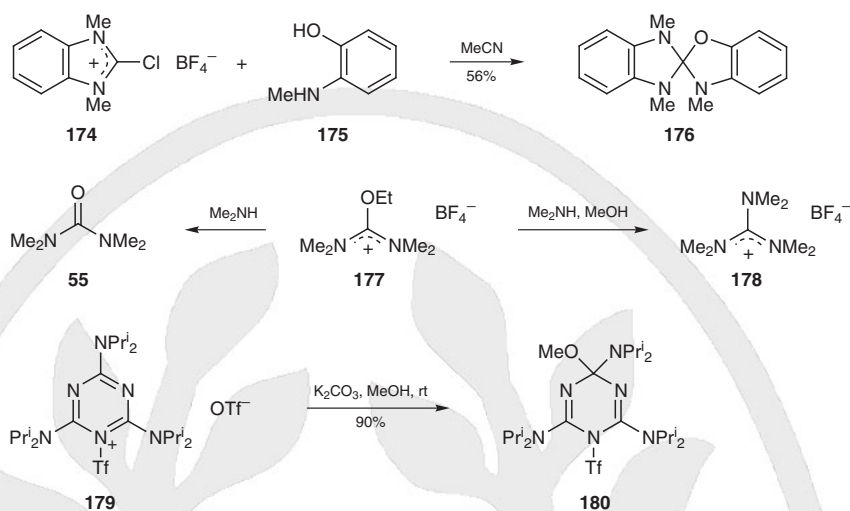
Scheme 41 Synthesis of Alkoxytriaminomethanes^[114,199–201,203,204]

18.16.9.1.1

Method 1:**Addition of Alkoxides to Hexaalkylguanidinium Chlorides**

Hexaalkylguanidinium chlorides such as **172** (which can be generated in situ from *N,N,N',N'*-tetraalkylchloroformamidinium chlorides, e.g. **56**) react with simple alkoxides to form alkoxytriaminomethanes (e.g., **173**) in moderate to high yields (Scheme 42).^[205,206] Unsymmetrical spirans such as **176** have been prepared by the addition of aminophenols (e.g., **175**) to cyclic chloroformamidinium salts (e.g., **174**).^[207] Addition of secondary amines to uronium tetrafluoroborates (e.g. **177**) or methylsulfates in alcohols, however, does not lead to alkoxytriaminomethanes but rather the stable guanidinium salts, e.g. **178**.^[206] Similar treatment in the absence of alcohols results in the isolation of the ureas, e.g. **55**. Methanol adds selectively at the 4-position of the triazinium trifluoromethanesulfonate **179** under basic conditions to form the triazine **180**.^[208]

Scheme 42 Addition of Alkoxides, Amines, and Aminophenols to Formamidinium, Uronium, and Guanidinium Salts^[205–208]



C-Ethoxy-*N,N,N',N'',N'''*-hexamethylmethanetriamine (173):^[205]

Hexamethylguanidinium chloride (**172**; 179 g, 1.0 mol) was added portionwise to a suspension of NaOEt (68 g, 1.0 mol) in anhyd Et₂O (1.5 L). The mixture was then stirred at rt for 48 h. The NaCl was removed by filtration and the Et₂O removed under reduced pressure. The resulting mixture was subjected to vacuum distillation using a Vigreux fractionating column to give the product; yield: 160–182 g (84–96%); bp 73 °C/10 Torr; ¹H NMR (CDCl₃, δ): 1.13 (t, *J* = 7 Hz, 3H, OCH₂CH₃), 2.55 (s, 18H, NCH₃), 3.55 (q, *J* = 7 Hz, 2H, OCH₂).

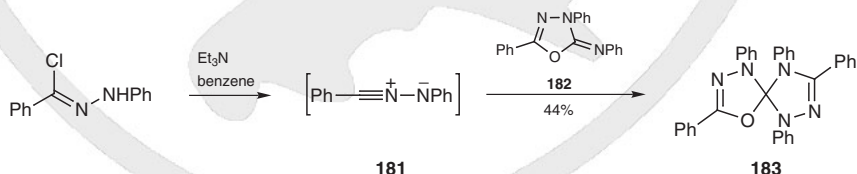
18.16.9.1.2

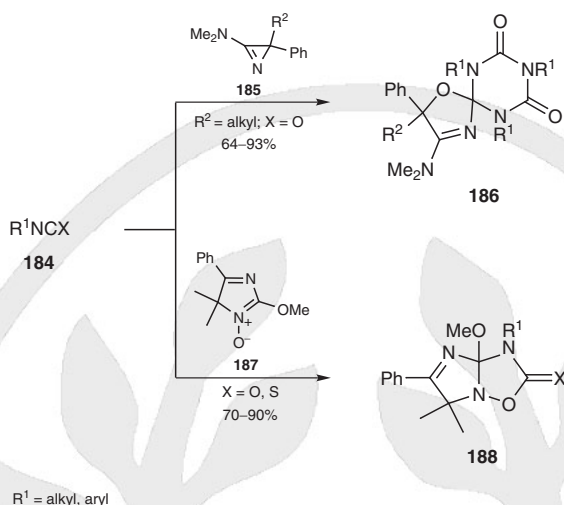
Method 2:

Heterocyclic Derivatives by Cycloaddition Reactions

Various alkoxytriaminomethane-containing heterocycles have been synthesized using cycloaddition reactions. 1,3-Dipolar cycloaddition of nitrilimine **181** with 1,3,4-oxadiazol-2-ylideneamine **182** produces the spiran **183** in moderate yield (Scheme 43).^[209] Alkyl isocyanates **184** react with azirines **185** to form the 3:1 spiran adducts **186**.^[210] Steric effects are important in this transformation and the use of the bulky isocyanates favors formation of the 1:1 urea adducts. Cyclic α-methoxynitrones such as **187** participate in 1,3-dipolar cycloadditions with isocyanates and isothiocyanates to afford the cycloadducts **188** at room temperature.^[211]

Scheme 43 Synthesis of Alkoxytriaminomethane Heterocycles by Cycloaddition Reactions^[209–211]





3a-Methoxy-6,6-dimethyl-3,5-diphenyl-3a,6-dihydro-3H-imidazo[1,2-b][1,2,4]oxadiazol-2(3H)-one (188, $R^1 = \text{Ph}$; $X = O$); Typical Procedure:^[211]

PhNCO (**184**, $R^1 = \text{Ph}$; $X = O$; 238 mg, 2.0 mmol) was added to a soln of nitron **187** (440 mg, 2.0 mmol) in CH_2Cl_2 (10 mL). The mixture was allowed to stand at rt for 5 min. The mixture was then purified by flash chromatography (silica gel, CHCl_3) to give the product; yield: 472 mg (70%); mp 107–108 °C; ^1H NMR (CDCl_3 , δ): 1.68 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 3.47 (s, 3H, OCH_3); ^{13}C NMR (CDCl_3 , δ): 21.0, 51.0, 77.5, 152.7, 124.1, 178.9.

18.16.10

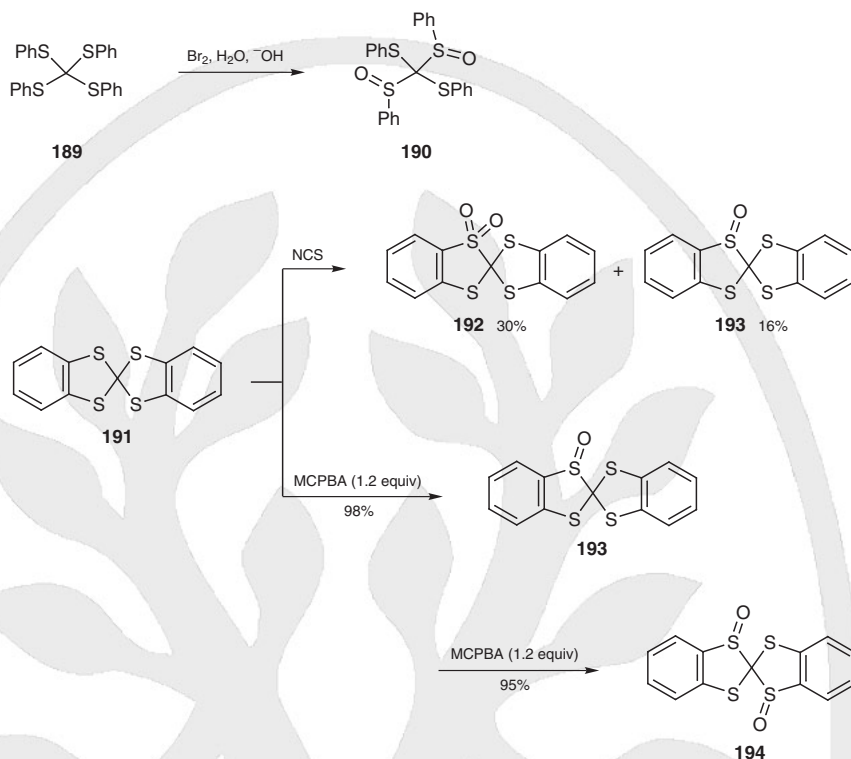
Product Subclass 10:

Tetrathioorthocarbonic Acid Tetraesters [Tetrakis(organosulfanyl)-methanes], Bis(organosulfanyl)bis(organosulfinyl)methanes, Tris(organosulfanyl)(organosulfonyl)methanes, and Bis(organosulfanyl)bis(organosulfonyl)methanes

A review tabulating known tetrathioorthocarbonic acid tetraesters through 1990 has been published.^[212]

Tetrathioorthocarbonic acid and its salts have not been isolated, but their stability and structure has been the subject of molecular model calculations.^[213,214] Tetrathioorthocarbonic acid tetraesters (generally referred to as tetrathioorthocarbonates) are stable and have been used in a number of applications. Simple derivatives such as tetramethyl tetrathioorthocarbonate are used as ligands in organometallic complexes.^[215] Spiro tetrathioorthocarbonates (STOCs) are also useful materials and have found use as accelerants in the vulcanization of rubber,^[216] as monomers for reduced shrinking polymers,^[217] and as curing agents.^[218] Synthetic applications of tetrathioorthocarbonates include the conversion of ketones into thioacetals,^[101] the generation of reactive tris(methylsulfanyl)methyl-lithium reagents,^[219–223] and as C^{4+} synthons in nickel-catalyzed alkenation with Grignard reagents.^[224]

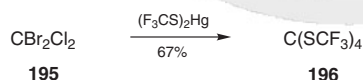
The oxidation chemistry of tetrathioorthocarbonates has been studied. Early work exploring the use of halogens as oxidants of tetraphenyl tetrathioorthocarbonate (**189**) reported its conversion into the bis-sulfoxide **190** (Scheme 44).^[225] The reaction of tetrathioorthocarbonates with benzyl peroxide results in decomposition, giving oxidized sulfur products.^[226,227] Treatment of spiro tetrathioorthocarbonate **191** with 1.2 equivalents of 3-chloroperoxybenzoic acid yields the sulfoxide **193**, which on exposure to a further equivalent of oxidant is converted into the 1,1'-bis-sulfoxide **194**.^[228] In contrast, oxidation of **191** with an *N*-halosuccinimide results in a mixture of the sulfone **192** and sulfoxide **193**.

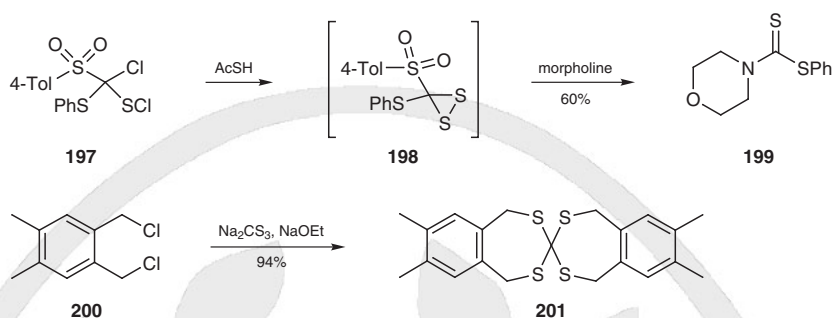
Scheme 44 Oxidation of Tetrathioorthocarbonates^[228]**18.16.10.1 Synthesis of Product Subclass 10**

Early preparations of tetrathioorthocarbonates were carried out by nitrosation of isothio-uronium salts followed by decomposition of the nitrosated adduct with ammonia.^[225,229] This method generally results in low isolated yields and has been superseded by later methodology. Spiro tetrathioorthocarbonates have also been isolated as byproducts in the synthesis of tetrathiafulvalenes, the latter being useful materials in solid-state physics.^[230,231]

18.16.10.1.1 Method 1: Substitution Reactions of Halomethanes with Thiolates

Although the reaction of a sodium thiolate and carbon tetrachloride has been claimed to give tetrathioorthocarbonates,^[232] most studies report the products of this reaction to be the trialkyl trithioorthoformates.^[233] (Trifluoromethylsulfanyl)copper(I) reacts with dibromodichloromethane (**195**) to give a complex mixture containing the tetrathioorthocarbonate **196**,^[234] whereas treatment with bis[(trifluoromethyl)sulfanyl]mercury(II) results in the isolation of **196** in 67% yield (Scheme 45).^[235]

Scheme 45 Synthesis of Tetrathioorthocarbonates from Halomethanes^[235–237]



Trichloromethanesulfonyl chloride reportedly reacts with thiols to give mixtures of disulfides and bis[tris(alkylsulfanyl)methyl] disulfides, and with benzenethiolates to form bis[tris(arylsulfanyl)methyl] trisulfides.^[238] Later studies, however, isolated disulfide dimers and trithiocarbonates when trichloromethanesulfonyl chloride was reacted with thiols and thiolates, respectively.^[34]

The intramolecular displacement of α -chloro disulfide **197** has been used to synthesize the reactive dithiirane **198**.^[236] Dithiiranes can equilibrate with the isomeric thio-sulfines^[239] and can be trapped by morpholine to give the dithiocarbamate **199** (Scheme 45).^[236]

Attempts to synthesize 1,3-dithiane-3-thione by reaction of sodium hydrogen sulfide, carbon disulfide, and 1,3-dibromopropane result in the isolation of the corresponding spiro tetrathioorthocarbonate as a byproduct in a very low yield.^[240] Modification of this procedure to generate sodium trithiocarbonate in situ from carbon disulfide, hydrogen sulfide, and sodium ethoxide in ethanol was later reported to give the spiro tetrathioorthocarbonate **201** in high yield from the dichloride **200** (Scheme 45).^[237] In an analogous manner to that described for orthocarbonates (Section 18.16.1.1.2), dichlorothioacetals undergo nucleophilic displacement with dithiols to give the corresponding spiro tetrathioorthocarbonates.^[241] An alternative procedure has been described that involves the electrochemical reduction of 1,3-dithiane-2-thione, which upon alkylation with a 1,2-dihaloethane yields 1,4,6,9-tetrathiospiro[4.4]nonane as the major product.^[242]

1,1',5,5'-Tetrahydro-7,7',8,8'-tetramethyl-3,3'-bisspiro[2,4-benzodithiepin] (201):^[237]

CAUTION: Hydrogen sulfide is extremely flammable and at higher levels causes respiratory paralysis and asphyxia.

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

A soln of Na₂CS₃ saturated with H₂S was prepared by passing H₂S through a soln of NaOEt (4.6 g, 0.1 mol) and CS₂ (5.0 g, 66 mmol) in EtOH (100 mL). This soln was added dropwise to a soln of 1,2-bis(chloromethyl)-4,5-dimethylbenzene (10.1 g, 50 mmol) in EtOH (350 mL). The mixture was allowed to stand overnight. Yellow crystals of the product were collected by filtration; yield: 9.5 g (94%); mp 255–258 °C.

18.16.10.1.2

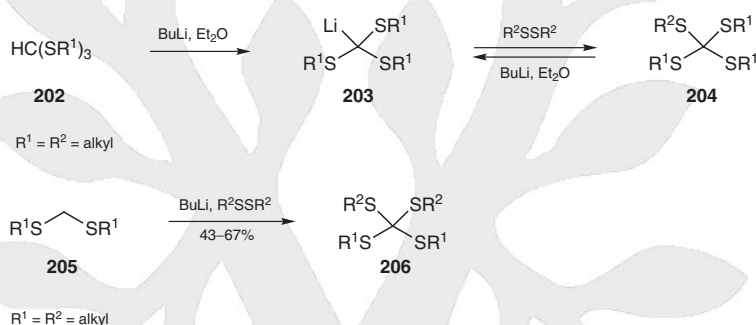
Method 2:**Substitution Reactions of Tris(organosulfanyl)methyl lithium Compounds and Bis(organosulfanyl)methanes**

The reaction of carbon nucleophiles with electrophilic sulfur derivatives such as disulfides or *N*-(arylsulfanyl)- or *N*-(alkylsulfanyl)phthalimides represents a direct and simple method of accessing tetrathioorthocarbonates.

18.16.10.1.2.1

Variation 1:**Substitution Reactions of Tris(organosulfanyl)methylithium Compounds with Diorgano Disulfides**

Tris(alkylsulfanyl) carbanions are more stable than the analogous alkoxy carbanions, owing to resonance interactions between the unshared electron pair on carbon and vacant d-orbitals of the sulfur atoms.^[136] They are easily generated from trithioorthocarbonates **202** or tetrathioorthocarbonates **204** by addition of an equimolar quantity of butyllithium (Scheme 46).^[243] These reactive species **203** can be quenched using disulfides to form the corresponding tetrathioorthocarbonates **204** in good yields. Deprotonation of thioacetals **205** with butyllithium^[244] or sodium amide^[245] followed by treatment with disulfides similarly gives tetrathioorthocarbonates **206**. Although other, more practical, methods exist for the synthesis of simple tetrathioorthocarbonates, studies into the generation of tetralithiomethane demonstrated that it can be quenched by dimethyl disulfide to give tetramethyl thioorthocarbonate **204** ($R^1 = R^2 = \text{Me}$).^[246]

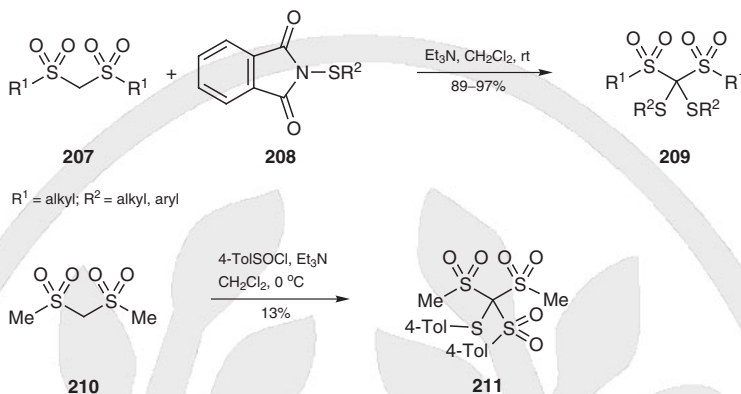
Scheme 46 Synthesis of Tetrathioorthocarbonates from Metalated Methanes^[244,245]**Tetrakis(methylsulfanyl)methane (204, $R^1 = R^2 = \text{Me}$); Typical Procedure:**^[244]

MeSSMe (3.0 g, 32 mmol) was added to a soln of [tris(methylsulfanyl)methyl]lithium (**203**, $R^1 = \text{Me}$; 3.2 g, 20 mmol) in THF at -78°C . The mixture was stirred for 5 h and was then allowed to warm to -40°C . Pentane and H_2O were added and the organic layer was separated and dried. The solvent and disulfide were removed under reduced pressure to give the crude product; yield: 3.80 g (96%); further purification was carried out by vacuum sublimation or by cooling in pentane to -50°C ; mp $65\text{--}66^\circ\text{C}$; $^1\text{H NMR}$ (CCl_4 , δ): 2.17 (s, 3H, SCH_3).

18.16.10.1.2.2

Variation 2:**Reaction of Bis(alkylsulfonyl)methanes with *N*-(Organosulfanyl)phthalimides**

Bis(alkylsulfonyl)methanes **207** are weak acids ($\text{p}K_{\text{a}} \approx 12$)^[247] that form sodium salts in ethanolic sodium ethoxide which react with *N*-(alkylsulfanyl)- or *N*-(arylsulfanyl)phthalimides **208** in the presence of an amine base to give bis(organosulfanyl)bis(organosulfonyl)methanes **209** in high yields (Scheme 47).^[248] These products can be selectively reduced with a sodium alkanethiolate and sodium hydride to give a (methylsulfanyl)-bis(methylsulfonyl)methane. This product is difficult to obtain directly by equimolar addition of sulfur transfer agents to bis(alkylsulfonyl)methanes **207**.

Scheme 47 Reaction of Bis(alkylsulfonyl)methanes with Sulfur Electrophiles^[249,250]

Treatment of bis(alkylsulfonyl)methanes **210** with arenesulfinyl chlorides does not result in the expected sulfoxides, but instead affords the unsymmetrical rearrangement products, (arylsulfanyltris(alkylsulfonyl)methanes **211** (Scheme 47).^[249] Similar treatment with arenesulfonyl chlorides leads to the isolation of tris(alkylsulfonyl)methanes.^[251]

Bis(alkylsulfonyl)bis(alkylsulfonyl)methanes **209**; General Procedure:^[248]

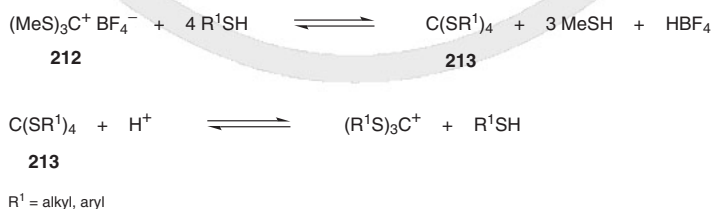
A soln of the bis(alkylsulfonyl)methane (2–20 mmol), *N*-(alkylsulfonyl)phthalimide (4–40 mmol), and Et₃N (4–40 mmol) in CH₂Cl₂ was stirred at rt until the starting material was completely consumed (TLC). The mixture was concentrated under reduced pressure and then the phthalimide was removed by trituration (CH₂Cl₂) to give the product; yield: 89–97%.

18.16.10.1.3

Method 3:

Addition of Thiols to Sulfanylcarbenium Salts

Sulfanylcarbenium salts **212** serve as convenient intermediates for a number of derivatives, including tetrathioorthocarbonates.^[182,220,252,253] Sulfanylcarbenium salts can be generated from tetrathioorthocarbonates by treatment with triphenylcarbenium cation^[253] or arsenic pentafluoride,^[254] but are more often prepared by alkylation of trithiocarbonates with Meerwein's salt,^[219] dimethyl sulfate,^[219] or nitrosyl tetrafluoroborate.^[255] Tris(methylsulfonyl)carbenium tetrafluoroborate (**212**) establishes an equilibrium with thiols which can be pushed toward the formation of tetrathioorthocarbonates **213** by removal of the volatile methanethiol (Scheme 48).^[256] A second acid-catalyzed equilibrium is thereby established, but the formation of tetrathioorthocarbonate **213** can be favored by use of excess alkanethiol (Method A) or by addition of sodium hydrogen carbonate to remove the acid (Method B). Method A is superior for the preparation of alkyl tetrathioorthocarbonates, whereas Method B is used for aryl derivatives.

Scheme 48 Addition of Thiols to Tris(methylsulfonyl)carbenium Tetrafluoroborate^[219,220,256]

Tetrakis(organosulfanyl)methanes 213 (R^1 = Alkyl, Aryl); General Procedure:^[256]

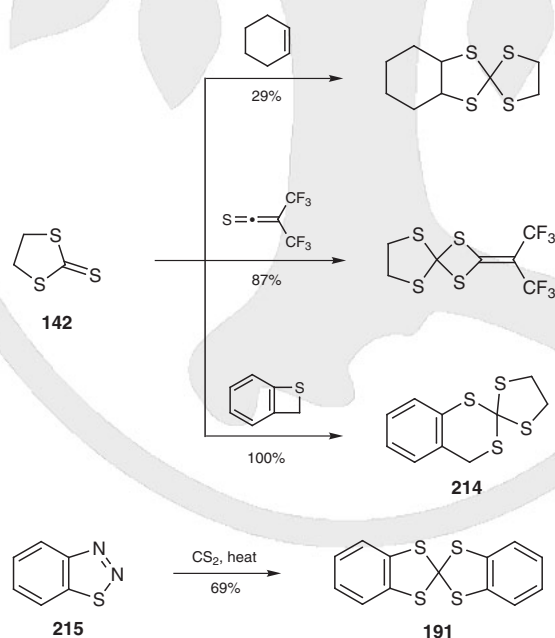
Method A: A mixture of the alkanethiol (1.15 mol) and tris(methylsulfanyl)carbenium tetrafluoroborate (0.1 mol) was refluxed for 48 h (anhyd 1,2-dichloroethane was used as a solvent with both MeSH and EtSH). After cooling, 10% aq NaOH (75 mL) was added and the organic layer was separated and washed with 10% NaOH and H₂O (3 ×). The mixture was concentrated under reduced pressure and the crude product was purified by recrystallization or by distillation under reduced pressure; yield: 86–97%.

Method B: A stirred mixture of the arenethiol (60 mmol), tris(methylsulfanyl)carbenium tetrafluoroborate (10 mmol), NaHCO₃ (10 mmol), and anhyd benzene (50 mL) (**CAUTION: carcinogen**) was refluxed for 12 h. After the solvent was removed under reduced pressure, the residue was washed with 10% NaOH and H₂O (3 ×). The residue was dried and the product was purified by recrystallization from an appropriate solvent; yield: 85–90%.

18.16.10.1.4

Method 4:**Tetrathiaspirans from Dithiolane-2-thione or Carbon Disulfide by Addition Reactions**

Although the spiro tetrathioorthocarbonate 1,5,7,11-tetrathiaspiro[5.5]undecane was originally isolated from the reaction of 1,3-dithiolane-2-thione (**142**) with diethanolamine,^[240] it was later shown to be present as an impurity in the starting material rather than as a reaction product.^[257] Spiro tetrathioorthocarbonates have been isolated as by-products in the Lewis acid catalyzed addition of epoxides to trithiocarbonates.^[187] Thione **142** has a relatively high electron density at the thiocarbonyl group. This allows it to participate in addition chemistry with alkenes,^[258] thioketenes,^[259] and 2H-benzo[*b*]thiete (a precursor to a highly reactive 8 π intermediate) to give spiro tetrathioorthocarbonates such as **214** (Scheme 49).^[260] 1,2,3-Benzothiadiazole (**215**) undergoes thermal decomposition in the presence of carbon disulfide to give the tetrathioorthocarbonate **191**.^[261]

Scheme 49 Addition Reactions of 1,3-Dithiolane-2-thione and Carbon Disulfide^[258–261]

Spiro[4H-1,3-benzodithiin-2,2'-[1,3]dithiolane] (214):^[260]

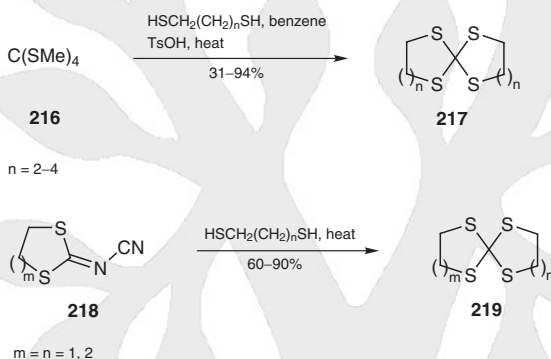
A soln of 2H-benzo[b]thiete (244 mg, 2.0 mmol) and 1,3-dithiane-2-thione (273 mg, 2.0 mmol) in toluene (10 mL) was refluxed until the starting material was completely consumed (TLC). The mixture was purified by flash chromatography (silica gel, toluene/hexane 10:1) to afford the product as colorless crystals; yield: 514 mg (quant); mp 104 °C; ¹H NMR (CDCl₃, δ): 3.49 (s, 4H), 3.92 (s, 2H); ¹³C NMR (CDCl₃, δ): 37.0, 41.3, 79.3.

18.16.10.1.5

Method 5:**Transesterification of Tetrathioorthocarbamic Acid Tetraesters with Dithiols**

Symmetrical spiro tetrathioorthocarbonates **217** are simply synthesized in high yield by transesterification of methyl tetrathioorthocarbonate **216** with alkanedithiols (Scheme 50).^[257] This methodology also works well for benzylic and aromatic dithiols.^[9,262] Nonsymmetrical spiro tetrathioorthocarbonates **219** can be synthesized by the condensation of dithiols with, for example, 1,3-dithiolan-2-ylidenecyanamide (**218**, *m* = 1).^[263]

Scheme 50 Synthesis of Spiro Tetrathioorthocarbonates by Transesterification of Tetrathioorthocarbonates and Cyanoiminodithiolanes with Dithiols^[257,263]

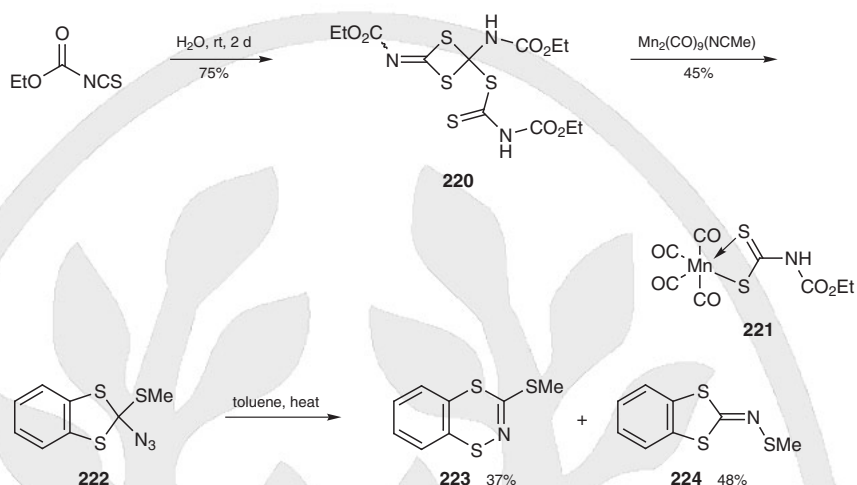
**Tetrathiaspirans 217; General Procedure:**^[257]

A soln of C(SMe)_4 (2.0 g, 10 mmol), an alkanedithiol (20 mmol), and TsOH (50 mg) in benzene (50 mL) (**CAUTION: carcinogen**) was refluxed for 24 h. The solvent was then removed under reduced pressure and the residues were triturated with EtOH. The crude products were filtered, washed with EtOH, and recrystallized ($\text{CH}_2\text{Cl}_2/\text{EtOH}$) to give the product; yield: 31–94%.

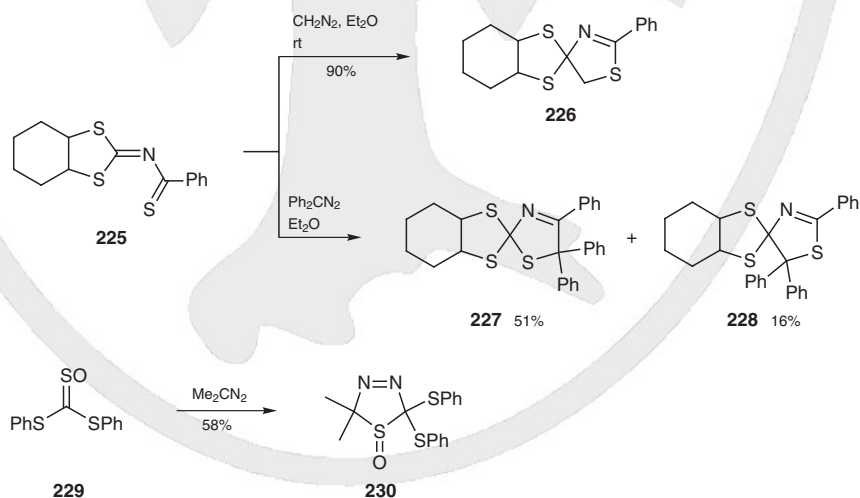
18.16.11

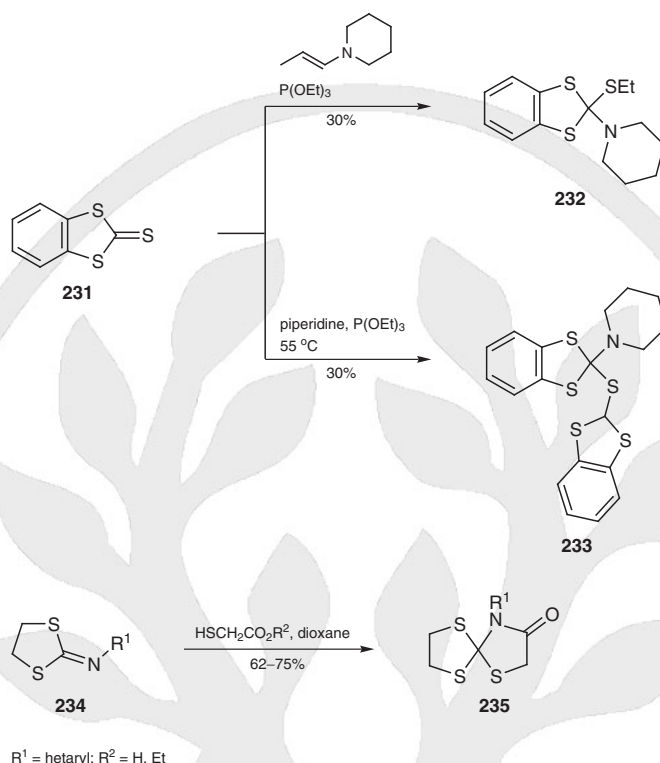
Product Subclass 11:**Trithioorthocarbamic Triesters [Aminotris(organosulfonyl)methanes] and Nitrotris(organosulfonyl)methanes**

Simple alkyl thioorthocarbamic triesters are moisture sensitive and are prone to decomposition to afford more stable products. However, heterocycles incorporating trithiaazaspirans have been investigated as antimicrobial agents.^[264] The dithietane **220** has been used as a source of dithiocarbamate ligands for the manganese complex **221** (Scheme 51).^[265] Synthetic use has been made of the azide **222**, which undergoes ring expansion in toluene to give the 1,4,2-dithiazine **223**. This method suffers from the competing formation of imine **224** via the intermediate nitrene.^[266]

Scheme 51 Synthesis and Applications of Heterocycles Containing Trithioorthocarbamic Esters^[265,266]**18.16.11.1 Synthesis of Product Subclass 11**

In addition to the methods described here, thioorthocarbamic esters have been isolated as byproducts in the reaction of iodo isothiocyanates with sulfur nucleophiles.^[267] They have also been synthesized by various addition reactions. Diphenyldiazomethane adds to the N-substituted benzenecarbothioamide **225**, resulting in the isolation of the thioorthocarbamic ester **227** as the major product as well as the minor 1,4-adduct **228**.^[268] This contrasts with the reaction of **225** with diazomethane, which exclusively leads to the 1,4-adduct **226** (Scheme 52). 2-Diazopropane reacts with sulfine **229** to give the sulfide **230**.^[269]

Scheme 52 Synthesis of Thioorthocarbamic Esters^[264,268–271]

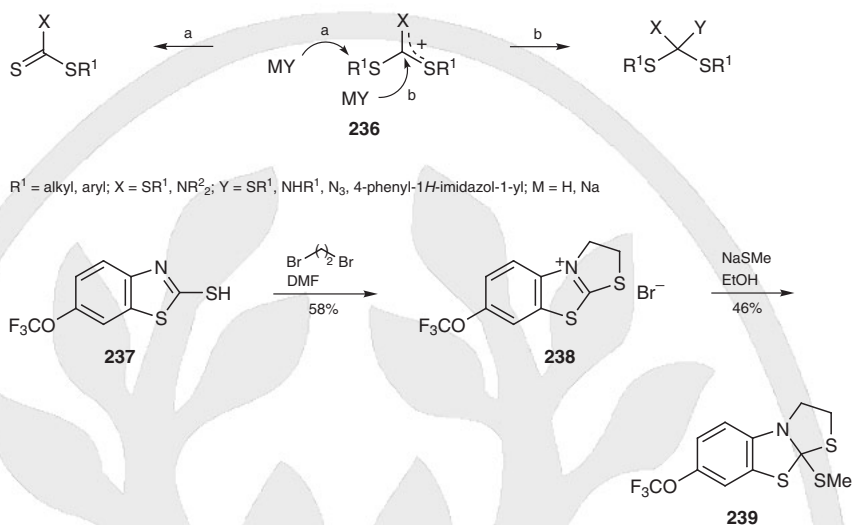


Other preparations of thioorthocarbamic esters include the reaction of triethyl phosphite with 1,3-benzodithiole-2-thione (**231**) in the presence of piperidine to give **233**, and with enamines to give products such as **232** in moderate yields.^[270] 2-Imino-1,3-dithiolanes **234** participate in cyclocondensation reactions with sulfanylacetic acid derivatives to form trithiaazaspirans **235** in good yields (Scheme 52).^[264,271]

18.16.11.1.1

Method 1:**Addition of Thiolates to Carbamidium Salts and Amines to Sulfanylcarbenium Salts**

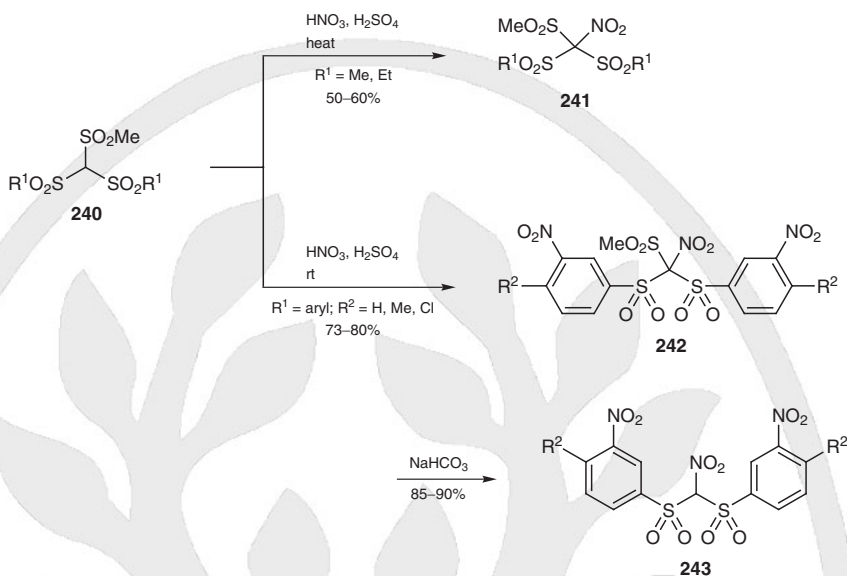
The electrophilic behavior of carbamidium and sulfanylcarbenium salts **236** with sulfur and nitrogen nucleophiles has been investigated (Scheme 53). These salts, e.g. **238**, are conveniently prepared by the alkylation of the corresponding dialkyldithiocarbamate^[272] or trithiocarbonates^[219] with dimethyl sulfate or the 4,5-dihydrothiazole-2-thiol **237** with 1,2-dihaloalkanes.^[273] Two possible modes of attack have been observed for the incoming nucleophile: pathway a, which is attack on the alkyl substituent of a thiol substituent, or pathway b, which is attack on the active methylene center. Generally, pathway b is favored, although examples of the alternate pathway have been documented.^[272] Despite the general preference for sulfur and nitrogen nucleophiles to attack via pathway b, the corresponding thioorthocarbamic esters are often not the isolated product owing to their low stability.^[272] However, a number of heterocyclic thioorthocarbamic esters, e.g. **239**, are sufficiently stable to allow their isolation, and in these cases this methodology provides a straightforward method for their synthesis.^[253,272–276]

Scheme 53 Reaction of Carbamidium and Sulfanylcarenium Salts with Sulfur and Nitrogen Nucleophiles^[219,272,273]**9a-(Methylsulfanyl)-7-(trifluoromethoxy)-2,3-dihydrothiazolo[2,3-b]benzothiazole (239):**^[273]

7-(Trifluoromethoxy)-2,3-dihydrobenzothiazolo[2,3-b]thiazol-4-ium bromide (**238**; 4.35 g, 12 mmol) was added to a stirred soln of MeSNa (0.9 g, 12 mmol) in EtOH (45 mL). After 30 min at rt, the precipitate was removed and the filtrate was concentrated under reduced pressure. Recrystallization (EtOH) gave the product as a colorless solid; yield: 1.8 g (46%); ¹H NMR (DMSO-*d*₆, δ): 2.20 (s, 3H, SCH₃), 2.90 and 3.20 (m, 2H, NCH₂CH₂S), 3.60 and 4.61 (m, 2H, NCH₂CH₂S).

18.16.11.1.2**Method 2:****Nitration of Tris(organosulfonyl)methanes**

Although bis(alkylsulfonyl)methanes are not sufficiently acidic to undergo nitration under standard conditions,^[277] tris(alkylsulfonyl)methanes **240** ($R^1 = \text{alkyl}$) do react with nitric acid in sulfuric acid on heating to give tris(alkylsulfonyl)nitromethanes **241**.^[278] It was later shown that bis(arylsulfonyl)(methylsulfonyl)methanes **240** ($R^1 = \text{aryl}$) undergo aromatic nitration at -40°C exclusively at the *meta* positions, whereas reaction at room temperature leads to the concomitant nitration at the methine carbon to give **242** in good yields (Scheme 54).^[279] Treatment of nitrotris(organosulfonyl)methanes with nucleophiles results in the preferential loss of the least electronegative group. Thus, reaction of **242** with aqueous sodium hydrogen carbonate eliminates the methylsulfonyl group to give bis(arylsulfonyl)nitromethanes **243**. Reaction of **242** with a basic solution of potassium hypobromite initially results in elimination in an analogous manner and then bromination selectively on the methine carbon to give bis(arylsulfonyl)bromonitromethanes.^[279]

Scheme 54 Nitration of Tris(organosulfonyl)methanes^[279]**Bis(Ethylsulfonyl)(methylsulfonyl)nitromethane (241, $\text{R}^1 = \text{Et}$); Typical Procedure:**^[279]

Bis(ethylsulfonyl)(methylsulfonyl)methane (0.56 g, 2.0 mmol) was added to a mixture of HNO_3 (d 1.56, 7 mL) and H_2SO_4 (d 1.84, 7 mL) with stirring. The mixture was heated to 100–110 °C, maintained at this temperature for 15–20 min, and was then poured onto ice (100 g). The oil which separated was washed with H_2O until the washings were pH 7. The oil was rubbed in EtOH, which resulted in crystallization to give the product; yield: 0.33 g (55%); mp 72 °C.

18.16.12

**Product Subclass 12:
Tris(alkylsulfanyl)phosphorylmethanes**

Of the possible permutations of oxidation states possible for this combination of heteroatoms, only the tris(alkylsulfanyl)phosphorylmethanes have been reported. They are sufficiently stable that they can be purified by flash chromatography on silica gel.

18.16.12.1

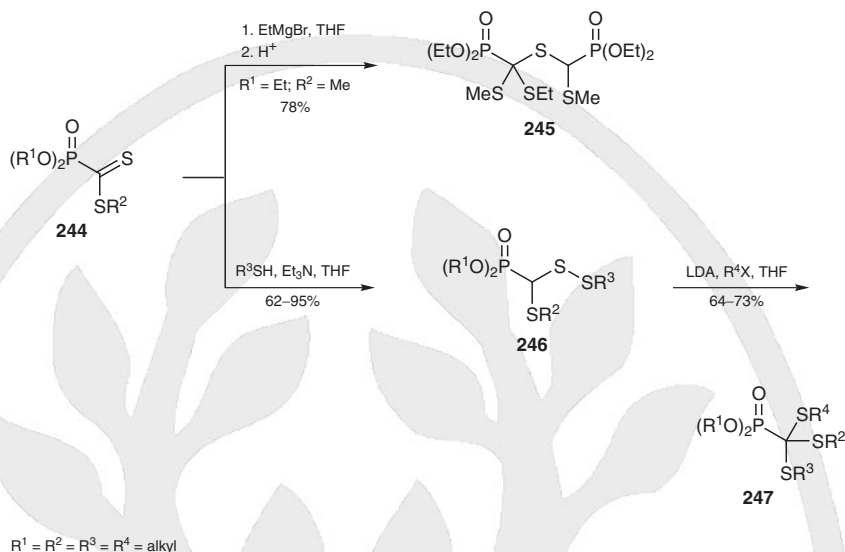
Synthesis of Product Subclass 12

Tris(alkylsulfanyl)phosphorylmethanes were originally isolated as minor byproducts in the synthesis of tetrathiafulvalenes by the reduction of 1,3-dithiole-2-thiones with trimethyl phosphite.^[280]

18.16.12.1.1

**Method 1:
Reaction of Phosphoryldithioformates with Organometallics**

Phosphoryldithioformates **244** are non-enethiolizable, functionalized dithioesters which are accessible from dialkyl phosphites and carbon disulfide.^[281] When they are treated with Grignard reagents they undergo thiophilic addition to generate metalated dithioacetals,^[282] which then participate in further thiophilic addition with the starting phosphoryldithioformate to give the dimer, e.g. **245** (Scheme 55).^[283]

Scheme 55 Synthesis of Tris(alkylsulfanyl)phosphorylmethanes^[282,284]

When phosphoryldithioformates **244** are reacted with thiols and a catalytic amine base at low temperature, thiophilic attack occurs to give the disulfides **246**.^[284] Deprotonation with lithium diisopropylamide followed by alkylation with alkyl or crotyl halides on the α -disulfide sulfur forms a sulfonium ylide which then undergoes a Stevens-type [1,2]-sigmatropic shift to form the tris(alkylsulfanyl)phosphorylmethanes **247** (Scheme 55). The success of this reaction sequence is dependent on the reaction conditions employed. If stoichiometric quantities of amine are used in the initial step, symmetrical disulfide dimers are formed as the major product. The choice of the organolithium base in the second step is also important. Use of butyllithium instead of lithium diisopropylamide results in the isolation of a mixture of oligomeric products.

Tris(alkylsulfanyl)phosphorylmethanes **247**; General Procedure:^[284]

BuLi (2.2 mmol) was added to a soln of iPr_2NH (2.3 mmol) in THF (20 mL) at $-20^\circ C$. The resulting soln was cooled to $-78^\circ C$ and the disulfide **246** (2 mmol) was added dropwise. The formation of a lithiated carbanion was evidenced by an orange coloration of the soln. After 15 min at $-78^\circ C$, the methyl halide (2.2 mmol) was added and the mixture was left to warm slowly to rt overnight. The solvent was then removed under reduced pressure and the mixture was poured onto sat. NH_4Cl soln overlaid with Et_2O . The combined organic phases were then washed with brine before being dried (Na_2SO_4). Further purification by flash chromatography (silica gel, Et_2O /petroleum ether 1:3) gave the product; yield: 64–73%.

18.16.13

Product Subclass 13:

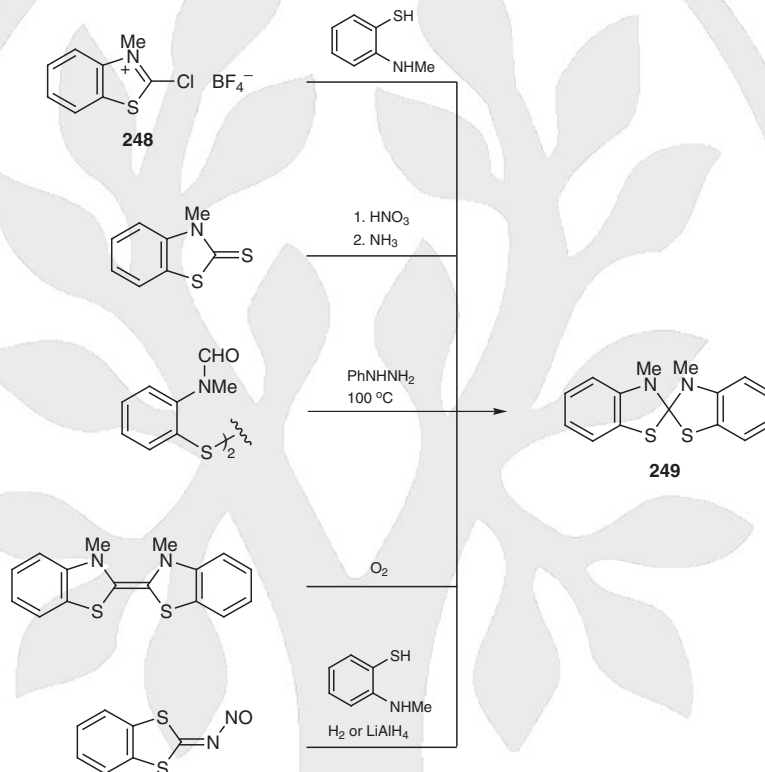
Dithioorthocarbonic Acid Diamide Diesters [Diaminobis(organosulfanyl)-methanes] and Bis(arylsulfanyl)dinitromethanes

Although a number of dithioorthocarbonic diester diamides have been synthesized, little is known about their toxicity. Most of the examples are heterocyclic or spiro structures. Their isolation and purification is generally achieved via recrystallization.

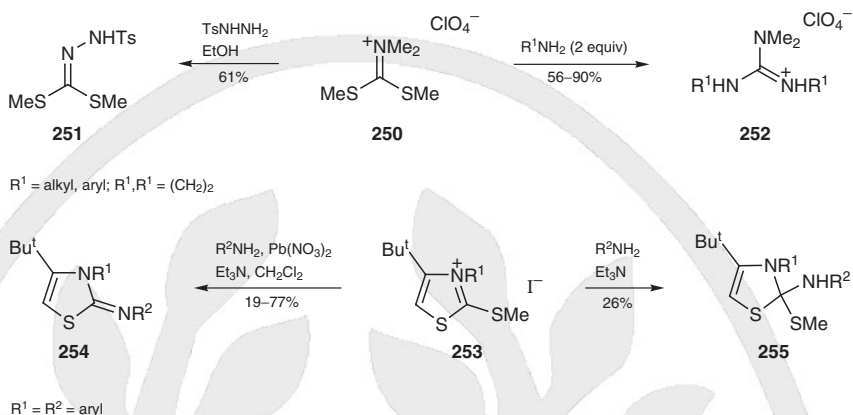
18.16.13.1 Synthesis of Product Subclass 13

There have been a number of different preparations dedicated toward the synthesis of specific derivatives, such as dithiadiazaspiran **249** (Scheme 56). However, these methods have not been utilized as general methods for the synthesis of dithioorthocarbonic diester diamides for various reasons.^[285–287]

Scheme 56 Preparations of 3,3'-Dimethyl-2,2'-spirobis(2,3-dihydro-benzothiazole)^[207,288,289]



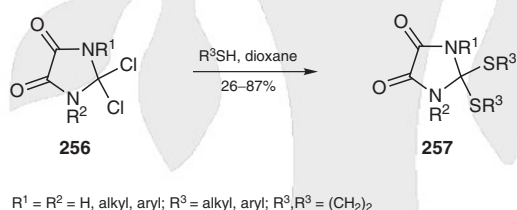
One example is the addition of 2-(methylamino)benzenethiol to carbamidium salt **248**, which is typical of the approach taken toward the synthesis of Product Class 16 derivatives (*vide supra*).^[207] Carbamidium salts, however, cannot be considered as general precursors of dithioorthocarbonic diester diamides. When the carbamidium salt **250** reacts with alkylamines or diamines, the stable guanidinium salts **252** are isolated (Scheme 57).^[272] Tosylhydrazine reacts with the carbamidium salt **250** to form the hydrazone **251**. In contrast, thiazolium iodides **253** do react with anilines to give dihydrothiazoles **255**, albeit in low yield.^[290] When this reaction is repeated in the presence of lead(II) nitrate, however, the isothiurea **254** is isolated.

Scheme 57 The Chemistry of Carbamidium Salts^[272,290]

18.16.13.1.1

Method 1:**Substitution Reactions of 2,2-Dichloroimidazolidine-4,5-diones with Organothiols**

The nucleophilic displacement of 2,2-dichloroimidazolidine-4,5-diones **256** by thiols has been used to generate a large number of 2,2-bis(organosulfanyl)imidazolidines **257** (Scheme 58).^[291,292] Both alkane- and arenedithiols have also been used in the synthesis of spiro analogues.^[161,201] Symmetrical 2,2-dichloroimidazolidines **256** are synthesized by the reaction of disubstituted carbodiimides with oxalyl chloride,^[161] whereas unsymmetrical dichloroimidazolidines can be prepared from cyanoamines.^[291]

Scheme 58 Nucleophilic Substitution of 2,2-Dichloroimidazolidine-4,5-diones^[201,291]**1,3-Diorgano-2,2-bis(organosulfanyl)imidazolidine-4,5-diones 257; General Procedure:**^[291]

A soln of oxalyl chloride (10 mmol) in dioxane (25 mL) was added dropwise over 30 min, with vigorous stirring, to a soln of the monosubstituted cyanamide (10 mmol) in dioxane (50 mL). The mixture was then stirred for a further 4 h at rt. A soln of the thiol (20 mmol) in dioxane (10 mL) was then added to the mixture. The mixture was stirred for 2 h and then left to stand for an additional 2 h at rt. The mixture was concentrated under reduced pressure and the crude residue was recrystallized (dioxane or EtOH) to give the product; yield: 26–87%.

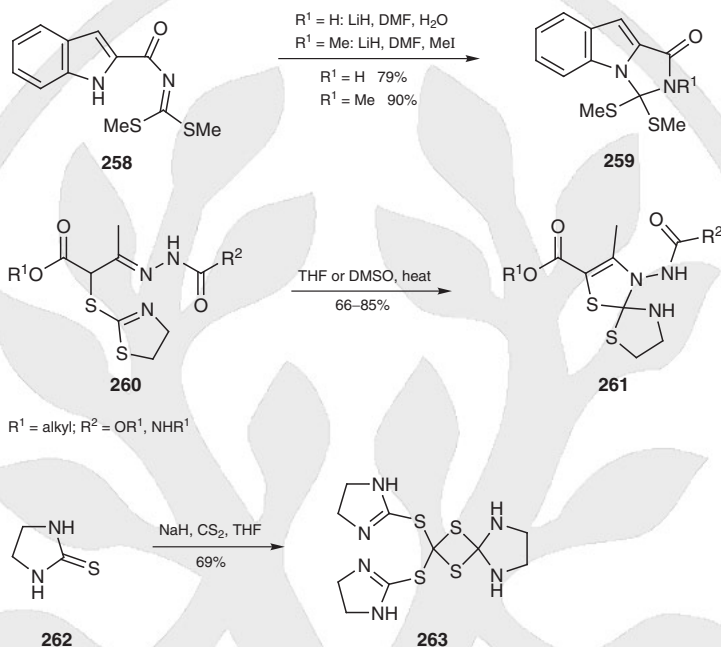
18.16.13.1.2

Method 2:**Ring Closure of Iminodithiocarbonates and Thioureas**

Attempts to N-methylate isobrassenin B (**258**) with iodomethane under basic conditions result instead in intramolecular ring closure to give the spiran **259** ($\text{R}^1 = \text{Me}$) in high yield (Scheme 59).^[293] When the reaction is quenched with water rather than iodomethane, the nonmethylated derivative is isolated. 1,2-Diazabuta-1,3-dienes react with 4,5-dihydrothi-

azole-2-thiol to give the 1,4-adducts **260**, which then undergo thermally induced intramolecular ring closure, resulting in the dithiadiazaspirans **261**.^[294] Both of these processes are attributed to internal nucleophilic attack of the thiocarbonyl center by nitrogen.

Scheme 59 Intramolecular Ring Closure of Iminodithiocarbonates and Thioureas^[293–295]



Conversely, intramolecular attack by sulfur anions on thiourea substrates has also been used to generate dithiadiazaspirans. Examples of this include the acid-mediated ring closure of methallibure,^[296] and the isolation of dithiadiazaspiran **263** from the reaction of imidazolidine-2-thione (**262**) with carbon disulfide under basic conditions (Scheme 59).^[295]

2-Methyl-3,3-bis(methylsulfanyl)-2,3-dihydro-1H-imidazo[1,5-a]indol-1-one
(**259**, R¹ = Me):^[297]

CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

Isobrasenin B (**258**; 254 mg, 0.96 mmol) was added to a stirred suspension of LiH (16 mg, 2 mmol) in DMF (6 mL) at rt. After 2 h, MeI (567 mg, 4 mmol) was added and stirring was continued for 5 h. The mixture was then poured into cold H₂O (100 mL) with intensive stirring and was left to stand for 30 min at 5 °C. The precipitate was collected by filtration with suction, washed with H₂O, and dried to give the product; yield: 240 mg (90%); mp 138–139 °C; ¹H NMR (CDCl₃, δ): 1.50 (s, 6H, SCH₃), 3.15 (s, 3H, NCH₃), 6.95 (s, 1H, NCH), 7.32 and 7.81 (m, 4H, C₆H₄).

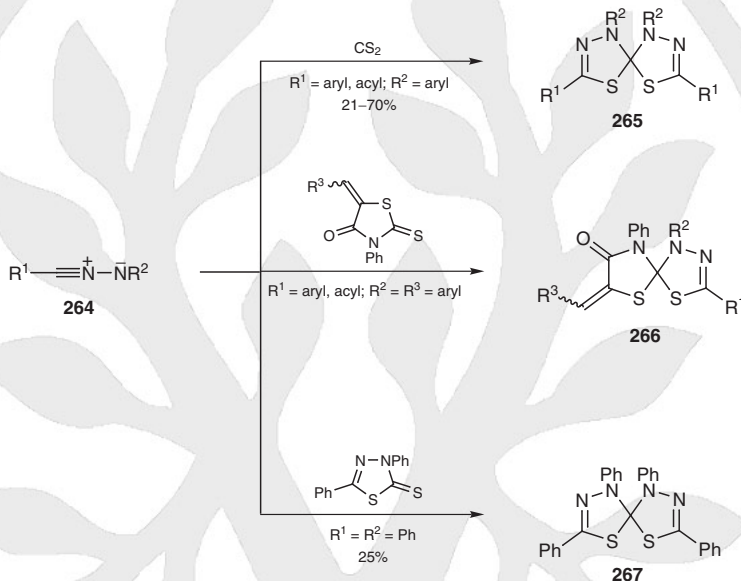
18.16.13.1.3

Method 3:
Cycloaddition of Thiocarbonyl Compounds with Nitrilimines

Nitrilimines **264** are reactive intermediates which participate in cycloaddition reactions with carbon disulfide to form the dithiadiazaspirans **265** (Scheme 60).^[298] This has also been used to generate polymers with a backbone formed from the repeating spiro units.^[299] The nitrilimines for this reaction can be generated in situ by the light-induced

decay of sydnone.^[300] However, their generation by the reaction of triethylamine with the corresponding hydrazoneyl halide is the method of choice for this transformation.^[298] Thiadiazole-2-thiones participate in analogous cycloaddition reactions to give the 1:1 adducts, e.g. **267**.^[301,302] The exclusive formation of adduct **266** from thioxothiazolidin-4-ones demonstrates that the C=S bond is more dipolarophilic toward nitrilimines than both the C=C and C=O bonds.^[303]

Scheme 60 Cycloaddition Reactions of Nitrilimines with Thiocarbonyl Compounds^[298,301–303]



Dimethyl 1,6-Bis(4-chlorophenyl)-4,9-dithia-1,2,6,7-tetraazaspiro[4.4]nona-2,7-diene-3,8-dicarboxylate (265, R¹ = CO₂Me; R² = 4-ClC₆H₄); Typical Procedure:^[298]

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

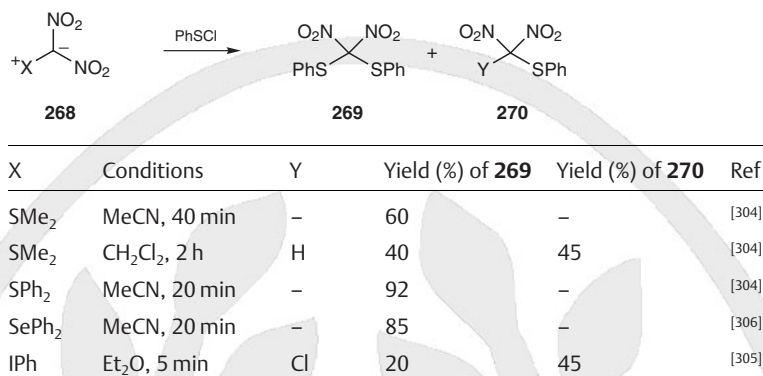
Methyl chloro[(4-chlorophenyl)hydrazone]ethanoate (2.0 g, 8.2 mmol) and Et₃N (1.4 mL, 9.8 mmol) were refluxed in CS₂ (75 mL) for 19 h. The mixture was then washed with H₂O and then dried (Na₂SO₄). The excess CS₂ was removed under reduced pressure and the residue was crystallized (MeOH) to give the product; yield: 2.0 g (50%); mp 161–163 °C; ¹H NMR (CDCl₃, δ): 3.9 (s, 3H), 7.3 (s, 4H).

18.16.13.1.4

Method 4:

Reaction of Sulfenyl Halides with Dinitro Ylides

Dinitro ylides **268** react with 2 equivalents of benzenesulfenyl chloride to form dinitro-bis(phenylsulfonyl)methane (**269**) in moderate to high yield (Scheme 61).^[304] The reactivity of iodonium,^[305] dimethylsulfonium,^[304] and dimethylselenonium^[306] dinitro ylides with electrophiles such as sulfenyl chlorides has been studied. Of these, the diphenylsulfonium ylide was found to give the highest yield. Acetonitrile was found to be the solvent of choice for this transformation. When either dichloromethane or diethyl ether was used, competitive formation of dinitro(bis(phenylsulfonyl)methanes **270** was observed. Although the generality of this methodology has not been established, it is the only reported route to dinitrobis(phenylsulfonyl)methane.

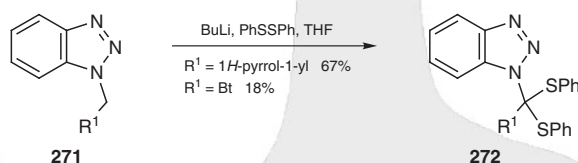
Scheme 61 Reaction of Dinitro Ylides with Benzenesulfonyl Chloride^[304–306]**Dinitrobis(phenylsulfanyl)methane (269):**^[304]

PhSCl (0.65 g, 4.5 mmol) was added to a stirred suspension of (dimethylsulfoniodinitro)methanide (0.37 g, 2.2 mmol) in MeCN (20 mL) at rt over 10 min. The mixture was stirred for a further 30 min. The solvent was removed under reduced pressure and the residue was dissolved in hot petroleum ether. Cooling with dry ice caused colorless crystals to precipitate, which were filtered and dried in a desiccator; yield: 0.43 g (60%); mp 61–62 °C.

18.16.13.1.5

**Method 5:
From Heterocyclic Aminals**

Heterocyclic aminals undergo lithiation with a strong base such as butyllithium or lithium diisopropylamide to form anions which can be quenched with benzenesulfonyl chloride or disulfides to give the bis(organosulfanyl)methanes **272** (Scheme 62). The outcome of this reaction is strongly dependent on the heterocycles employed. Both bis(benzotriazolyl)methane (**271**, R¹ = Bt)^[307] and pyrrole **271** (R¹ = 1H-pyrrol-1-yl)^[308] can be lithiated and react with diphenyl disulfide successfully. Bis(azolyl)methanes, however, undergo competitive ring substitution, resulting in the formation of complex mixtures.^[309]

Scheme 62 Lithiation and Sulfanylation of Heterocyclic Aminals^[307,308]**1-[Bis(phenylsulfanyl)(1H-pyrrol-1-yl)methyl]-1H-benzotriazole (272, R¹ = 1H-Pyrrol-1-yl):**^[308]

A 2.5 M hexane soln of BuLi (1.63 mL, 4.8 mmol) was added dropwise, very slowly, to a soln of 1-(pyrrol-1-ylmethyl)-1H-benzotriazole (0.79 g, 4.0 mmol) in anhyd THF (100 mL) at –78 °C. The mixture developed an intense dark color and was maintained at this temperature for 1 h. Then, a soln of (PhS)₂ (1.1 g, 5.0 mmol) in THF (2 mL) was added slowly. The soln was allowed to warm to rt over 12 h. Sat. NH₄Cl soln (100 mL) was added with vigorous stirring and then H₂O (25 mL) was added. The mixture was extracted with Et₂O (3 × 150 mL). The organic layer was washed with H₂O (150 mL) and dried (MgSO₄). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel) to give the product; yield: 1.25 g (67%); mp 163–165 °C.

18.16.14

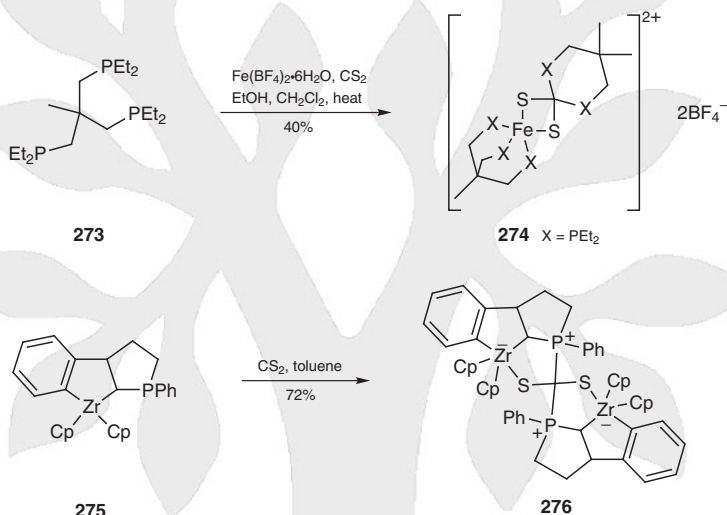
Product Subclass 14:**Bis(alkylsulfanyl)- and Bis(alkylselanyl)bis(phosphino)methanes and -bis(phosphoryl)methanes**

18.16.14.1

Synthesis of Product Subclass 14

Examples of Product Subclass 14 in the literature are scarce, although organometallic complexes have been reported containing this structural motif. Reaction of carbon disulfide with iron(II) tetrafluoroborate in the presence of the 1,1,1-tris(diethylphosphino)ethane (etripfos, **273**) ligand results in the isolation of complex **274**, which was the first example of a diamagnetic five-coordinate iron(II) complex (Scheme 63).^[310,311] The bis-zwitterionic anionic zirconocene complex **276** was produced by the addition of 0.5 equivalents of carbon disulfide to metallocene **275**, which dimerized via successive cyclo-addition reactions onto the two C=S double bonds.^[312]

Scheme 63 Organometallic Complexes Containing Bis(organosulfanyl)bis(phosphonio)-methanes^[311,312]

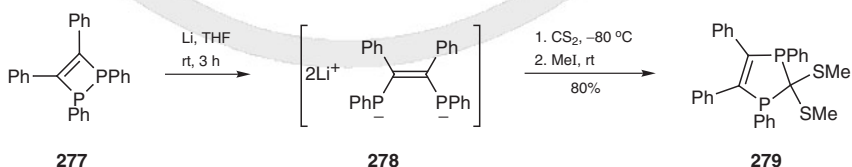


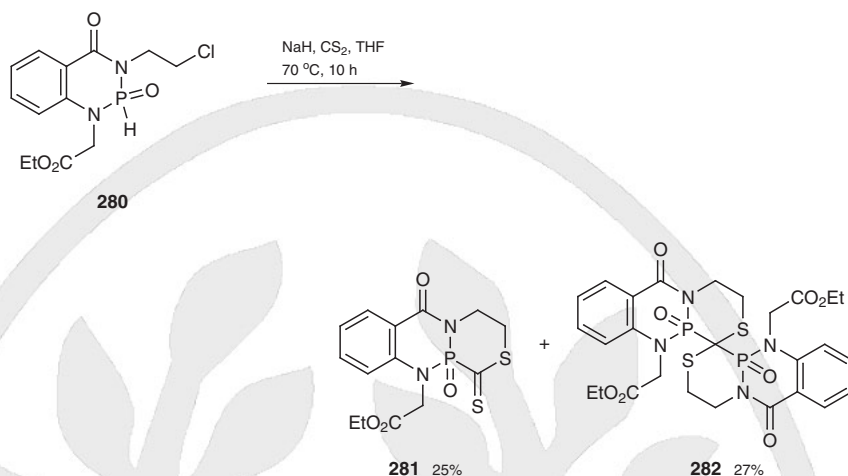
18.16.14.1.1

Method 1:**Reaction of Metalated Phosphines or Phosphorines with Carbon Disulfide**

Cleavage of the diphosphete **277** with lithium results in the formation of the 1,3-diphosphide ion **278** (Scheme 64), which on quenching with carbon disulfide and alkylation gives the diphosphole **279** as an inseparable mixture of diastereomers (*cis* major isomer).^[313] This intermediate is used in the synthesis of 4,5-diphenyl-1,3-diphosphaferrocene.

Scheme 64 Reactions of Metalated Phosphines and Phosphorines with Carbon Disulfide^[313,314]





Deprotonation of the diazaphosphorine **280** followed by reaction with carbon disulfide leads to a mixture of the heterocycle **281** and the dimer **282**.^[314] The formation of the dimer is strongly dependent on the substrate used. Switching the alkyl halide substituent to the other nitrogen prevents dimer formation.^[315]

2,2-Bis(methylsulfanyl)-1,3,4,5-tetraphenyl-2,3-dihydro-1H-1,3-diphosphole (279):^[313]

CAUTION: Inhalation, ingestion, or absorption of iodomethane through the skin can be fatal.

CAUTION: Carbon disulfide is extremely flammable, and toxic by inhalation, skin absorption, and ingestion.

Li (140 mg, 20 mmol) was added to a soln of 1,2,3,4-tetraphenyl-1,2-dihydro-1,2-diphosphite (3.94 g, 10 mmol) in THF (20 mL) under an argon atmosphere. After stirring for 3 h the soln was then cooled to –80 °C and CS₂ (600 µL, 10 mmol) was added. After 15 min, MeI (1.24 mL, 20 mmol) was added dropwise. After stirring for an additional 15 min at –80 °C, the mixture was slowly warmed to rt. After concentration under reduced pressure, the mixture was purified by flash chromatography (silica gel, hexane/toluene 1:1, then toluene) to give the product as pale yellow crystals as a mixture of isomers; yield: 80%; *cis*-isomer: ¹H NMR (CD₂Cl₂, δ): 1.62 (s, 3H, SCH₃), 2.44 (t, *J* = 1.36 Hz, 3H, SCH₃); ³¹P NMR (CD₂Cl₂, δ): 60.3; *trans*-isomer: ¹H NMR (CD₂Cl₂, δ): 1.98 (s, 6H, SCH₃); ³¹P NMR (CD₂Cl₂, δ): 74.2.

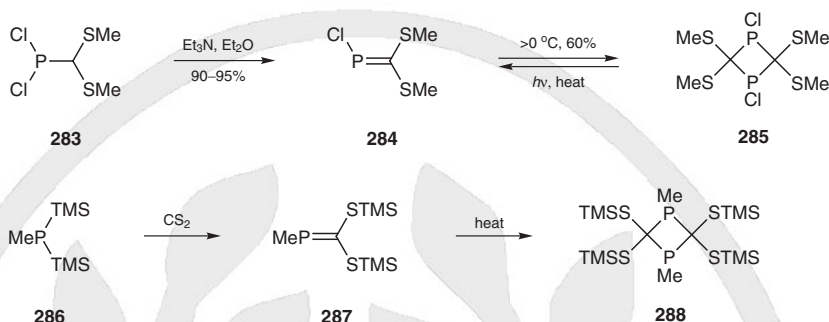
18.16.14.1.2

Method 2:

Dimerization of [Bis(alkylsulfanyl)methylene]phosphines

[Bis(alkylsulfanyl)methylene]chlorophosphines (e.g., **284**) are generated by the dehydrochlorination of dichlorophosphines such as **283**. They are thermally unstable and in solution at temperatures greater than 0 °C they dimerize to form diphosphetanes such as **285** (Scheme 65).^[316] These dimers are stable and have been isolated by recrystallization. However, UV irradiation with heating at 100–150 °C results in the reversion of **285** to the monomeric chlorophosphine **284**. The chlorine substituents of dimer **285** are readily displaced by primary amines to give 1,3-bis(alkylamino)-1,3-diphosphetanes.^[316] Attempts to introduce more sterically demanding substituents onto the dimer by reaction with lithium hexamethyldisilazane or lithium *tert*-butyl(trimethylsilyl)amide lead to 1,3-diphosphetanes which decompose under the reaction conditions.

Scheme 65 Dimerization of [Bis(alkylsulfanyl)methylene]phosphines and [Bis(silylsulfanyl)methylene]phosphines^[316,317]



Similarly, phosphalkene **287** is also thermally unstable. Its dimerization to the 1,3-diphosphetane **288**^[318] was confirmed by X-ray crystallography.^[317] The phosphalkene **287** was generated by the reaction of carbon disulfide with the silylphosphine **286** (Scheme 65).^[317]

1,3-Dichloro-2,2,4,4-tetrakis(methylsulfanyl)-1,3-diphosphetane (285):^[319]

A soln of Et₃N (1.4 mL, 10 mmol) in Et₂O (2 mL) was added to a soln of bis(methylsulfanyl)-methylphosphonous dichloride (2.0 g, 10 mmol) in Et₂O (4 mL) at -10°C , with stirring. The mixture was kept at -10°C for 5 min. The Et₃N•HCl was rapidly filtered off and washed with Et₂O. The solvent was removed under reduced pressure and the resulting residue was recrystallized (toluene) to give colorless crystals; yield: 1.0 g (60%); mp $115\text{--}117^{\circ}\text{C}$; ¹H NMR (CDCl₃, δ): 2.44 (s, 12H, SCH₃); ³¹P NMR (CDCl₃, δ): 134.5.

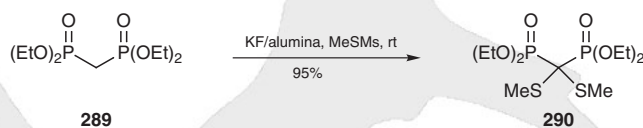
18.16.14.1.3

Method 3:

Sulfonation of Bis(phosphoryl)methanes

The treatment of active methylene compounds with 2 equivalents of *S*-methyl methanesulfonylthioate using alumina–potassium fluoride as base results in the formation of thioacetals.^[320] This methodology has been applied to the bis(phosphoryl)methane **289**, resulting in the thioacetal **290** in high yield (Scheme 66). This derivative was designed as a potential prodrug of carbonyldiphosphonate, a known antiviral agent.^[321]

Scheme 66 Sulfonation of Bis(phosphoryl)methanes^[320]



Bis(diethoxyphosphoryl)bis(methylsulfanyl)methane (290):^[320]

Bis(diethoxyphosphoryl)methane (1.4 g, 5.0 mmol) and *S*-methyl methanesulfonylthioate (1.26 g, 10 mmol) were absorbed on KF/alumina (8.0 g) and left at rt. The reaction was monitored by TLC until the starting material was completely consumed. The products were extracted with CH₂Cl₂ (3 × 20 mL). The solvent was removed under reduced pressure and the residue purified by chromatography (silica gel, CH₂Cl₂/MeOH 99:1) to give a colorless oil; yield: 1.81 g (95%); ¹H NMR (CCl₄, δ): 1.30 (t, 12H, $J = 7$ Hz, CH₂CH₃), 2.15 and 2.20 (s, 6H, SCH₃), 4.17 (dq, 4H, $J = 7, 4$ Hz, POCH₂), 4.20 (q, 2H, $J = 7$ Hz, COCH₂); ³¹P NMR (CDCl₃, δ): 15.9.

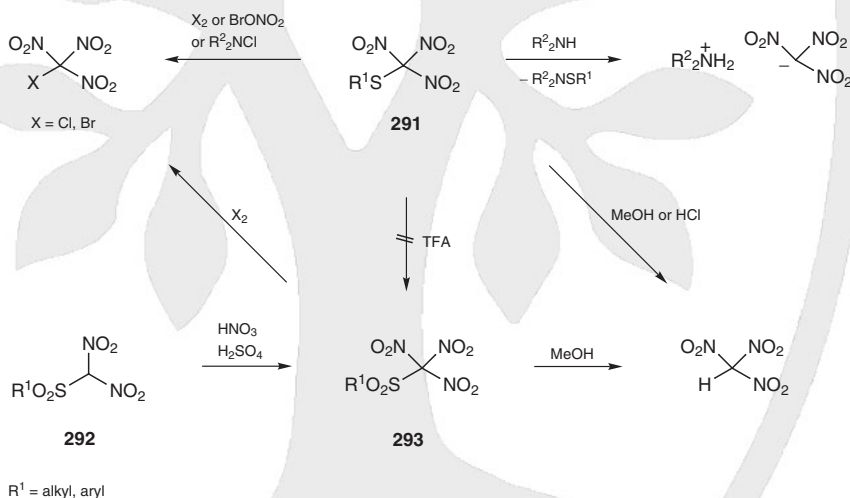
18.16.15

Product Subclass 15:**Thio- and Selenoorthocarbonic Acid Triamide Esters [Triamino-(organosulfanyl)- and Triamino(organoselanyl)methanes] and Trinitro(organosulfanyl)- and Trinitro(organoselanyl)methanes**

Although reports of simple thioorthocarbonic acid triamide esters are scarce, tris(azolyl)-methanethiolates^[322] and -sulfonates (Section 18.16.15.1.3) have been used as ligands in coordination chemistry.

The chemistry of trinitro(organosulfanyl)methanes **291** and their selenium analogues has been investigated in detail. It has been demonstrated that the C–S or C–Se bond of these derivatives is readily cleaved by both nucleophilic and electrophilic reagents (Scheme 67).^[323,324] The thermal degradation of trinitro(organosulfanyl)- and trinitro(organosulfonyl)methanes has been studied at 100 °C, whereas the selenium analogues are less stable and slowly decompose at room temperature.^[325,326] Attempts to oxidize trinitro(organosulfanyl)methanes **291** to the sulfones **293** with peroxides fail owing to the low reactivity of the substrate toward this class of oxidant.^[327] However, **293** can be synthesized by the nitration of dinitro(organosulfonyl)methanes **292**. The trinitro(organosulfonyl)methanes **293** also undergo the facile loss of sulfur when treated with electrophiles and nucleophiles.^[328] Trinitromethylsulfonium salts can similarly be prepared by the nitration of dinitromethylsulfonium salts.^[329]

Scheme 67 The Chemistry of Trinitro(organosulfanyl)- and Trinitro(organosulfonyl)-methanes^[323,324,327,328,330]



18.16.15.1

Synthesis of Product Subclass 15

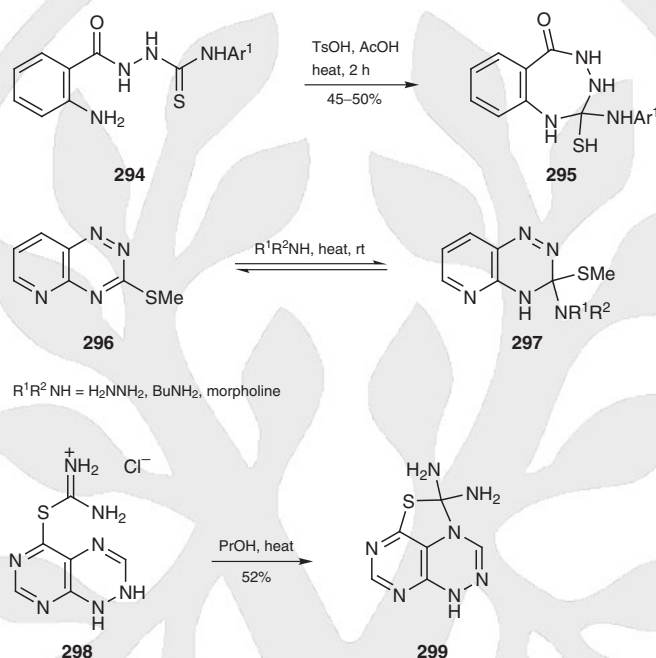
18.16.15.1.1

Method 1:**Addition of Amines to Thioureas or Isothioureas**

The addition of amines and hydrazines to the electrophilic carbon center of isothioureas and thioureas can generate unstable derivatives which eliminate one of the substituents to form stable urea products.^[331,332] However, there are examples of specific heterocycles containing hydrazine or azo functionality which form adducts that are sufficiently stable to be isolated. The cyclization of thiosemicarbazides **294** under acidic conditions has been used to prepare benzotriazepinones **295** by intramolecular attack of the aromatic amine on the thiocarbonyl center (Scheme 68).^[333] Although the expected nucleophilic

substitution of the isothiurea **296** occurs when reacted with amines or hydrazine at elevated temperatures, it is reported that reaction at room temperatures leads to the adducts **297**.^[334] These derivatives are thermally unstable and revert to the isothiurea **296** when heated.

Scheme 68 Heterocycles from Thioureas, Isothioureas, and Isothiuronium Salts by Addition of Amines^[333–335]



Attempts to prepare 2,4a-dihydro-1H-pyrimido[5,4-e][1,2,4]triazine-5-thione via the isothiuronium salt **298** (generated by chloride displacement with thiourea) result in low yields owing to the preferential formation of **299** resulting from intramolecular addition of the ring nitrogen (Scheme 68).^[335]

Benzothiazole derivatives have been synthesized by the addition of nitrogen and/or sulfur nucleophiles to guanidinium and isothiuronium salts in an analogous manner to that described for other members of Product Class 16 (*vide supra*).^[207,336]

2-Anilino-2-sulfanyl-1,2,3,4-tetrahydro-5H-1,3,4-benzotriazepin-5-one (**295**, $\text{Ar}^1 = \text{Ph}$):^[333]

A mixture of 2-(2-aminobenzoyl)-N-phenylhydrazinecarbothioamide (1.1 g, 3.8 mmol) and TsOH (20 mg) in AcOH (10 mL) was refluxed for 2 h. The product precipitated on cooling and was isolated by filtration. Recrystallization from acetone gave the product; yield: 0.48–0.54 g (45–50%); mp 309 °C; ^1H NMR (CDCl_3 , δ): 4.2 (s, 1H, SH), 5.9 (bs, 2H, NH); ^{13}C NMR (CDCl_3 , δ): 114.3, 116.3, 124.7, 125.4, 125.6, 127.9, 128.8, 132.3, 139.2, 150.0, 168.4, 181.5.

18.16.15.1.2

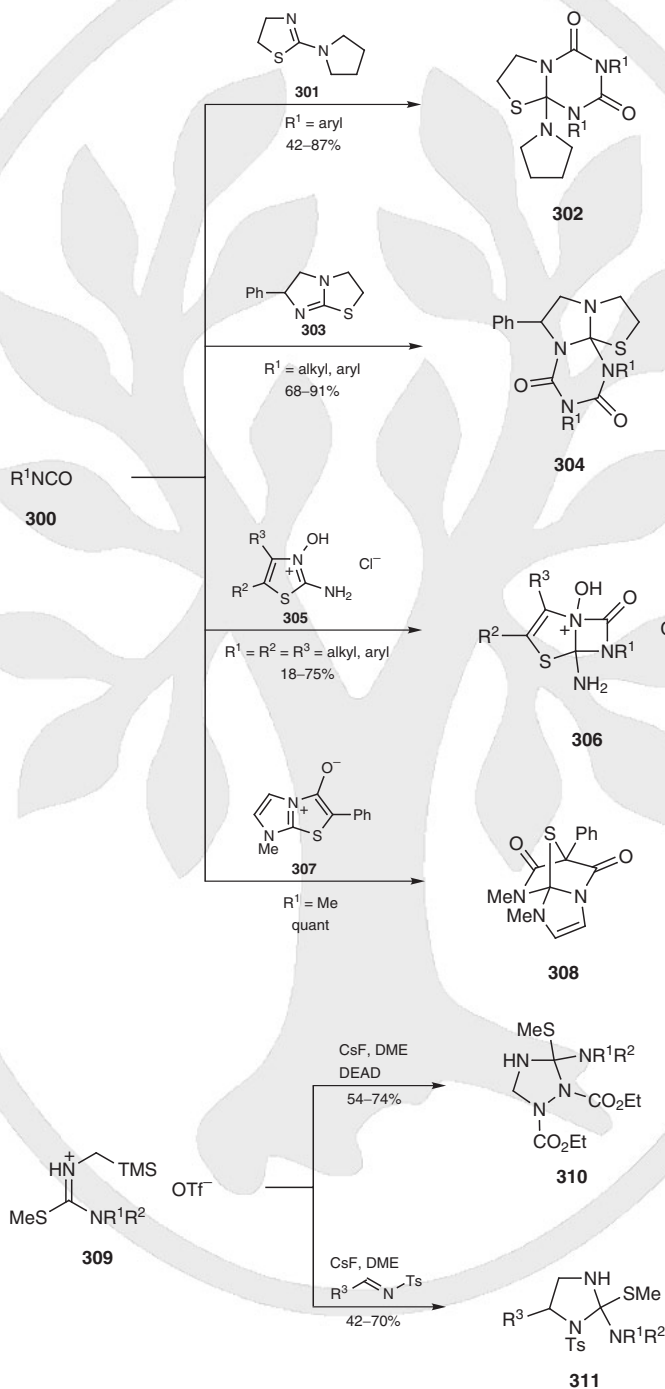
Method 2:

Cycloaddition of Thioureas and Isothioureas with Isocyanates

The cycloaddition of isocyanates **300** with a range of substrates has been used to synthesize a number of thioorthocarbonic acid triamide ester heterocycles (Scheme 69). Dihydrothiazoles **301** and **303** bearing electron-donating substituents at the 2-position undergo cycloaddition with aryl isocyanates **300** to form the 2:1 adducts **302** and **304**, respec-

tively.^[337] The outcome of these cycloaddition reactions is sensitive to the substitution on both the isocyanate and isothiurea. Introducing electron-withdrawing or sterically demanding substituents favors the formation of 1:1 adducts.^[338]

Scheme 69 Cycloaddition Reactions of Isocyanates and Azomethine Ylides^[337–341]



$R^1 = R^2 = \text{alkyl, aryl}$

The cycloaddition of other substrates with isocyanates has also been studied. In contrast to the corresponding *N*-oxide, which undergoes *O*-acylation with aryl isocyanates, the *N*-hydroxythiazolium salt **305** forms 1:1 cycloadducts **306**.^[339]

1,3-Dipolar cycloaddition reactions of mesoionic ring systems with heterocumulenes has been studied in detail.^[342] The resulting 1:1 cycloadducts are often unstable and extrude fragments to generate mesoionic heterocycles or six-membered heteroatomic betaines.^[343] However, the thiazolium ylide **307** has been reported to react with methyl isocyanate to form the stable cycloadduct **308** (Scheme 69).^[340]

Azomethine ylides **309** (generated *in situ* by the fluoride-induced desilylation of *N*-[(trimethylsilyl)methyl]iminium trifluoromethanesulfonates) react with dipolarophiles such as diethyl azodicarboxylate to form the 1:1 cycloadducts **310** (Scheme 69).^[341] Azomethine ylides generated through 3,4-dihydroisoquinolinium salts and aziridines have been shown to react with imines to form imidazolidines.^[344,345] The reactive *N*-benzylidene-4-toluenesulfonamides react with azomethine ylides to form the tosylimidazolidines **311**.^[341] These heterocycles are thermally unstable and eliminate thiols on heating.

1,3-Bis(4-chlorophenyl)-8a-(pyrrolidin-1-yl)tetrahydro-2*H*-[1,3]thiazolo[3,2-*a*][1,3,5]triazine-2,4(3*H*)-dione (302, R¹ = 4-ClC₆H₄); Typical Procedure:^[337]

4-Chlorophenyl isocyanate (3.84 g, 25 mmol) was added dropwise to a stirred soln of 2-(pyrrolidin-1-yl)-4,5-dihydro-1,3-thiazole (1.95 g, 12.3 mmol) in petroleum ether (bp 60–80 °C) (10 mL). The slurry was filtered after 18 h and the white solid was washed with petroleum ether (bp 40–60 °C) to give the product; yield: 5.0 g (86%); mp 126–128 °C; ¹H NMR (DMSO-*d*₆, δ): 1.7–2.0 (m, 4H, CH₂CH₂N), 3.1–3.5 (m, 6H, CH₂N, CH₂S), 3.9 (t, 2H, CH₂NCO).

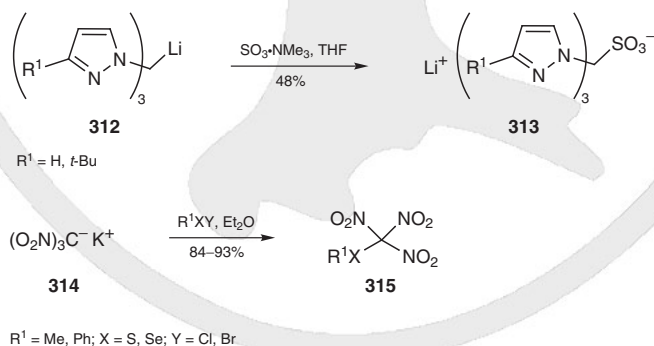
18.16.15.1.3

Method 3:

Substitution Reactions of Metalated Methanes with Sulfenyl and Selenenyl Halides

The methine proton of tripyrazolylmethane is sufficiently acidic to be removed by strong bases such as butyllithium.^[346] The resulting anions **312** are sufficiently reactive to react with electrophiles such as the sulfur trioxide–trimethylamine complex to form tripyrazolylmethanesulfonates **313**, a class of water-soluble ligands which have been used to form complexes with rhodium,^[347,348] copper,^[349,350] and zinc (Scheme 70).^[351]

Scheme 70 Reaction of Carbanions with Sulfur and Selenium Electrophiles^[326,346,352,353]



The potassium salt of trinitromethane **314** reacts with sulfenyl halides via C-sulfonylation to give the trinitro(organosulfanyl)methane **315** in high yield (Scheme 70).^[352] This reactivity is also observed when selenenyl halides are used.^[326] The choices of counterion and solvent are not crucial in influencing the course of this reaction provided that soft electro-

philes are employed. When harder electrophiles such as sulfenium salts are used, the alternate O-sulfonylation pathway predominates.^[353]

Lithium Tripyrazolylmethanesulfonate (313, $R^1 = H$):^[346]

A 1.6 M hexane soln of BuLi (7.5 mmol, 4.7 mL) was added to a soln of tripyrazolylmethane (1.3 g, 6.1 mmol) in THF (25 mL) at -60°C . The soln immediately turned yellow and turbid. After 1 h, the $\text{SO}_3\cdot\text{NMe}_3$ complex (10.0 g, 7.5 mmol) was added at -50°C . Under constant stirring, the resulting suspension was allowed to warm to 0°C over 90 min. After 3 h, the solvent was removed under reduced pressure. The residue was stirred with CHCl_3 for 1 h and then filtered over a membrane filter. Recrystallization (hot MeOH) yielded colorless crystals; yield: 0.88 g (48%).

18.16.16

Product Subclass 16:

Tetraselenoorthocarbonic Acid Tetraesters [Tetrakis(alkylselanyl)methanes]

18.16.16.1

Synthesis of Product Subclass 16

Reports dealing with the synthesis and reactivity of tetrakis(organoselanyl)methanes are scarce. Simple symmetrical derivatives can be synthesized using organometallic reagents. Symmetrical tetraselenaspirans such as **316** and **317** (Scheme 71) have been isolated as side products during the synthesis of tetrachalcogenofulvalenes.^[354,355] The structure of the selenaspiran **317** was confirmed by X-ray crystallographic analysis.^[356] It was observed that the stable crystal decomposed in chlorinated solvents such as chloroform or dichloromethane.

Scheme 71 Examples of Tetraselenaspirans^[354,355]



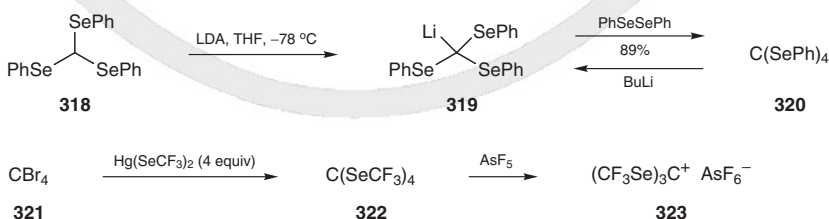
18.16.16.1.1

Method 1:

Substitution Reactions of [Tris(organoselanyl)methyl]lithium Reagents with Diorganodiselenium Compounds

In an analogous fashion to their sulfur analogues (Section 18.16.10.1.2.1), treatment of tris(phenylselanyl)methane (**318**) with lithium diisopropylamide at -78°C results in the formation of the lithiated species **319**, which can be quenched with various electrophiles including diphenyl diselenide to produce tetrakis(phenylselanyl)methane (**320**).^[357] Subsequent treatment of **320** with butyllithium regenerates the lithiated species **319** (Scheme 72).

Scheme 72 Preparation and Reactivity of Tetrakis(organoselanyl)methanes^[358,359]



The preparation of fluorinated tetrakis(alkylselanyl)methanes such as **322** has been achieved by reacting tetrabromomethane (**321**) with mercury(II) reagents.^[360] This can be used to generate the tris(trifluoromethylselanyl)methyl salt **323** by reaction with arsenic(V) fluoride in sulfur dioxide.^[358] Potassium halides react with the salt **323** to give halo-tris(trifluoromethylselanyl)methanes in good yield.

Tetrakis(phenylselanyl)methane (320); Typical Procedure:^[359]

A soln of (PhSe)₂ (6.24 g, 20 mmol) in THF (20 mL) was added to a soln of [tris(phenylselanyl)methyl]lithium (9.62 g, 20 mmol) in THF (120 mL) at -78 °C. The brown soln was allowed to warm to -40 °C and then stirred at -30 °C for 2 h. The precipitate was removed by filtration and H₂O was added to the filtrate. The layers were separated and the organic layer dried and concentrated under reduced pressure. The residue and precipitate were recrystallized (pentane/cyclohexane) to give colorless crystals; yield: 11.2 g (89%); mp 130–134 °C.

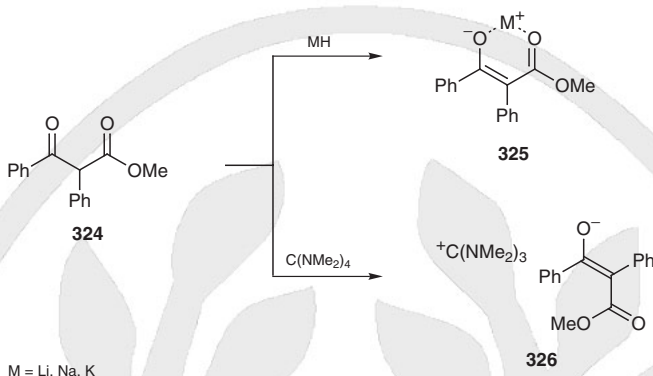
18.16.17

**Product Subclass 17:
Orthocarbonic Acid Tetraamides [Tetrakis(dialkylamino)methanes] and
Tetranitromethane**

The chemistry and reactivity of tetrakis(dialkylamino)methanes (also termed orthocarbamides)^[35] and tetranitromethane^[361] have been reviewed previously.

Methanetetraamine is not a known compound and only its ammonia-deficient decomposition products guanidine and carbodiimide have been detected.^[362] Substituted orthocarbamides are sufficiently stable to be prepared and isolated. Thermal degradation generally occurs at temperatures slightly above the melting point, resulting in polymeric tars.^[363] These derivatives are moisture sensitive and exposure to water leads to hydrolysis to the stable hexaalkylguanidinium salts and secondary amines.^[362]

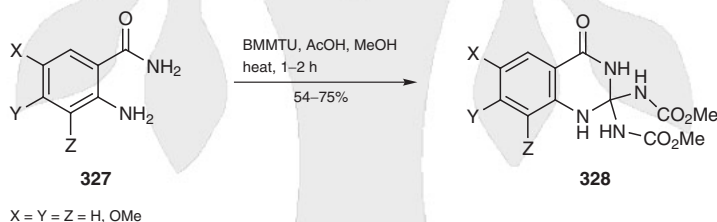
Treatment of carbon acids such as malonic esters and 1,2-bis(tolylsulfonyl)methanes with tetrakis(dimethylamino)methane results in the rapid formation of hexaalkylguanidinium salts.^[364–366] This provides a method for the preparation and storage of malonate-type anions with a counter ion which is incapable of forming a chelate.^[367] Thus, deprotonation of methyl 3-oxo-2,3-diphenylpropanoate (**324**) with tetrakis(dimethylamino)methane leads to the formation of the stable hexamethylguanidinium enolate **326** with the *E* configuration exclusively, owing to steric interactions of the two phenyl substituents (Scheme 73). This contrasts with the use of metalated hydrides, which form the *Z* configuration enolate **325** owing to chelation with the metal cation, overriding the steric influence of the two phenyl substituents. Tetrakis(dimethylamino)methane also reacts with other active methylene compounds to afford bis(dimethylamino)methylene derivatives. This is exemplified by the reaction of fluorene with tetrakis(tetramethylamino)methane at elevated temperature to give 9-[bis(dimethylamino)methylene]fluorene.^[364]

Scheme 73 Generation of *E* or *Z* Configuration Enolates from Tetrakis-(dimethylamino)methane or Metal Hydrides, Respectively^[367]

The tendency for tetrakis(dimethylamino)methane to lose dimethylamine and form hexamethylguanidinium ions as been used to introduce the ions as ligands into a number of transition-metal complexes.^[362,368–372]

18.16.17.1 Synthesis of Product Subclass 17

The reaction of 2-aminobenzamides **327** with 1,3-bis(methoxycarbonyl)-2-methylisothiourea (BMMTU) under mildly acidic conditions results in the formation of **328** rather than the expected monocarbamates (Scheme 74).^[199]

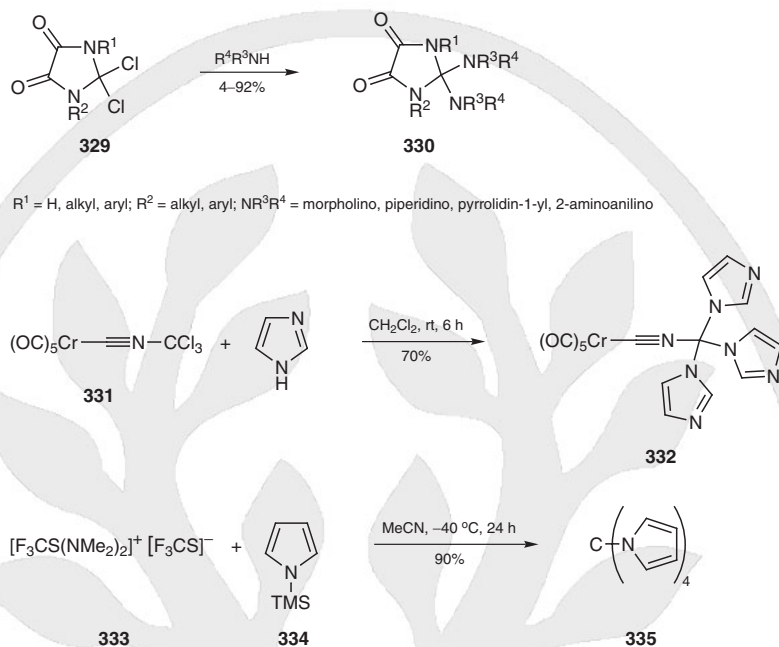
Scheme 74 Synthesis of Methyl [2-[(Methoxycarbonyl)amino]-4-oxo-1,2,3,4-tetrahydroquinazolin-2-yl]carbamates^[199]

18.16.17.1.1

Method 1:

Substitution of Halomethanes with Amines

The nucleophilic displacement of di- and trichloromethanes has been used in the synthesis of a number of specific orthocarbamides. Symmetrical 2,2-dichloroimidazolidines **329** are readily accessed from carbodiimides (*vide supra*), and their reaction with secondary amines results in the isolation of the orthocarbonic acid derivative **330** (Scheme 75).^[200,373] Byproducts generally associated with this process are unsymmetrical ureas and oxamides. The proportions of these components in the mixture are dependent on the substituents on the imidazolidine nitrogen and the amine basicity.

Scheme 75 Nucleophilic Substitution of Halomethanes with Nitrogen Nucleophiles^[201,322,373,374]

In addition to using simple secondary amines, nucleophilic nitrogen-containing heterocycles have also been used. Tetrapyrrolylmethane can be prepared from carbon tetrachloride under potassium hydroxide–potassium carbonate phase-transfer conditions.^[375] Pentacarbonyl(trichloromethyl isocyanide)chromium (**331**) reacts with imidazole to give the isocyanide complex **332**.^[374] The outcome of this reaction, however, is dependent on the amine. Benzimidazole attacks at both the trichloromethyl and isocyano centers, resulting in the formation of *N,N'*-carbene complexes. The choice of heterocycle has also been shown to be important in determining the outcome of the reaction between salt **333** and silylated azoles (Scheme 75).^[322] Tetrapyrrolylmethane (**335**) was isolated on reaction with the trimethylsilylpyrrole **334**, whereas similar treatment with a silylated pyrazole or trimethyltriazoles results in the reaction stopping at the tris(azolyl)methanethioate stage. Exchanging the salt counterion in **333** has been shown to have a minimal effect on these displacement reactions. The displacement of fluorine from trifluoromethylamine with aniline has been used in the synthesis of *N,N',N''*-triphenylmethane-tetramine.^[376]

1,3-Dialkyl-2,2-bis(dialkylamino)imidazolidine-4,5-diones **330**; General Procedure:^[201]

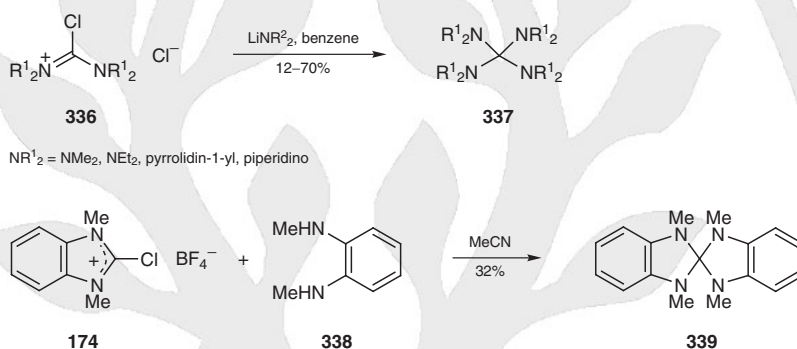
The diamine (10 mmol) was added to a soln of 2,2-dichloroimidazolidine-4,5-dione (10 mmol) in dioxane (25 mL) at rt. The mixture instantly became yellow and then became cloudy with the precipitating diamine hydrochloride salt. A soln of Et_3N (20 mmol) in dioxane (10 mL) was added and the mixture was stirred for 2 h. The mixture was filtered and washed with dioxane. The filtrate was concentrated under reduced pressure and the residue was then recrystallized to give the product; yield: 4–92%.

18.16.17.1.2

Method 2:**Tetrakis(dialkylamino)methanes from Formamidine Salts by Addition of Metalated Dialkylamines**

The synthesis of symmetrical tetrakis(dialkylamino)methanes **337** proceeds in moderate yields by the addition of lithiated dialkylamines to tetraalkylchloroformamidine salts **336** (Scheme 76).^[362] Tetraazaspirans have also been synthesized from formamidine salts. Addition of the 1,2-diamine **338** to the formamidine tetrafluoroborate salt **174** gives the tetraazaspiran **339** in moderate yield.^[207] This method has also been applied to the synthesis of symmetrical tetraazaspirans based on naphthalene-1,8-diamines.^[9]

Scheme 76 Synthesis of Tetrakis(dialkylamino)methanes and Tetraazaspirans from Formamidine Salts^[207,362]



Addition of chlorotetramethylformamidine chloride **336** ($R^1 = \text{Me}$) to a solution of dimethylamine, trimethyl borate, and sodium hydride results in the formation of tetrakis(dimethylamino)methane in 11% yield.^[150] Reduction of the salt, however, is the dominant reaction pathway under these reaction conditions, resulting in the isolation of the corresponding orthoformic acid amide as the major product (50% yield).

The synthesis of 1,4,7,10-tetraazatetracyclo[5.5.1.0^{4,13}.0^{10,13}]tridecane (**27**; Scheme 8, Section 18.16.1.2.2) has been reported by initially treating cyclen with ethyl orthocarbonate under acidic conditions to give the guanidinium salt **26**, which is then converted into **27** on exposure to 1 M sodium hydroxide.^[90]

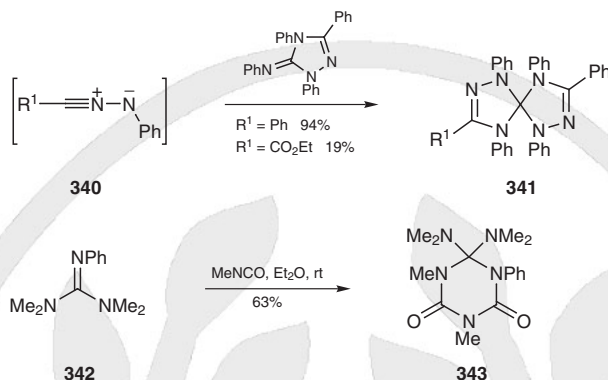
Tetrakis(dialkylamino)methanes 337; General Procedure:^[362,377]

The tetraalkylchloroformamidine chloride (1 equiv) was added to a slurry of lithium dialkylamide (2 equiv) in anhyd benzene (**CAUTION: carcinogen**) at rt. The mixture was stirred for several h. The solvent was removed under reduced pressure and the hygroscopic tetramine was isolated and purified by either recrystallization (pentane) or sublimation; yield: 12–70%.

18.16.17.1.3

Method 3:**Tetraaminomethanes from Cycloaddition Reactions**

Carbodiimides undergo 1,3-dipolar cycloaddition with 2 equivalents of nitrilimines (*vide supra*) to yield the corresponding tetraazaspirans in low to good yields.^[209] 1,3-Dipolar cycloaddition reactions between triazoles and diphenylnitrilimine **340** ($R^1 = \text{Ph}$) afford the tetraazaspirans **341** (Scheme 77).^[209]

Scheme 77 Synthesis of Orthocarbamides via Cycloaddition Reactions^[209,378]

N-Substituted guanidines such as **342** form 1:2 adducts with isocyanates to give triazinanes **343**.^[378] Different substitution patterns can be accessed on the nitrogens of the triazinane ring by forming a 1:1:1 adduct between the N-substituted guanidine **342** and equimolar quantities of two different isocyanates. In the absence of solvent, the reaction of phenyl isocyanate with guanidines does not lead to the triazinane but rather the corresponding 1,3-diphenyldiazetidine-2,4-dione, which decomposes to give triphenyl isocyanurate.

1,3,4,6,8,9-Hexaphenyl-1,2,4,6,7,9-hexaazaspiro[4.4]nona-2,7-diene (**341**, $\text{R}^1 = \text{Ph}$);

Typical Procedure:^[209]

A soln of N-phenylbenzenecarbohydrazonoyl chloride (339 mg, 1.47 mmol), phenyl(2,4,5-triphenyl-2,4-dihydro-1,2,4-triazol-3-ylidene)amine (433 mg, 1.40 mmol), Et_3N (1.0 mL), and benzene (8 mL) (**CAUTION: carcinogen**) was stirred for 2 d. The ammonium salt was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was crystallized ($\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give colorless crystals; yield: 0.76 g (94%); mp 171–173 °C.

18.16.17.1.4

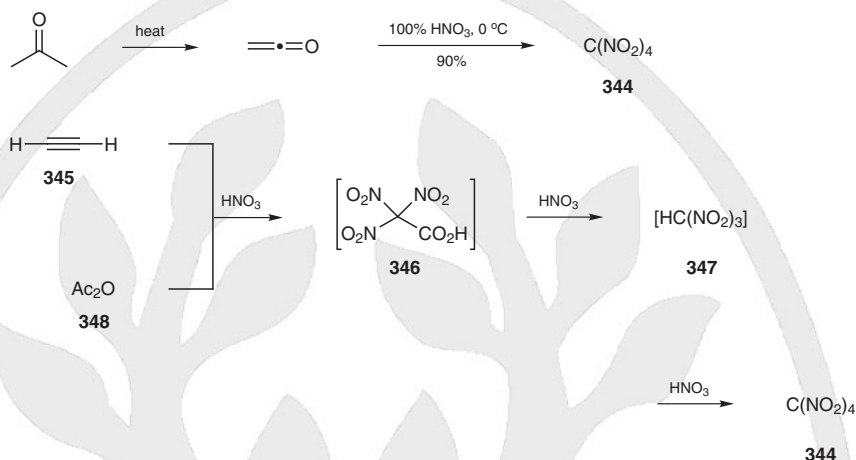
Method 4:

Tetranitromethane from Trinitromethane Derivatives by Nitration

Tetranitromethane (**344**) is a readily available, highly volatile liquid which has found considerable use in organic synthesis.^[361] Its properties have been extensively studied and it has been found to be carcinogenic and highly toxic, attacking the respiratory tracts and the central nervous system.^[361,379,380] This reagent should not be purified by distillation as it can explode on thermal decomposition.^[381] It should also be stored out of contact with aromatic compounds as it can react with them explosively.^[381] Tetranitromethane was first obtained in 1857 by the reaction of nitric and sulfuric acids on sodium 2-cyanoacetamide, followed by hydrolysis and nitration with fuming nitric acid.^[382] A number of different procedures were subsequently developed to improve the efficiency of the tetranitromethane synthesis. These include the reaction of acetic anhydride with diacetylorthonitric acid,^[383] acetyl nitrate,^[384] or nitrogen pentoxide–nitrogen peroxide.^[385] Nitric acid has also been used to synthesize tetranitromethane from other sources of carbon,^[361] the most notable being ketene which gives a 90% yield.^[386] Other high-yielding methods to synthesize tetranitromethane include the reactions of picrylpyridinium nitrate with nitromethane^[361] and nitril chloride with the potassium salt of trinitromethane.^[387] Of the numerous procedures available, the nitration of acetylene (**345**)^[388,389] or acetic anhydride (**348**)^[381] with nitric acid have been the most commonly used (Scheme 78), and have been developed for producing tetranitromethane on an industrial scale.^[361] Both reactions pro-

ceed via trinitroacetic acid (**346**), which decarboxylates to trinitromethane (**347**). This is then nitrated to give tetranitromethane.^[390]

Scheme 78 Nitration of Acetic Anhydride and Acetylene with Nitric Acid^[361,386]



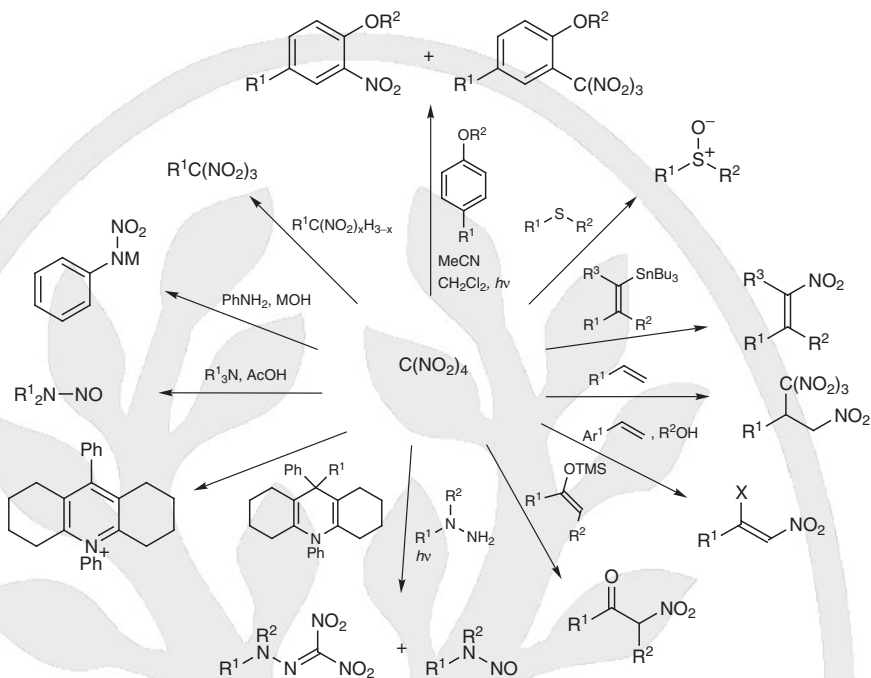
Tetranitromethane (**344**):^[386]

A current of ketene (generated by the pyrolysis of acetone) was passed slowly into 100% HNO_3 at 0°C . The reaction was immediate. The resulting mixture was poured onto ice and then purified by steam distillation. The product was separated from the upper layer of H_2O , washed with dilute alkali and then H_2O , and finally dried (Na_2SO_4); yield: 90%.

18.16.17.2 Applications of Product Subclass 17 in Organic Synthesis

18.16.17.2.1 Method 1: Nitrations using Tetranitromethane

The defining characteristic in the reactivity and synthetic applications of tetranitromethane is its ability to form donor–acceptor (charge transfer) complexes which can be transformed into a range of different functionalities, depending on the substrates involved.^[361] This is readily demonstrated by the addition of unsaturated compounds to tetranitromethane solutions, which results in an instantaneous color change indicative of charge transfer complex formation. Detailed mechanistic studies of this phenomenon have been carried out and are reviewed elsewhere.^[391,392] Although a comprehensive description of the chemistry of tetranitromethane is beyond the scope of this article,^[361] a number of synthetically useful transformations are highlighted (Scheme 79).

Scheme 79 Selected Reactions of Tetranitromethane^[393–405]

Photochemical addition of tetranitromethane to aromatic compounds leads to nitration and/or alkylation products.^[392] The reaction outcome is dependent on both the substrates and solvents used.^[393] Selective nitrations have been reported using tetranitromethane for specific substrates, including tyrosine residues in peptides^[406] and zinc(II)-mediated nitration of 3,4-dihydroxynitrostyrene.^[407] Similarly, the outcome of the reaction of tetranitromethane with alkenes is also strongly influenced by the choice of substrate and reaction conditions.^[394,395,408–410] Selective introduction of the nitro functionality into alkenes^[396] and heteroaromatic compounds^[411,412] has been achieved via nitrodestannylation. α -Nitration of ketones can be achieved selectively via the silyl enol ether.^[397] Nitroalkanes and *gem*-nitroalkanes both undergo mild nitration with tetranitromethane under alkali conditions to give trinitroalkanes (Scheme 79).^[398]

Tetranitromethane is also used as an oxidant, and has been employed in the conversion of sulfides into sulfoxides^[399] and in the aromatization of dihydroaromatic compounds such as 1,4-dihydropyridines.^[400] *N,N'*-Disubstituted hydrazines initially undergo nitration on nitrogen when treated with tetranitromethane, to give the nitrohydrazones.^[401] Irradiation of these products results in nitrosation.^[402] Nitrosation of aliphatic amines and anilines occurs with tetranitromethane under acidic conditions,^[403] whereas under basic conditions, *N*-nitration becomes the dominant process for aromatic amines (Scheme 79).^[404,405]

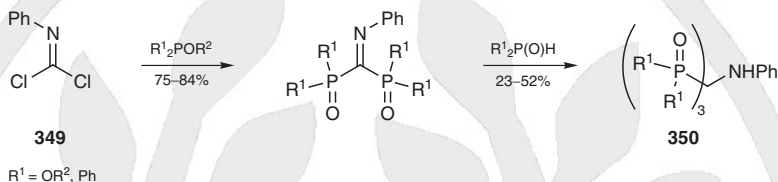
18.16.18

Product Subclass 18:
Aminotris(phosphoryl)methanes

Aminotris(phosphoryl)methanes are moisture sensitive and reaction with water results in the loss of one of the phosphonate substituents to give aminobis(phosphoryl)methanes.^[413]

18.16.18.1 Synthesis of Product Subclass 18

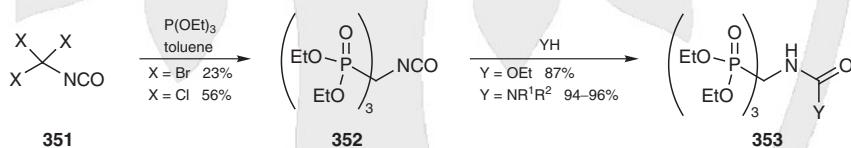
Only two synthetic approaches have been reported in the literature for aminotris(phosphoryl)methanes. A two-step alternative to the Arbuzov reaction is the double displacement of dichloroimine **349** with triethyl phosphite, followed by addition of an alkylphosphinoylmethane to give aminotris(phosphoryl)methanes **350** (Scheme 80).^[414,415]

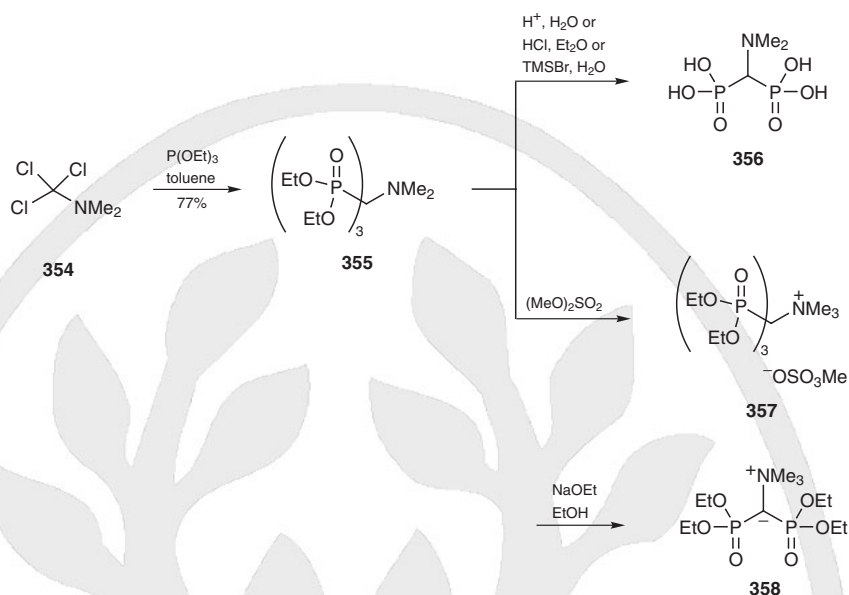
Scheme 80 Two-Step Synthesis of Aminotris(phosphoryl)methanes^[414]

18.16.18.1.1

Method 1:
Substitution Reactions of (Trihalomethyl)amines with Trialkyl Phosphites

Trihalomethyl isocyanates **351** (prepared by the Curtius rearrangement of trihaloacetyl azides) undergo Arbuzov reaction with 3 equivalents of triethyl phosphite to afford the tris(phosphoryl)methyl isocyanate **352** in moderate yield (Scheme 81).^[416,417] This process is accompanied by the formation of triethyl phosphate and tetraethyl pyrophosphate by-products in varying quantities, depending on the conditions used. The isocyanate **352** is inert toward alcohol unless an amine base is added. Slow addition is then observed, resulting in the formation of the corresponding carbamate **353** (Y = OEt). The carbamate is not thermally stable and reverts to the isocyanate on heating.^[417] Amine nucleophiles react with tris(phosphoryl)methyl isocyanates to give ureas **353** (Y = NR¹R²) in high yield.

Scheme 81 Synthesis and Reactivity of Isocyanato- and (Dialkylamino)triphosphoryl-methanes^[416-419]



Dimethyl(trichloromethyl)amine (**354**) undergoes facile Arbuzov reaction with triethyl phosphite to give the aminotris(phosphoryl)methane **355**.^[418] Hydrolysis with aqueous acid, anhydrous hydrogen chloride in diethyl ether, or bromotrimethylsilane in water results in concomitant loss of one of the phosphonate substituents to give the diphosphonic acid **356** (Scheme 81).^[419] The quaternary ammonium salt **357** can be synthesized by the addition of dimethyl sulfate to aminotris(phosphoryl)methane **355**. Treatment of these salts with sodium ethoxide results in loss of phosphonate to give the ylide **358**.

The Arbuzov reaction has also been used in the synthesis of sulfur analogues of these derivatives. (Alkylsulfanyl)tris(organophosphoryl)methanes have been synthesized by the reaction of triethyl phosphite with trichloromethanesulfenyl chloride.^[414]

Tris(diethoxyphosphoryl)isocyanatomethane (**352**):^[416]

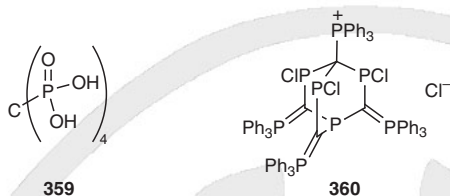
A soln of $\text{P}(\text{OEt})_3$ (25 g, 0.15 mol) in toluene (40 mL) was added slowly to a soln of tribromomethyl isocyanate (14.7 g, 0.05 mol) at rt. The mixture was heated for 90 min at 80–90 °C. The solvent and EtBr were removed under reduced pressure and the residue was purified by distillation under reduced pressure; yield: 5.35 g (23%); bp 139–141 °C/0.06 Torr; ^{31}P NMR (CCl_4 , δ): 40.73.

18.16.19

Product Subclass 19:

Tetrakis(phosphanyl)methanes, Tetrakis(phosphinoyl)methanes, and Tetrakis(phosphoryl)methanes

Simple tetrakis(phosphanyl)methanes and their oxides are extremely moisture sensitive.^[420] The phosphonic acid **359** (Scheme 82) and its sodium salts have been used as sequestration and chelating agents in detergent compositions.^[421,422] Only one example of a tetraphosphaspiran has been reported in the literature; its electronic structure has been investigated by photoelectron spectroscopy.^[10] The reaction of [bis(trimethylsilyl)methylene]triphenyl- λ^5 -phosphane with phosphorus trichloride results in the formation of a number of oligomers, including the tetramer **360** which was isolated and characterized by X-ray crystallography.^[423]

Scheme 82 Examples of Tetrakis(phosphanyl)methanes and Tetrakis(phosphoryl)methanes^[421,423]

18.16.19.1

Synthesis of Product Subclass 19

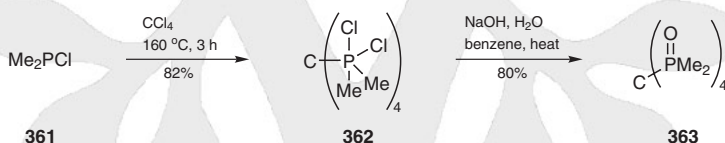
18.16.19.1.1

Method 1:
Reactions of Carbon Tetrachloride

18.16.19.1.1.1

Variation 1:
With Chlorodimethylphosphine

Chlorodimethylphosphine (**361**) adds to aliphatic halides such as carbon tetrachloride in the absence of catalyst to afford the adduct **362** in high yield (Scheme 83).^[420] The adduct **362** can be readily converted into the oxide **363** by treatment with aqueous alkali. Both the adduct **362** and the tetrakis(phosphinoyl)methane **363** are extremely hygroscopic and rapidly deliquesce on exposure to atmospheric moisture.

Scheme 83 Synthesis of Tetrakis(phosphinoyl)methanes^[420]**Tetrakis(dimethylphosphinoyl)methane (363):**^[420]

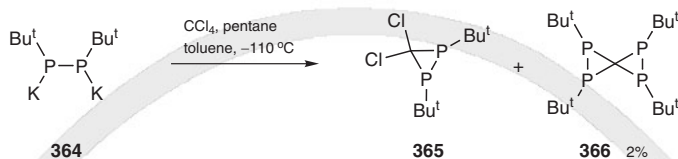
CCl_4 (1 equiv) (**CAUTION: toxic**) and Me_2PCl (1 equiv) were heated in a sealed tube at 160 °C for 3 h to afford adduct **362**. The residue was dissolved in benzene (**CAUTION: carcinogen**) and the soln transferred to a Dean–Stark apparatus. NaOH was added to the mixture and the H_2O was azeotropically removed under reflux. The solvent was removed under reduced pressure and the residue was dissolved in EtOH and filtered. The filtrate was then heated under reduced pressure at 60–80 °C for 8 h to afford the product; yield: 86%; mp 84–86 °C.

18.16.19.1.1.2

Variation 2:
By [2 + 1] Cyclocondensation with Dipotassium 1,2-Di-*tert*-butyldiphosphide

[2 + 1] Cyclocondensation of dipotassium diphosphide **364** with geminal dihalides results in the formation of diphosphiranes. When this methodology is applied to carbon tetrachloride, a mixture of the diphosphirane **365**, tetraphosphaspiran **366**, and polymeric cyclophosphophanes is recovered (Scheme 84).^[424] The tetraphosphaspiran **366** (which was confirmed by X-ray crystallography)^[425] is formed as a mixture of isomers (17:3), differing in the relative arrangement of the *trans*-oriented *tert*-butyl groups at the two three-membered rings.

Scheme 84 [2 + 1] Cyclocondensation of Carbon Tetrachloride and Dipotassium 1,2-Di-*tert*-butyldiphosphide^[424]



1,2,4,5-Tetra-*tert*-butyl-1,2,4,5-tetraphosphaspiro[2.2]pentane (366):^[424]

A soln of CCl_4 (10.3 g, 67 mmol) (**CAUTION: toxic**) in toluene (60 mL) was cooled to -78°C and added dropwise to a stirred suspension of dipotassium 1,2-di-*tert*-butyldiphosphide (**364**; 17.6 g, 60 mmol) in pentane/toluene (1:1, 150 mL) at -110°C . The mixture was stirred for a further 5 h at -78°C , after which time the precipitate was filtered off under suction and then washed with toluene (3×20 mL). The combined filtrates were concentrated under reduced pressure and the resulting black-brown residue was purified by column chromatography (alumina, hexane). The fractions with the highest content of product were combined, the solvent was removed under reduced pressure, and the residue was successively recrystallized from hexane (9 \times), dioxane (3 \times), and MeOH (2 \times), with concomitant monitoring by ^{31}P NMR, to give the product as an 17:3 mixture of isomers; yield: 0.19 g (2%); major isomer: ^1H NMR (benzene- d_6 , δ): 1.25 (s, 36H); ^{13}C NMR (benzene- d_6 , δ): 24.5, 29.9, 30.4; ^{31}P NMR (benzene- d_6 , δ): -132.0 .

References

- [1] Eveland, J. R.; Whitmire, K. H., *Angew. Chem.*, (1997) **109**, 1241; *Angew. Chem. Int. Ed. Engl.*, (1997) **36**, 1193.
- [2] Millich, F.; Eick, J. D.; Jeang, L.; Byerley, T. J., *J. Polym. Sci., Part A: Polym. Chem.*, (1993) **31**, 1667.
- [3] Bromley, M. K.; Solomon, D. H., *Polymer*, (1999) **40**, 6539.
- [4] Zhou, Z.; Jin, B.; He, P., *J. Appl. Polym. Sci.*, (2002) **84**, 1457.
- [5] Kostoryz, E. L.; Tong, P. Y.; Chappelow, C. C.; Glaros, A. G.; Eick, J. D.; Yourtee, D. M., *J. Biomater. Sci., Polym. Ed.*, (2000) **11**, 187.
- [6] Yourtee, D. M.; Tong, P. Y.; Rose, L. A.; Eick, J. D.; Chappelow, C. C.; Bean, T. A., *Res. Commun. Mol. Pathol. Pharmacol.*, (1994) **86**, 347.
- [7] Kobayashi, M.; Gleiter, R.; Coffen, D. L.; Bock, H.; Schulz, W.; Stein, U., *Tetrahedron*, (1977) **33**, 433.
- [8] Gleiter, R.; Haider, R.; Quast, H., *J. Chem. Res., Synop.*, (1978), 138.
- [9] Gleiter, R.; Uschmann, J., *J. Org. Chem.*, (1986) **51**, 370.
- [10] Gleiter, R.; Uschmann, J.; Baudler, M., *J. Chem. Soc., Dalton Trans.*, (1986), 1659.
- [11] Spanget-Larsen, J.; Uschmann, J.; Gleiter, R., *J. Phys. Chem.*, (1990) **94**, 2334.
- [12] Smolinski, S.; Balazy, M.; Iwamura, H.; Sugawara, T.; Kawada, Y.; Iwamura, M., *Bull. Chem. Soc. Jpn.*, (1982) **55**, 1106.
- [13] Andoni, E.; Bossa, M.; Cauletti, C.; Furlani, C.; Palma, A., *J. Organomet. Chem.*, (1983) **244**, 343.
- [14] Minkin, V. I., *Chem. Rev.*, (2004) **104**, 2751.
- [15] Al-Shemali, M.; Boldyrev, A. I., *J. Phys. Chem. A*, (2002) **106**, 8951.
- [16] Bronsted, J. N.; Wynne-Jones, W. F. K., *Trans. Faraday Soc.*, (1929) **25**, 59.
- [17] Bisesi, M. S., In *Patty's Toxicology*, 5th ed., Bingham, B.; Cochrane, B.; Powell, C., Eds.; Wiley-Interscience: New York, (2001); Vol. 6, p 933.
- [18] Sanda, F.; Endo, T., *J. Polym. Sci., Part A: Polym. Chem.*, (2001) **39**, 265.
- [19] Takata, T.; Endo, T., In *Expanding Monomers: Synthesis, Characterisation, and Application*, Sadhir, R. K.; Luck, R. M., Eds.; CRC: Boca Raton, FL, (1992); p 416.
- [20] Pogany, S. A.; Zentner, G. M., EP 537 000, (1993); *Chem. Abstr.*, (1994) **120**, 55328.
- [21] Choi, N. S., *Polymer (Korea)*, (1980) **4**, 35.
- [22] Taguchi, H.; Kato, H.; Kato, H., JP 05 105 684, (1993); *Chem. Abstr.*, (1993) **119**, 139990.
- [23] Zhang, J.; Colbow, K., US 2004 053 084, (2004); *Chem. Abstr.*, (2004) **140**, 238505.
- [24] Morelli, J. P.; Miracle, G. S.; Price, K. N.; Gray, L. M.; Jones, K. D., WO 98 47 995, (1998); *Chem. Abstr.*, (1998) **129**, 332488.
- [25] Gumerova, V. K.; Pastushenko, E. V.; Zlatskii, S. S.; Rakhmankulov, D. L., *J. Gen. Chem. USSR (Engl. Transl.)*, (1987) **57**, 2111.
- [26] Seyfarth, H. E.; Rieche, A.; Hesse, A.; Kahl, H., *Chem. Ber.*, (1969) **102**, 2866.
- [27] Gumerova, V. K.; Pastushenko, E. V.; Zlatskii, S. S.; Rakhmankulov, D. L., *J. Appl. Chem. USSR (Engl. Transl.)*, (1988) **61**, 863.
- [28] Rebek, J.; McCready, R.; Wolf, S.; Mossman, A., *J. Org. Chem.*, (1979) **44**, 1485.
- [29] Fuhry, M. A. M., In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A., Ed.; Wiley: Chichester, UK, (1995); Vol. 7, p 4819.
- [30] Gilligan, W. H.; Sitzmann, M. E., *J. Energ. Mat.*, (1983) **1**, 95.
- [31] Martin, D.; Herrmann, H. J.; Rackow, S.; Nadolski, K., *Angew. Chem.*, (1965) **77**, 96; *Angew. Chem. Int. Ed. Engl.*, (1965) **4**, 73.
- [32] Basset, H., *Justus Liebigs Ann. Chem.*, (1864) **132**, 54.
- [33] Tieckelmann, H.; Post, H. W., *J. Org. Chem.*, (1948) **13**, 265.
- [34] Islam, N. B.; Kwart, H.; Khan, S., *J. Chem. Eng. Data*, (1985) **30**, 509.
- [35] Kantlehner, W.; Funke, B.; Haug, E.; Sefh, P.; Kienitz, L.; Maier, T., *Synthesis*, (1977), 73.
- [36] Fries, G.; Kirchhoff, J., EP 1 207 147, (2002); *Chem. Abstr.*, (2002) **136**, 385875.
- [37] Findeisen, K.; Wagner, K.; Holtschmidt, H., *Synthesis*, (1972), 599.
- [38] Chan, T. H.; Harrod, J. F.; Van Gheluwe, P., *Tetrahedron Lett.*, (1974), 4409.
- [39] Hill, M. E.; Carty, D. T.; Tegg, D.; Butler, J. C.; Stang, A. F., *J. Org. Chem.*, (1965) **30**, 411.
- [40] Latimer, D. R.; Weil, J. A.; Quail, J. W.; Robinson, W. T., *Can. J. Chem.*, (1989) **67**, 143.
- [41] Kantlehner, W.; Maier, T.; Kapassakalidis, J. J., *Liebigs Ann. Chem.*, (1981), 70.
- [42] Ingold, C. K.; Powell, J., *J. Chem. Soc.*, (1921), 1228.
- [43] Adcock, J. L.; Robin, M. L.; Zuberi, S., *J. Fluorine Chem.*, (1987) **37**, 327.
- [44] Mues, P.; Buysch, H. J., *Synthesis*, (1990), 249.

- [45] Webb, R. L.; Labano, C. S., *J. Heterocycl. Chem.*, (1982) **19**, 1205.
- [46] Eremenko, L. T.; Oreshko, G. V.; Fadeev, M. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1991), 180.
- [47] Gross, H.; Rieche, A.; Hoft, E., *Chem. Ber.*, (1961) **49**, 544.
- [48] Bromley, M. K.; Gason, S. J.; Looney, M. G.; Solomon, D. H., *Aust. J. Chem.*, (1999) **52**, 657.
- [49] Lee, A. G., *J. Chem. Soc. A*, (1970), 467.
- [50] Sakai, S.; Kuroda, Y.; Ishii, Y., *J. Org. Chem.*, (1972) **37**, 4198.
- [51] Sakai, S.; Kiyohara, Y.; Itoh, K.; Ishii, Y., *J. Org. Chem.*, (1970) **35**, 2347.
- [52] Sakai, S.; Kobayashi, Y.; Ishii, Y., *J. Org. Chem.*, (1971) **36**, 1176.
- [53] Narasimhamurthy, N.; Samuelson, A. G., *Tetrahedron Lett.*, (1986) **27**, 991.
- [54] Kandanarachchi, P.; Sinnott, M. L., *J. Am. Chem. Soc.*, (1994) **116**, 5592.
- [55] Shibuya, I.; Gama, Y.; Shimizu, M., *Heterocycles*, (1998) **48**, 461.
- [56] Meerwein, H.; Florian, W.; Schon, N.; Stopp, G., *Justus Liebig's Ann. Chem.*, (1961) **641**, 1.
- [57] Meerwein, H., *Chem. Ber.*, (1956) **89**, 2060.
- [58] Kabab, S., *Angew. Chem.*, (1966) **78**, 714; *Angew. Chem. Int. Ed. Engl.*, (1966) **5**, 675.
- [59] Yoder, C. M. S.; Zuckermann, I. J., *J. Heterocycl. Chem.*, (1967) **4**, 166.
- [60] Kuran, W.; Listos, T., *Makromol. Chem.*, (1992) **193**, 945.
- [61] Tagoshi, H.; Endo, T., *Bull. Chem. Soc. Jpn.*, (1989) **62**, 945.
- [62] Zaitseva, V. V.; Tyurina, T. G.; Suikov, S. Y.; Bogza, S. L.; Kobzev, S. P., *Russ. J. Org. Chem. (Engl. Transl.)*, (2002) **38**, 588.
- [63] Lee, S. B.; Takata, T.; Endo, T., *Chem. Lett.*, (1990), 2019.
- [64] DeWolfe, R. H., *Synthesis*, (1974), 153.
- [65] Arbuzov, B. A.; Shavsha, T. G., *Dokl. Chem. (Engl. Transl.)*, (1949) **68**, 515.
- [66] Endo, T.; Okawara, M., *Synthesis*, (1984), 837.
- [67] Gross, H.; Rusche, J.; Bornowski, H., *Justus Liebig's Ann. Chem.*, (1964) **675**, 142.
- [68] Stetter, H.; Hunds, A., *Liebigs Ann. Chem.*, (1984), 1577.
- [69] Takata, T.; Endo, T., *Bull. Chem. Soc. Jpn.*, (1988) **61**, 1818.
- [70] Meerwein, H.; Bodenbrenner, K.; Borner, P.; Kunert, F.; Wunderlich, K., *Justus Liebig's Ann. Chem.*, (1960) **632**, 38.
- [71] Pindur, U.; Muller, J.; Flo, C.; Witzel, H., *Chem. Soc. Rev.*, (1987) **16**, 75.
- [72] Pindur, U.; Flo, C., *Synth. Commun.*, (1989) **19**, 2307.
- [73] Akgun, E.; Tunalı, M., *Doga Bilim Dergisi A1*, (1985) **9**, 258; *Chem. Abstr.*, (1987) **106**, 84432.
- [74] Picotin, G.; Miginiaç, P., *J. Organomet. Chem.*, (1987) **328**, 249.
- [75] Pelter, A.; Al-Bayati, R., *Tetrahedron Lett.*, (1982) **23**, 5229.
- [76] Kirchmeyer, S.; Mertens, A.; Arvanaghi, M.; Olah, G. A., *Synthesis*, (1983), 498.
- [77] Johnson, S. J., *Synthesis*, (1991), 75.
- [78] Flo, C.; Pindur, U., *Liebigs Ann. Chem.*, (1987), 509.
- [79] Stachel, H. D.; Zoukas, T., *Arch. Pharm. (Weinheim, Ger.)*, (1991) **324**, 131.
- [80] Selva, M.; Trotta, F.; Tundo, P., *J. Chem. Soc., Perkin Trans. 2*, (1992), 519.
- [81] Meyer, R. F., *J. Org. Chem.*, (1963) **28**, 2902.
- [82] Stibranyi, L.; Peeva, M.; Kozempelova, Z.; Lesko, J.; Kovac, J., *Collect. Czech. Chem. Commun.*, (1986) **51**, 2817.
- [83] Goessnitzer, E.; Punkenhofer, A., *Monatsh. Chem.*, (2003) **134**, 909.
- [84] Brown, D. J.; Lynn, R. K., *J. Chem. Soc., Perkin Trans. 1*, (1974), 349.
- [85] Makino, S.; Suzuki, N.; Nakanishi, E.; Tsuji, T., *Synlett*, (2000), 1670.
- [86] Echavarren, A.; Galan, A.; Demendoza, J.; Salmeron, A.; Lehn, J. M., *Helv. Chim. Acta*, (1988) **71**, 685.
- [87] Hoffmann, A. W., *Justus Liebig's Ann. Chem.*, (1866) **139**, 114.
- [88] Tieckelmann, H.; Post, H. W., *J. Org. Chem.*, (1948) **13**, 268.
- [89] Richman, J. E.; Simmons, H. E., *Tetrahedron*, (1974) **30**, 1769.
- [90] Li, Z.; Undheim, K., *Acta Chem. Scand.*, (1998) **52**, 1247.
- [91] Shasha, B. S.; Doane, W. M.; Russell, C. R.; Rist, C. E., *Nature (London)*, (1964) **204**, 186.
- [92] Stout, E. I.; Shasha, B. S.; Trimnell, D.; Doane, W. M.; Russell, C. R., *Carbohydr. Res.*, (1974) **36**, 311.
- [93] Li, S.; Deslongchamps, P., *Tetrahedron Lett.*, (1994) **35**, 5641.
- [94] Deslongchamps, P.; Dory, Y. L.; Li, S., *Tetrahedron*, (2000) **56**, 3533.
- [95] Niaz, G. R.; Reese, C. B., *Chem. Commun.*, (1969), 552.

- [96] Deslongchamps, P.; Belanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P., *Can. J. Chem.*, (1990) **68**, 153.
- [97] Gentil, E.; Potier, M.; Boullanger, P.; Descotes, G., *Carbohydr. Res.*, (1990) **197**, 75.
- [98] Ruyle, W. V.; Shen, T. Y.; Patchett, A. A., *J. Org. Chem.*, (1965) **30**, 4353.
- [99] Shasha, B. S.; Doane, W. M.; Rohwedder, W. K., *Tetrahedron Lett.*, (1966), 1479.
- [100] Scaringe, S.; Caruthers, M. H., WO 96 41 809, (1996); *Chem. Abstr.*, (1996) **126**, 157764.
- [101] Barton, D. H. R.; Dawes, C. C.; Magnus, P. D., *J. Chem. Soc., Chem. Commun.*, (1975), 432.
- [102] Ishii, S.; Nakayama, H.; Yoshida, Y.; Yamashita, T., *Bull. Chem. Soc. Jpn.*, (1989) **62**, 455.
- [103] Huisgen, R.; Mack, W., *Chem. Ber.*, (1972) **105**, 2815.
- [104] Doane, W. M.; Shasha, B. S.; Russell, C. R.; Rist, C. E., *J. Org. Chem.*, (1965) **30**, 3071.
- [105] Adley, T. J.; Anisuzzaman, A. K. M.; Owen, L. N., *J. Chem. Soc. C*, (1967), 807.
- [106] Sitzmann, M. E.; Gilligan, W. H., *J. Org. Chem.*, (1983) **48**, 3354.
- [107] Shasha, B. S.; Doane, W. M.; Russell, C. R.; Rist, C. E., *J. Org. Chem.*, (1965) **30**, 2324.
- [108] Martinez, A. J.; Pendri, A.; Greenwald, R. B.; Choe, Y. H., WO 99 53 951, (1999); *Chem. Abstr.*, (1993) **131**, 322 821.
- [109] Ihara, H.; Arimura, T.; Imamura, T.; Satoh, E.; Kunitake, T.; Hirayama, C., *Polym. J.*, (1992) **24**, 1017.
- [110] Sakai, S.; Niimi, H.; Ishii, Y., *J. Organomet. Chem.*, (1974) **72**, 103.
- [111] Sakai, S.; Asai, Y.; Kiyohara, Y.; Itoh, K.; Ishii, Y., *Organomet. Chem. Synth.*, (1970) **1**, 45.
- [112] Baba, A.; Seki, K.; Matsuda, H., *J. Org. Chem.*, (1991) **56**, 2684.
- [113] Bakunova, S. M.; Grigor'ev, I. A.; Kirilyuk, I. A.; Gatilov, Y. V.; Bagryanskaya, I. Y.; Volodarskii, L. B., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1992), 758.
- [114] Fokin, A. V.; Gukov, A. M.; Studnev, Y. N.; Komarov, V. A.; Uzun, A. T., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1978), 422.
- [115] Eilingsfeld, H.; Neubauer, G.; Seefelder, M.; Weidinger, H., *Chem. Ber.*, (1964) **97**, 1232.
- [116] Graziano, M. L.; Iesce, M. R.; Palombi, R.; Scarpato, R., *Tetrahedron Lett.*, (1974), 3067.
- [117] Brederick, H.; Effenberger, F.; Beyerlein, H. P., *Chem. Ber.*, (1964) **97**, 1834.
- [118] Kassam, K.; Pole, D. L.; El-Saidi, M.; Warkentin, J., *J. Am. Chem. Soc.*, (1994) **116**, 1161.
- [119] Yang, R. Y.; Dai, L. X., *J. Org. Chem.*, (1993) **58**, 3381.
- [120] Chiba, T.; Okimoto, M., *J. Org. Chem.*, (1992) **57**, 1375.
- [121] Bekhazi, M.; Smith, P. J.; Warkentin, J., *Can. J. Chem.*, (1984) **62**, 1646.
- [122] Warkentin, J., *J. Chem. Soc., Perkin Trans. 1*, (2000), 2161.
- [123] Lu, X.; Reid, D. L.; Warkentin, J., *Can. J. Chem.*, (2001) **79**, 319.
- [124] Warkentin, J., In *Advances in Carbene Chemistry*, Brinker, U. H., Ed.; JAI: Greenwich, CT, (1998); Vol. 2, p 245.
- [125] Tomioka, H.; Heydt, H.; Dehmlow, E.; Regitz, M.; Bertrand, G.; Schank, K., In *Houben-Weyl*, (1989); Vol. E 19b, p 1410.
- [126] Rigby, J. H.; Cavezza, A.; Heeg, M. J., *J. Am. Chem. Soc.*, (1998) **120**, 3664.
- [127] Prishchenko, A. A.; Livantsov, M. V.; Boganova, N. V.; Lutsenko, I. F., *J. Gen. Chem. USSR (Engl. Transl.)*, (1988) **58**, 1720.
- [128] Moskva, V. V.; Maikova, A. I.; Razumov, A. I., *J. Gen. Chem. USSR (Engl. Transl.)*, (1967) **37**, 2027.
- [129] Costisella, B.; Keitel, I., *Synthesis*, (1987), 44.
- [130] Prishchenko, A. A.; Livantsov, M. V.; Boganova, N. V.; Lutsenko, I. F., *J. Gen. Chem. USSR (Engl. Transl.)*, (1988) **58**, 1932.
- [131] Mavrin, V. Y.; Moskva, V. V., *J. Gen. Chem. USSR (Engl. Transl.)*, (1988) **58**, 1930.
- [132] Prishchenko, A. A.; Livantsov, M. V.; Boganova, N. V.; Lutsenko, I. F., *J. Gen. Chem. USSR (Engl. Transl.)*, (1988) **58**, 1290.
- [133] Bucher, G.; Strehl, A.; Sander, W., *Eur. J. Org. Chem.*, (2003), 2153.
- [134] Schroth, W.; Bahn, H.; Huck, G., *Z. Chem.*, (1973) **13**, 465.
- [135] Zoller, U.; Chen, F.-P., *Sulfur Lett.*, (2002) **25**, 115.
- [136] DeWolfe, R. H., In *Carboxylic Ortho Acid Derivatives*, Blomquist, A. T., Ed.; Academic: New York, (1970); p 426.
- [137] Kantlehner, W.; Haug, E.; Frick, W.; Speh, P.; Braeuner, H. J., *Synthesis*, (1984), 358.
- [138] Cabiddu, S.; Marongiu, E.; Sotgiu, F., *Gazz. Chim. Ital.*, (1972) **102**, 558.
- [139] Kantlehner, W.; Mergen, W.; Haug, E.; Speh, P.; Kapassakalidis, J. J.; Braeuner, H. J., *Liebigs Ann. Chem.*, (1985), 1804.

- [140] Closs, F.; Gompper, R.; Noeth, H.; Wagner, H. U., *Angew. Chem.*, (1988) **100**, 875; *Angew. Chem. Int. Ed. Engl.*, (1988) **27**, 843.
- [141] Moskva, V. V.; Mavrin, V. Y., *J. Gen. Chem. USSR (Engl. Transl.)*, (1988) **58**, 1490.
- [142] David, S.; De Sennyey, G., *J. Chem. Soc., Perkin Trans. 1*, (1982), 385.
- [143] David, S.; De Sennyey, G.; Pascard, G.; Guilhem, J., *J. Chem. Soc., Chem. Commun.*, (1981), 780.
- [144] Moss, R. A., In *Chemistry of Diazirines*, Liu, M. T. H., Ed.; CRC: Boca Raton, FL, (1987); Vol. 1, p 99.
- [145] Moss, R. A.; Wlostowski, M.; Terpinski, J.; Kmiecik-Lawrynowicz, G.; Krogh-Jespersen, K., *J. Am. Chem. Soc.*, (1987) **109**, 3811.
- [146] Ge, C.-S.; Jefferson, E. A.; Moss, R. A., *Tetrahedron Lett.*, (1993) **34**, 7549.
- [147] Moss, R. A.; Ge, C.-S., *J. Fluorine Chem.*, (1995) **73**, 101.
- [148] Fede, J.-M.; Jockusch, S.; Lin, N.; Moss, R. A.; Turro, N. J., *Org. Lett.*, (2003) **5**, 5027.
- [149] Du, X. M.; Fan, H.; Goodman, J. L.; Kesselmayr, M. A.; Krogh-Jespersen, K.; LaVilla, J. A.; Moss, R. A.; Shen, S.; Sheridan, R. S., *J. Am. Chem. Soc.*, (1990) **112**, 1920.
- [150] Kantlehner, W.; Stieglitz, R.; Hauber, M.; Haug, E.; Regele, C., *J. Prakt. Chem.*, (2000) **342**, 256.
- [151] Miyamoto, M.; Itoh, Y.; Horii, K.; Kanayama, R.; Kimura, Y., *Polym. J.*, (1997) **29**, 854.
- [152] Grigor'ev, I. A.; Gogolev, A. Z.; Sagdeev, R. Z.; Volodarskii, L. B., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1989), 930.
- [153] Zykov, B. G.; Grigor'ev, I. A.; Martin, V. V., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1990), 1603.
- [154] Dikanov, S. A.; Gulin, V. I.; Tsvetkov, Y. D.; Grigor'ev, I. A., *J. Chem. Soc., Faraday Trans.*, (1990) **86**, 3201.
- [155] Voinov, M. A.; Volodarsky, L. B., *Russ. Chem. Bull.*, (1997) **46**, 126.
- [156] Grigor'ev, I. A.; Kirilyuk, I. A.; Starichenko, V. F.; Volodarskii, L. B., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1989), 1488.
- [157] Grigor'ev, I. A.; Volodarskii, L. B.; Starichenko, V. F.; Shchukin, G. I.; Kirilyuk, I. A., *Tetrahedron Lett.*, (1985) **26**, 5085.
- [158] Couture, P.; Terlouw, J. K.; Warkentin, J., *J. Am. Chem. Soc.*, (1996) **118**, 4214.
- [159] Couture, P.; Warkentin, J., *Can. J. Chem.*, (1997) **75**, 1281.
- [160] Couture, P.; Warkentin, J., *Can. J. Chem.*, (1997) **75**, 1264.
- [161] Zinner, G.; Vollrath, R., *Chem. Ber.*, (1970) **103**, 766.
- [162] Zinner, G.; Gross, H., *Chem. Ber.*, (1972) **105**, 1714.
- [163] Stachel, H. D., *Angew. Chem.*, (1959) **71**, 246.
- [164] Richter, R.; Barsa, E. A., *J. Org. Chem.*, (1986) **51**, 417.
- [165] Kappe, C. O.; Faerber, G.; Wentrup, C.; Kollenz, G., *J. Org. Chem.*, (1992) **57**, 7078.
- [166] Moss, R. A.; Shen, S.; Wlostowski, M., *Tetrahedron Lett.*, (1988) **29**, 6417.
- [167] Moss, R. A.; Wlostowski, M.; Shen, S.; Krogh-Jespersen, K.; Matro, A., *J. Am. Chem. Soc.*, (1988) **110**, 4443.
- [168] Rigby, J. H.; Cavezza, A.; Heeg, M. J., *Tetrahedron Lett.*, (1999) **40**, 2473.
- [169] Gross, H.; Medved, T. Y.; Nowak, S.; Bel'skii, F. I.; Keitel, I.; Kabachnik, M. I., *J. Gen. Chem. USSR (Engl. Transl.)*, (1985) **55**, 654.
- [170] Zolotukhina, M. M.; Krutikov, V. I.; Lavrent'ev, A. N., *Russ. Chem. Rev.*, (1993) **62**, 647.
- [171] Verma, S.; Kansal, N. M.; Mishra, R. S.; Bokadia, M. M., *Heterocycles*, (1981) **16**, 1537.
- [172] Verma, S.; Kansal, N. M.; Bokadia, M. M., *Acta Chim. Acad. Sci. Hung.*, (1982) **109**, 341.
- [173] Kabachnik, M. I.; Rossiiskaya, P. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1957), 51.
- [174] Kabachnik, M. I.; Rossiiskaya, P. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1958), 1398.
- [175] Gross, H.; Engelhardt, G.; Freiberg, J.; Buerger, W.; Costisella, B., *Justus Liebigs Ann. Chem.*, (1967) **707**, 35.
- [176] Gross, H.; Keitel, I.; Costisella, B., *Acta Chim. Hung.*, (1984) **116**, 229.
- [177] Quimby, O. T.; Prentice, J. B.; Nicholson, D. A., *J. Org. Chem.*, (1967) **32**, 4111.
- [178] McKenna, C. E.; Kashemirov, B. A.; Li, Z.-M., *Phosphorus, Sulfur Silicon Relat. Elem.*, (1999) **144–146**, 313.
- [179] McKenna, C. E.; Kashemirov, B. A.; Roze, C. N., *Bioorg. Chem.*, (2002) **30**, 383.
- [180] Yung, T. W. K.; Sammes, M. P., *Tetrahedron Lett.*, (1991) **32**, 4329.
- [181] Bonini, B. F.; Foresti, E.; Maccagnani, G.; Mazzanti, G.; Sabatino, P.; Zani, P., *Tetrahedron Lett.*, (1985) **26**, 2131.
- [182] Fanghaenel, E.; Mayer, R., *Z. Chem.*, (1964) **4**, 384.
- [183] Mono, S.; Pritzkow, H.; Sundermeyer, W., *Chem. Ber.*, (1993) **126**, 2111.
- [184] Ueno, Y.; Okawa, M., *Bull. Chem. Soc. Jpn.*, (1972) **45**, 1797.

- [185] Holm, S.; Boerma, J. A.; Nilsson, N. H.; Senning, A., *Chem. Ber.*, (1976) **109**, 1069.
- [186] Ueno, Y.; Nakai, T.; Okawara, M., *Bull. Chem. Soc. Jpn.*, (1970) **43**, 168.
- [187] Oremus, V.; Linden, A.; Heimgartner, H., *Helv. Chim. Acta*, (1991) **74**, 1500.
- [188] Barbero, M.; Degani, I.; Dughera, S.; Fochi, R.; Piscopo, L., *J. Chem. Soc., Perkin Trans. 1*, (1996), 289.
- [189] Nace, H. R., *Org. React.*, (1962) **12**, 57.
- [190] Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C., *Tetrahedron*, (1993) **49**, 7193.
- [191] Faure, A.; Descotes, G., *Synthesis*, (1978), 286.
- [192] Barton, D. H. R.; Stick, R. V.; Subramanian, R., *J. Chem. Soc., Perkin Trans. 1*, (1976), 2112.
- [193] Descotes, G.; Faure, A., *Synthesis*, (1976), 449.
- [194] Faure, A.; Kryczka, B.; Descotes, G., *Carbohydr. Res.*, (1979) **74**, 127.
- [195] Shasha, B. S.; Trimmell, D.; Doane, W. M.; Russell, C. R., *Carbohydr. Res.*, (1971) **19**, 383.
- [196] Rosales-Jasso, A.; Allen, N. S.; Sasaki, M., *Polym. Degrad. Stab.*, (1999) **64**, 277.
- [197] Gasparutto, D.; Ravanat, J.-L.; Gerot, O.; Cadet, J., *J. Am. Chem. Soc.*, (1998) **120**, 10283.
- [198] Kantlehner, W.; Mergen, W. W.; Haug, E., *Liebigs Ann. Chem.*, (1983), 290.
- [199] White, J.; Baker, D. C., *Synthesis*, (1990), 151.
- [200] Ried, W.; Nenninger, H., *Chem.-Ztg.*, (1988) **112**, 382.
- [201] Block, H. J.; Fischer, E.; Rembarz, G., *J. Prakt. Chem.*, (1978) **320**, 335.
- [202] Zollinger, J. L.; Wright, C. D.; McBrady, J. J.; Dybrig, D. H.; Flemming, F. A.; Kurhajec, G. A.; Mitsch, R. A.; Neuvar, U. E. W., *J. Org. Chem.*, (1973) **38**, 1065.
- [203] Fokin, A. V.; Komarov, V. A.; Gukov, A. M., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1976) **8**, 1712.
- [204] Yoshimura, J.; Sekiya, T.; Iida, T., *Bull. Chem. Soc. Jpn.*, (1972) **45**, 1227.
- [205] Kantlehner, W.; Mergen, W. W., *Synthesis*, (1979), 343.
- [206] Kantlehner, W.; Kienitz, L.; Jaus, H.; Brederick, H., *Liebigs Ann. Chem.*, (1979), 2089.
- [207] Quast, H.; Schmitt, E., *Chem. Ber.*, (1968) **101**, 1137.
- [208] Norris, W. P.; Merwin, L. H.; Ostrom, G. S.; Gilardi, R. D., *J. Org. Chem.*, (1997) **62**, 9070.
- [209] Huisgen, R.; Grashey, R.; Kunz, R.; Wallbillich, G.; Aufderhaar, E., *Chem. Ber.*, (1965) **98**, 2174.
- [210] Schaumann, E.; Grabley, S.; Adiwidjaja, G., *Liebigs Ann. Chem.*, (1981), 264.
- [211] Bakunova, S. M.; Kirilyuk, I. A.; Grigor'ev, I. A., *Russ. Chem. Bull.*, (2001) **50**, 882.
- [212] Senning, A., *Sulfur Lett.*, (1991) **12**, 247.
- [213] Johnson, D. K.; Wasson, J. R., *Inorg. Nucl. Chem. Lett.*, (1974) **10**, 891.
- [214] Charkin, O. P.; Marsden, C. J., *Russ. J. Inorg. Chem. (Engl. Transl.)*, (1995) **40**, 1545.
- [215] Abel, E. W.; Mackenzie, T. E.; Orrell, K. G.; Sik, V., *Polyhedron*, (1987) **6**, 1785.
- [216] D'Amico, J. J.; Campbell, R. H., US 3 525 752, (1970); *Chem. Abstr.*, (1970) **73**, 99845.
- [217] Takata, T.; Kanamaru, M.; Endo, T., *Macromolecules*, (1997) **30**, 6721.
- [218] Utsu, H.; Toriumi, S.; Miki, Y., JP 2004 035 413, (2004); *Chem. Abstr.*, (2004) **140**, 147287.
- [219] Barbero, M.; Cadamuro, S.; Degani, I.; Fochi, R.; Gatti, A.; Regondi, V., *Synthesis*, (1988), 22.
- [220] Barbero, M.; Cadamuro, S.; Degani, I.; Dughera, S.; Fochi, R., *J. Chem. Soc., Perkin Trans. 1*, (1993), 2075.
- [221] Barbero, M.; Cadamuro, S.; Degani, I.; Dughera, S.; Fochi, R., *J. Org. Chem.*, (1995) **60**, 6017.
- [222] Degani, I.; Dughera, S.; Fochi, R.; Gazzetto, S., *J. Org. Chem.*, (1997) **62**, 7228.
- [223] Degani, I.; Dughera, S.; Fochi, R.; Serra, E., *J. Org. Chem.*, (1996) **61**, 9572.
- [224] Cheng, W. L.; Luh, T. Y., *J. Chem. Soc., Chem. Commun.*, (1992), 1392.
- [225] Backer, H. J.; Stedehouder, P. L., *Recl. Trav. Chim. Pays-Bas*, (1933) **52**, 1039.
- [226] Backer, H. J., *Recl. Trav. Chim. Pays-Bas*, (1948) **67**, 894.
- [227] Backer, H. J., *Recl. Trav. Chim. Pays-Bas*, (1951) **70**, 254.
- [228] Sato, R.; Yamashita, M.; Fujiwara, M.; Chida, S.; Ogawa, S., *Sulfur Lett.*, (1993) **16**, 109.
- [229] Arndt, F., *Justus Liebigs Ann. Chem.*, (1913) **396**, 1.
- [230] Nakayama, J., *Synthesis*, (1975), 168.
- [231] Nakayama, J., *J. Chem. Soc., Chem. Commun.*, (1974), 166.
- [232] Korchev, O. I.; Puzin, Y. I.; Lepyanin, G. V., *Polym. Sci. USSR (Engl. Transl.)*, (1986) **28**, 520.
- [233] Backer, H. J.; Stedehouder, P. L., *Recl. Trav. Chim. Pays-Bas*, (1933) **52**, 437.
- [234] Munavalli, S.; Rossman, D. I.; Rohrbaugh, D. K.; Ferguson, C. P.; Durst, H. D., *J. Fluorine Chem.*, (1996) **76**, 7.
- [235] Harris, J. F., Jr., *J. Org. Chem.*, (1967) **32**, 2063.
- [236] Senning, A., *Angew. Chem.*, (1979) **91**, 1006; *Angew. Chem. Int. Ed. Engl.*, (1979) **18**, 941.
- [237] Mikolajczyk, M.; Potrzebowski, M. J.; Kazmierski, S. L.; Gross, H.; Costisella, B.; Keitel, I.; Wiczorek, M.-L. W.; Wawer, I., *J. Org. Chem.*, (1995) **60**, 6335.

- [238] Backer, H. J.; Westerhuls, E., *Recl. Trav. Chim. Pays-Bas*, (1952) **71**, 1065.
- [239] El-Sayed, I.; Hazell, R. G.; Madsen, J. O.; Norrby, P.-O.; Senning, A., *Eur. J. Org. Chem.*, (2003), 813.
- [240] Johnston, T. P.; Stringfellow, C. R., Jr.; Gallagher, A., *J. Org. Chem.*, (1962) **27**, 4068.
- [241] Maletzko, C.; Sundermeyer, W.; Pritzkow, H.; Irngartinger, H.; Huber-Patz, U., *Chem. Ber.*, (1991) **124**, 2025.
- [242] Goodman, F. J.; Chambers, J. Q., *J. Org. Chem.*, (1976) **41**, 626.
- [243] Seebach, D., *Angew. Chem.*, (1967) **79**, 468; *Angew. Chem. Int. Ed. Engl.*, (1967) **6**, 442.
- [244] Seebach, D.; Geiss, K. H.; Beck, A. K.; Graf, B.; Daum, H., *Chem. Ber.*, (1972) **105**, 3280.
- [245] Frohling, A.; Arens, J. F., *Recl. Trav. Chim. Pays-Bas*, (1962) **1962**, 1009.
- [246] Maercker, A.; Theis, M., *Angew. Chem.*, (1984) **96**, 990; *Angew. Chem. Int. Ed. Engl.*, (1984) **23**, 995.
- [247] March, J., *Advanced Organic Chemistry*, Wiley: New York, (1992).
- [248] Grossert, J. S.; Dubey, P. K., *J. Chem. Soc., Chem. Commun.*, (1982), 1183.
- [249] Schank, K.; Buegler, S., *Sulfur Lett.*, (1982) **1**, 63.
- [250] Zhu, Y.; Drucekhammer, D. G., *Tetrahedron Lett.*, (2002) **43**, 1377.
- [251] Boehme, H.; Marx, R., *Chem. Ber.*, (1941) **74**, 1667.
- [252] Iwamatsu, M.; Ueda, K.; Sugimoto, T.; Fujita, H., *Synth. Met.*, (1999) **102**, 1617.
- [253] Tucker, W. P.; Roof, G. L., *Tetrahedron Lett.*, (1967), 2747.
- [254] Boese, R.; Haas, A.; Krüger, C.; Moeller, G.; Waterfeld, A., *Chem. Ber.*, (1994) **127**, 597.
- [255] Doyle, M. P.; Hedstrand, D. M., *J. Chem. Soc., Chem. Commun.*, (1977), 643.
- [256] Roof, G. L.; Tucker, W. F., *J. Org. Chem.*, (1968) **33**, 3333.
- [257] Coffen, D. L., *J. Heterocycl. Chem.*, (1970) **7**, 201.
- [258] Okazaki, R.; Ishii, F.; Okawa, K.; Ozawa, K.; Inamoto, N., *J. Chem. Soc., Perkin Trans. 1*, (1975), 270.
- [259] Raasch, M. S., *J. Org. Chem.*, (1970) **35**, 3470.
- [260] Meier, H.; Groschl, D.; Beckert, R.; Weiss, D., *Liebigs Ann./Recl.*, (1997), 1603.
- [261] Huisgen, R.; Weberndorfer, V., *Experientia*, (1961) **17**, 566.
- [262] Takata, T.; Endo, T., *Macromolecules*, (1988) **21**, 2314.
- [263] D'Amico, J. J.; Campbell, R. H., *J. Org. Chem.*, (1967) **32**, 2567.
- [264] Khan, M. H.; Nizamuddin, *Indian J. Chem., Sect. B*, (1997) **36**, 625.
- [265] Adams, R. D.; Huang, M., *Polyhedron*, (1998) **17**, 2759.
- [266] Bryce, M. R.; Davison, G. R.; Howard, J. A. K.; Batsanov, A. S., *J. Chem. Soc., Chem. Commun.*, (1992), 478.
- [267] Cambie, R. C.; Mayer, G. D.; Rutledge, P. S.; Woodgate, P. D., *J. Chem. Soc., Perkin Trans. 1*, (1981), 52.
- [268] Ooka, M.; Kitamura, A.; Okazaki, R.; Inamoto, N., *Bull. Chem. Soc. Jpn.*, (1978) **51**, 301.
- [269] Thijs, L.; Wagenaar, A.; Van Rens, E. M. M.; Zwanenburg, B., *Tetrahedron Lett.*, (1973), 3589.
- [270] Scherowsky, G.; Weiland, J., *Chem. Ber.*, (1974) **107**, 3155.
- [271] Khodairy, A.; Abdel-Ghany, H., *Phosphorus, Sulfur Silicon Relat. Elem.*, (2000) **162**, 259.
- [272] Nakai, T.; Okawara, M., *Bull. Chem. Soc. Jpn.*, (1970) **43**, 3528.
- [273] Jimonet, P.; Audiau, F.; Barreau, M.; Blanchard, J.-C.; Boireau, A.; Bour, Y.; Coleno, M.-A.; Doble, A.; Doerflinger, G.; Do Huu, C.; Donat, M.-H.; Duchesne, J. M.; Ganil, P.; Guerey, C.; Honore, E.; Just, B.; Kerphirique, R.; Gontier, S.; Hubert, P.; Laduron, P. M.; Le Blevec, J.; Meunier, M.; Miquet, J.-M.; Nemecek, C.; Pasquet, M.; Piot, O.; Pratt, J.; Rataud, J.; Reibaud, M.; Stutzmann, J.-M.; Mignani, S., *J. Med. Chem.*, (1999) **42**, 2828.
- [274] Bradsher, C. K.; Jones, W. J., Jr., *J. Org. Chem.*, (1967) **32**, 2074.
- [275] Fanghaenel, E., *Z. Chem.*, (1965) **5**, 386.
- [276] Weiss, R.; Compner, R., *Tetrahedron Lett.*, (1970), 481.
- [277] Backer, H. J., *Recl. Trav. Chim. Pays-Bas*, (1949) **68**, 844.
- [278] Backer, H. J., *Recl. Trav. Chim. Pays-Bas*, (1949) **68**, 827.
- [279] Neplyuev, V. M.; Sinenko, T. A., *Russ. J. Org. Chem. (Engl. Transl.)*, (1976) **12**, 2583.
- [280] Yoshida, Z.; Kawase, T.; Yoneda, S., *Tetrahedron Lett.*, (1975), 331.
- [281] Grisley, D. W., Jr., *J. Org. Chem.*, (1961) **26**, 2544.
- [282] Bulpin, A.; Masson, S.; Sene, A., *Tetrahedron Lett.*, (1989) **30**, 3415.
- [283] Alberti, A.; Benaglia, M.; Bona, M. A. D.; Macciantelli, D.; Heuze, B.; Masson, S.; Hudson, A., *J. Chem. Soc., Perkin Trans. 2*, (1996), 1057.
- [284] Bulpin, A.; Masson, S., *J. Org. Chem.*, (1992) **57**, 4507.
- [285] Takeshima, T.; Miyauchi, T.; Fukada, N.; Koshizawa, S.; Muraoka, M., *J. Chem. Soc., Perkin Trans. 1*, (1973), 1009.
- [286] L'abbé, G.; Yu, C.-C., *J. Heterocycl. Chem.*, (1976) **13**, 883.

- [287] Abdou, W. M.; El-Khoshnieh, Y. O.; Kamel, A. A., *Phosphorus, Sulfur Silicon Relat. Elem.*, (1996) **119**, 225.
- [288] Akiba, K.; Kawamura, T.; Ochiuni, M.; Inamoto, N., *Bull. Chem. Soc. Jpn.*, (1976) **49**, 1913.
- [289] Hocker, J.; Merten, R., *Justus Liebigs Ann. Chem.*, (1971) **751**, 145.
- [290] Hanefeld, W.; Wurtz, S., *J. Prakt. Chem.*, (2000) **342**, 554.
- [291] Rembarz, G.; Fischer, E.; Block, H. J.; Michalik, M., *J. Prakt. Chem.*, (1977) **319**, 163.
- [292] Rembarz, G.; Fischer, E.; Michalik, M.; Kositzki, D., *Z. Chem.*, (1979) **19**, 100.
- [293] Kutschy, P.; Suchy, M.; Dzurilla, M.; Takasugi, M.; Kovacik, V., *Collect. Czech. Chem. Commun.*, (2000) **65**, 1163.
- [294] Arcadi, A.; Attanasi, O. A.; Guidi, B.; Rossi, E.; Santeusano, S., *Synlett*, (2000), 1464.
- [295] Yokoyama, M.; Ohtuki, S.; Muraoka, M.; Takeshima, T., *Tetrahedron Lett.*, (1978), 3823.
- [296] Olthoff, U.; Matthey, K., *Pharmazie*, (1974) **29**, 20.
- [297] Kutschy, P.; Dzurilla, M.; Takasugi, M.; Sabova, A., *Collect. Czech. Chem. Commun.*, (1999) **64**, 348.
- [298] Alemagna, A.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Trave, R., *Tetrahedron*, (1984) **40**, 971.
- [299] Stille, J. K.; Harris, F. W., *J. Polym. Sci., Polym. Chem. Ed.*, (1968) **6**, 2317.
- [300] Gotthardt, H.; Reiter, F., *Chem. Ber.*, (1979) **112**, 1206.
- [301] Greig, D. J.; McPherson, M.; Paton, R. M.; Crosby, J., *J. Chem. Soc., Perkin Trans. 1*, (1985), 1205.
- [302] Huisgen, R.; Grashey, R.; Seidel, M.; Knupfer, H.; Schmidt, R., *Justus Liebigs Ann. Chem.*, (1962) **658**, 169.
- [303] Hassaneen, H. M.; Shawali, A. S.; Farag, D. S.; Ahmed, E. M., *Phosphorus, Sulfur Silicon Relat. Elem.*, (1996) **113**, 53.
- [304] Shevelev, S. A.; Semenov, V. V.; Fainzil'berg, A. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1977), 120.
- [305] Semenov, V. V.; Shevelev, S. A.; Fainzil'berg, A. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1978), 2080.
- [306] Shevelev, S. A.; Semenov, V. V.; Fainzil'berg, A. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1978), 945.
- [307] Hong, Y.-S.; Kim, H.-M.; Lee, J.-G.; Park, Y.-T.; Kim, H.-S., *J. Korean Chem. Soc.*, (1996) **40**, 615.
- [308] Katritzky, A. R.; Drewniak-Deyrup, M.; Lan, X.; Brunner, F., *J. Heterocycl. Chem.*, (1989) **26**, 829.
- [309] Diez-Barra, E.; de la Hoz, A.; Sanchez-Migallon, A.; Tejada, J., *J. Chem. Soc., Perkin Trans. 1*, (1993), 1079.
- [310] Bianchini, C.; Meli, A.; Orlandini, A.; Sacconi, L., *J. Organomet. Chem.*, (1981) **218**, 81.
- [311] Cadierno, V.; Zablocka, M.; Donnadiu, B.; Igau, A.; Majoral, J.-P., *Organometallics*, (1999) **18**, 1882.
- [312] Bianchini, C.; Meli, A.; Orlandini, A.; Sacconi, L., *Angew. Chem.*, (1980) **92**, 1055; *Angew. Chem. Int. Ed. Engl.*, (1980) **19**, 1021.
- [313] Maigrot, N.; Ricard, L.; Charrier, C.; Mathey, F., *Angew. Chem.*, (1990) **102**, 575; *Angew. Chem. Int. Ed. Engl.*, (1990) **29**, 534.
- [314] Chen, R.; Bao, R., *Synthesis*, (1990), 137.
- [315] Huang, J. M.; Chen, H.; Chen, R. Y., *Chin. Chem. Lett.*, (2002) **13**, 125.
- [316] Kolodyazhnyi, O. I.; Shevchenko, I. V.; Povolotskii, M. I.; Boldeskul, I. E.; Kukhar, V. P., *J. Gen. Chem. USSR (Engl. Transl.)*, (1985) **55**, 2489.
- [317] Becker, G.; Massa, W.; Schmidt, R. E.; Uhl, G., *Z. Anorg. Allg. Chem.*, (1984) **517**, 75.
- [318] Becker, G.; Becker, W.; Uhl, G.; Uhl, W.; Wessely, H. J., *Phosphorus Sulfur Relat. Elem.*, (1983) **18**, 7.
- [319] Kukhar, V. P.; Shevchenko, I. V.; Kolodyazhnyi, O. I., *J. Gen. Chem. USSR (Engl. Transl.)*, (1985) **55**, 230.
- [320] Villemin, D.; Ben Alloum, A.; Thibault-Starzyk, F., *Synth. Commun.*, (1992) **22**, 1359.
- [321] Vrang, L.; Oberg, B., *Antimicrob. Agents Chemother.*, (1986) **29**, 867.
- [322] Muller, M.; Lork, E.; Mews, R., *Angew. Chem.*, (2001) **113**, 1285; *Angew. Chem. Int. Ed.*, (2001) **40**, 1247.
- [323] Erashko, V. I.; Sultanov, A. V.; Shevelev, S. A.; Fainzil'berg, A. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1974), 1269.
- [324] Shevelev, S. A.; Sultanov, A. V.; Erashko, V. I.; Fainzil'berg, A. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1977), 334.
- [325] Grebennikov, V. N.; Erashko, V. I.; Nazin, G. M.; Sultanov, A. V.; Shevelev, S. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1977), 273.
- [326] Erashko, V. I.; Sazonova, O. M.; Tishaninova, A. A.; Fainzil'berg, A. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1982), 152.

- [327] Sultanov, A. V.; Erashko, V. I.; Shevelev, S. A.; Fainzil'berg, A. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1975), 2636.
- [328] Erashko, V. I.; Sultanov, A. V.; Shevelev, S. A.; Fainzil'berg, A. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1975), 337.
- [329] Shevelev, S. A.; Semenov, V. V.; Fainzil'berg, A. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1977), 2345.
- [330] Erashko, V. I.; Baryshnikov, A. T.; Zubanova, N. I.; Tishaninova, A. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1989), 1939.
- [331] Lill, S. O. N.; Rauhut, G.; Anders, E., *Chem.-Eur. J.*, (2003) **9**, 3143.
- [332] Wermann, K.; Walther, M.; Gunther, W.; Gorls, H.; Anders, E., *Eur. J. Org. Chem.*, (2003), 1389.
- [333] Reddy, C. K.; Reddy, P. C. S.; Reddy, P. S. N.; Ratnam, C. V.; Reddy, V. M., *Indian J. Heterocycl. Chem.*, (1997) **7**, 17.
- [334] Postovskii, I. Y.; Azev, Y. A.; Mokrushina, G. A., *Chem. Heterocycl. Compd. (Engl. Transl.)*, (1976), 942.
- [335] Temple, C., Jr.; Kussner, C. L.; Montgomery, J. A., *J. Org. Chem.*, (1969) **34**, 3161.
- [336] Balli, H., *Helv. Chim. Acta*, (1974) **57**, 1912.
- [337] Bigg, D. C. H.; Purvis, S. R., *J. Heterocycl. Chem.*, (1976) **13**, 977.
- [338] Bigg, D. C. H.; Faull, A. W.; Purvis, S. R., *J. Heterocycl. Chem.*, (1977) **14**, 989.
- [339] Entenmann, G., *Tetrahedron Lett.*, (1974), 3279.
- [340] Potts, K. T.; Kanemasa, S., *J. Org. Chem.*, (1979) **44**, 3803.
- [341] Tsuge, O.; Hatta, T.; Tashiro, H.; Maeda, H., *Heterocycles*, (2001) **55**, 243.
- [342] Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jimenez, J. L.; Palacios, J. C.; Raithby, P. R., *J. Org. Chem.*, (2000) **65**, 5089.
- [343] Avalos, M.; Babiano, R.; Dıanez, M. J.; Espinosa, J.; Estrada, M. D.; Jimenez, J. L.; Lopez-Castro, A.; Mendez, M. M.; Palacios, J. C., *Tetrahedron*, (1992) **48**, 4193.
- [344] Bende, Z.; Bitter, I.; Toke, L.; Weber, L.; Toke, G.; Janke, F., *Liebigs Ann. Chem.*, (1982), 2146.
- [345] Lown, J. W.; Landberg, B. E., *Can. J. Chem.*, (1974) **52**, 798.
- [346] Klauı, W.; Berghahn, M.; Rheinwald, G.; Lang, H., *Angew. Chem.*, (2000) **112**, 2590; *Angew. Chem. Int. Ed.*, (2000) **39**, 2464.
- [347] Klauı, W.; Schramm, D.; Peters, W.; Rheinwald, G.; Lang, H., *Eur. J. Inorg. Chem.*, (2001), 1415.
- [348] Klauı, W.; Schramm, D.; Peters, W., *Eur. J. Inorg. Chem.*, (2001), 3113.
- [349] Santini, C.; Pellei, M.; Lobbıa, G. G.; Fedeli, D.; Falcioni, G., *J. Inorg. Biochem.*, (2003) **94**, 348.
- [350] Santini, C.; Pellei, M.; Lobbıa, G. G.; Cingolani, A.; Spagna, R.; Camalli, M., *Inorg. Chem. Commun.*, (2002) **5**, 430.
- [351] Klauı, W.; Berghahn, M.; Frank, W.; Reib, G. J.; Schonherr, T.; Rheinwald, G.; Lang, H., *Eur. J. Inorg. Chem.*, (2003), 2059.
- [352] Erashko, V. I.; Sultanov, A. V.; Shevelev, S. A.; Fainzil'berg, A. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1972), 1194.
- [353] Erashko, V. I.; Sultanov, A. V.; Shevelev, S. A., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1975), 1560.
- [354] Petrov, M. L.; Rubtsova, I. K., *Russ. J. Org. Chem. (Engl. Transl.)*, (1994) **30**, 1065.
- [355] Fabian, J.; Krebs, A.; Schoenemann, D.; Schaefer, W., *J. Org. Chem.*, (2000) **65**, 8940.
- [356] Ovchinnikov, Y. E.; Potekhin, K. A.; Panov, V. N.; Struchkov, Y. T., *Dokl. Chem. (Engl. Transl.)*, (1995) **340**, 1.
- [357] Seebach, D.; Peleties, N., *Angew. Chem.*, (1969) **81**, 465; *Angew. Chem. Int. Ed. Engl.*, (1969) **8**, 450.
- [358] Haas, A.; Moeller, G., *Chem. Ber.*, (1996) **129**, 1383.
- [359] Seebach, D.; Peleties, N., *Chem. Ber.*, (1972) **105**, 511.
- [360] Haas, A.; Kempf, K. W., *Tetrahedron*, (1984) **40**, 4963.
- [361] Altukhov, K. V.; Perekalın, V. V., *Russ. Chem. Rev.*, (1976) **45**, 1052.
- [362] Jockisch, A.; Schier, A.; Schmidbauer, H., *Chem. Ber./Recl.*, (1997) **130**, 1739.
- [363] Weingarten, H., *J. Org. Chem.*, (1967) **32**, 3713.
- [364] Weingarten, H.; Edelman, N. K., *J. Org. Chem.*, (1967) **32**, 3293.
- [365] Kantlehner, W.; Jaus, H.; Kienitz, L.; Bredereck, H., *Liebigs Ann. Chem.*, (1979), 2096.
- [366] Reetz, M. T.; Bingel, C.; Harms, K., *J. Chem. Soc., Chem. Commun.*, (1993), 1558.
- [367] Meier, H.; Bulb, M.; Adam, M., *Liebigs Ann.*, (1996), 2131.
- [368] Petz, W.; Neumuller, B.; Lorberth, J.; Megges, K.; Massa, W., *Z. Naturforsch., B*, (2001) **56**, 306.
- [369] Petz, W.; Neumuller, B., *Z. Anorg. Allg. Chem.*, (2001) **627**, 2274.
- [370] Petz, W., *J. Organomet. Chem.*, (1975) **90**, 223.

- [371] Petz, W., *J. Organomet. Chem.*, (1981) **203**, 203.
- [372] Mayr, A.; Lin, Y. C.; Boag, N. M.; Kampe, C. E.; Knobler, C. B.; Kaesz, H. D., *Inorg. Chem.*, (1984) **23**, 4640.
- [373] Gross, H.; Zinner, G., *Chem. Ber.*, (1973) **106**, 2315.
- [374] Ahn, S.; Sperber, W.; Fehlhammer, W. P., *J. Organomet. Chem.*, (1995) **489**, 27.
- [375] Julia, S.; del Mazo, J. M.; Avila, L., *Org. Prep. Proced. Int.*, (1984) **16**, 299.
- [376] Makarov, S. P.; Yakubovich, A. Y.; Filatov, A. S.; Englin, M. A.; Nikiforova, T. Y., *J. Gen. Chem. USSR (Engl. Transl.)*, (1968) **38**, 685.
- [377] Weingarten, H.; White, W. A., *J. Am. Chem. Soc.*, (1966) **88**, 2885.
- [378] Richter, R., *Tetrahedron Lett.*, (1968), 5037.
- [379] Ton, T. V. T.; Hong, H. H. L.; Anna, C. H.; Dunnick, J. K.; Devereux, T. R.; Sills, R. C.; Kim, Y., *Toxicol. Pathol.*, (2004) **32**, 16.
- [380] Bucher, J. R.; Huff, J. E.; Jokinen, M. P.; Haseman, J. K.; Stedham, M.; Cholakakis, J. M., *Cancer Lett.*, (1991) **57**, 95.
- [381] Liang, P., *Org. Synth., Coll. Vol. III*, (1941), 803.
- [382] Shishkov, L. N., *Ann. Chim. Phys.*, (1857) **49**, 310.
- [383] Pictet, A.; Genequand, P., *Ber. Dtsch. Chem. Ges.*, (1903) **36**, 2225.
- [384] Pictet, A.; Khotinsky, E., *Ber. Dtsch. Chem. Ges.*, (1907) **49**, 1163.
- [385] Schenck, R., *DRP 211 198*, (1908); *Chem. Abstr.*, (1909) **18**, 2205.
- [386] Darzens, G.; Levy, G., *C. R. Hebd. Seances Acad. Sci.*, (1949) **229**, 1081.
- [387] Urbanski, T.; Nowak, Z.; Moray, E., *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, (1963) **11**, 77.
- [388] McKie, P. V., *J. Chem. Soc.*, (1927), 962.
- [389] Hager, K. F., *Ind. Eng. Chem.*, (1949) **41**, 2168.
- [390] Mints, E. S.; Golod, E. L.; Bagal, U. L. I., *Russ. J. Org. Chem. (Engl. Transl.)*, (1969) **5**, 1538.
- [391] Kochi, J. K., *Adv. Phys. Org. Chem.*, (1994) **29**, 185.
- [392] Ebersson, L.; Hartshorn, M. P., *Aust. J. Chem.*, (1998) **51**, 1061.
- [393] Sankararaman, S.; Haney, W. A.; Kochi, J. K., *J. Am. Chem. Soc.*, (1987) **109**, 7824.
- [394] Agafonov, N. E.; Sedishev, I. P.; Zhulin, V. M., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1989), 2153.
- [395] P'Yankova, V. I.; Altukhov, K. V.; Perekalin, V. V.; Berkova, G. A.; Pozdnyakov, V. P., *Dokl. Chem. (Engl. Transl.)*, (1984) **278**, 341.
- [396] Corey, E. J.; Estreicher, H., *Tetrahedron Lett.*, (1980) **21**, 1113.
- [397] Rathore, R.; Kochi, J. K., *J. Org. Chem.*, (1996) **61**, 627.
- [398] Malik, A. A.; Archibald, T. G.; Tzeng, D.; Garver, L. C.; Baum, K., *J. Fluorine Chem.*, (1989) **43**, 291.
- [399] Ramkumar, D.; Sankararaman, S., *Synthesis*, (1993), 1057.
- [400] Kaminskii, V. A.; Pavlova, V. S., *Chem. Heterocycl. Compd. (Engl. Transl.)*, (2001) **37**, 513.
- [401] Boyer, J. H.; Krishnan, A. M., *J. Chem. Soc., Chem. Commun.*, (1988), 715.
- [402] Kranyushkin, M. M.; Andreeva, T. G.; Shvarts, I. S.; Sevost'yanova, V. V.; Yarovenko, V. N.; Novikov, S. S., *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, (1980), 462.
- [403] Schmidt, E.; Schumacher, R.; Bajen, W.; Wagner, A., *Ber. Dtsch. Chem. Ges.*, (1922) **55**, 1751.
- [404] Mayants, A. G.; Pyreseva, K. G.; Gordeichuk, S. S., *Russ. J. Org. Chem. (Engl. Transl.)*, (1986) **22**, 1900.
- [405] Mayants, A. G.; Pyreseva, K. G.; Gordeichuk, S. S., *Russ. J. Org. Chem. (Engl. Transl.)*, (1988) **24**, 798.
- [406] Riordan, J. F.; Sokolovsky, M.; Vallee, B. L., *J. Am. Chem. Soc.*, (1966) **88**, 4104.
- [407] Novellino, L.; D'Ischia, M.; Protà, G., *Synthesis*, (1999), 793.
- [408] Masnovi, J. M.; Kochi, J. K., *Recl. Trav. Chim. Pays-Bas*, (1986) **105**, 286.
- [409] Mathew, L.; Varghese, B.; Sankararaman, S., *J. Chem. Soc., Perkin Trans. 2*, (1993), 2399.
- [410] Bedford, C. D.; Nielsen, A. T., *J. Org. Chem.*, (1978) **43**, 2460.
- [411] Fargeas, V.; Favresse, F.; Mathieu, D.; Beaudet, I.; Charrue, P.; Lebre, B.; Piteau, M.; Quintard, J.-P., *Eur. J. Org. Chem.*, (2003), 1711.
- [412] Einhorn, J.; Demerseman, P.; Royer, R., *Synthesis*, (1984), 978.
- [413] Gross, H.; Costisella, B.; Gnauk, T.; Brennecke, L., *J. Prakt. Chem.*, (1976) **318**, 116.
- [414] Gross, H.; Costisella, B., *J. Prakt. Chem.*, (1972) **314**, 87.
- [415] Schindler, N.; Ploeger, W.; Haeusler, G., *DE 2 237 879*, (1974); *Chem. Abstr.*, (1974) **80**, 121096.
- [416] Silina, E. B.; Kozhushko, B. N.; Shokol, V. A., *J. Gen. Chem. USSR (Engl. Transl.)*, (1989) **59**, 505.
- [417] Shokol, V. A.; Kozhushko, B. N.; Kirsanov, A. V., *J. Gen. Chem. USSR (Engl. Transl.)*, (1973) **43**, 547.
- [418] Kukhar, V. P.; Pasternak, V. I.; Kirsanov, A. V., *J. Gen. Chem. USSR (Engl. Transl.)*, (1972) **42**, 1161.
- [419] Gross, H.; Costisella, B., *J. Prakt. Chem.*, (1986) **328**, 231.

- [420] Gladshtein, B. M.; Noskov, V. G.; Soborovskii, L. Z., *J. Gen. Chem. USSR (Engl. Transl.)*, (1967) **37**, 2391.
- [421] Budnick, E. G., US 4 020 091, (1977); *Chem. Abstr.*, (1977) **87**, 135 912.
- [422] Budnick, E. G., US 3 892 676, (1975); *Chem. Abstr.*, (1975) **83**, 117 635.
- [423] Schroedel, H.-P.; Jochem, G.; Schmidpeter, A.; Noeth, H., *Angew. Chem.*, (1995) **107**, 2006; *Angew. Chem. Int. Ed. Engl.*, (1995) **34**, 1853.
- [424] Baudler, M.; Leonhardt, W., *Angew. Chem.*, (1983) **95**, 633; *Angew. Chem. Int. Ed. Engl.*, (1983) **22**, 632.
- [425] Tebbe, K. F.; Heinlein, T.; Feher, M., *Z. Kristallogr.*, (1985) **172**, 89.

