L. Cotarca, H. Eckert

Phosgenations –
A Handbook

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Phosgenations – A Handbook

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Contents

Preface

Phosgene is a typical *highly reactive chemical* that has been in use since the early days of the chemical industry. In phosgene, the organic chemist will easily recognize either a building block providing the carbonyl function in many classes of organic compounds or a versatile reagent for carrying out selective chlorocarbonylation, chlorination, dehydration, and carbonylation reactions.

Because of its highly toxic nature, the handling of phosgene *gas*, either on a small scale, as in the laboratory, or on a medium-to-large scale, as in the agrochemical and pharmaceutical industries, *needs special expertise*. In spite of the high rates of nucleophilic phosgene reactions, there is a constant danger in carrying out phosgenation reactions that stems from the need to store phosgene, and the use of phosgene solutions is inevitably associated with hazards relating to the dynamics of external feeding.

A handbook on phosgenation requires a review of the organic chemistry of phosgene, with particular emphasis on the needs of organic chemists who require practical procedures to enable them to use the reagent safely and, in specific cases, to offer alternative methods when phosgene is not easily available.

The substitution of phosgene by alternative reagents is an important subject in the fine chemicals industry, particularly for pharmaceutical and agrochemical syntheses.

Most of the patents relating to phosgenation processes claim not only phosgenation by phosgene gas, but also by the main phosgene substitutes. The term *''the synthesis was performed by using phosgene or its derivatives (oligomers)''* has become not only a patent covering expression, but a true indication of the utility of alternative phosgene equivalents.

The principal aim of the book is to review, select, and order in a practical way the numerous methods known as ''phosgenation''.

The authors have both gained experience in phosgenation chemistry over several decades.

H.E. writes: – ''Thirty years ago, I started my doctoral thesis with a preparation of 2-chloroethyl chloroformate from phosgene on a 600 g scale. My supervisor was Ivar Ugi, an expert in phosgene chemistry, and Ugi's tradition in this field has been continued, particularly in isocyanide chemistry. In 1986, I rediscovered *triphosgene* and realized its potential, in principal, as a substitute for phosgene in

nearly all reactions of the latter. This methodology led to patent applications. For several years, my company ''Dr. Eckert GmbH'' was the sole producer and distributor of triphosgene on the world market. Some further patents followed on ''safety phosgenation'' and ''tetrachloromethane-free'' phosgene. In 2002, the 25th year of Dr. Eckert GmbH, I placed the leadership in the hands of the next generation, in order to give them the opportunity to demonstrate competence and responsibility.''

L.C. writes: – ''My interest in the preparative chemistry and reactivity of phosgene equivalents started in 1974 during PhD studies on carbonic acid derivatives with regard to technologically important chlorinated alkyl carbonates. The search for a synthetic strategy that would exploit good leaving groups adjacent to carbonyl functions and, thus, equivalent to the chlorine atoms of phosgene led to the rediscovery of triphosgene as a phosgene substitute. One main contribution devoted to the synthesis of this compound concerned the scale-up (10–100 kg) of the solvent-free method for its preparation, and the coupled ''cyclic phosgenation process'' starting from dimethyl carbonate, methanol, and chlorine. I studied the multi membered cyclic transition-state mechanism of nucleophilic substitution (alcoholysis and aminolysis) of chlorinated carbonates and isocyanates, and found several medium-scale applications in the synthesis of active pharmaceutical ingredients (APIs). Recently, several studies on the catalytic and safe decomposition of triphosgene have been published.''

Our feeling, according to our long experience in the development of practical routes employing phosgene or phosgene equivalents, is that the '*palette*' of phosgenation reactions will grow more and more. Our task in writing this book has thus been to present the appropriate methods for carrying out reactions and for the preparation of reagents.

July 2003
Livius Cotarca Heiner Eckert

1
Contradictions

Phosgene is a substance of great contradictions.

On the one hand, **phosgene** is central to the chemistry of pharmaceuticals, polyurethanes, and polycarbonates; a huge market sector generating 8 million tons of products with an immense market value has been established. **Phosgene** is also useful in recently developed production processes for the manufacture of high purity *diamonds* [1] and of the nutritive sweetener *aspartame* [2] (see Section 4.3.5.4), as well as in highly innovative nanotechnology research as a *"fuel"* for the first *"molecular motor"* [3] (see Section 5.5). On the other hand, for some people **phosgene** is the incarnation of evil, primarily stemming from its use as a warfare agent in World War I [4], but it has also gained a fearsome reputation through its role in chlorine chemistry and as a highly reactive chemical.

Central to the concerns about the use of **phosgene** is its high toxicity, which has led to a TLV of 0.1 ppm (for a definition of TLV, see Section 3.4), and people fear the gas enormously. There is another highly volatile chemical with the same TLV of 0.1 ppm, namely *acrolein* (vapor pressure 29,000 Pa at 20 °C; for comparisons see Table 3.3, Section 3.3), which is generated in substantial amounts in everyday life at barbecue parties by roasting foods; people do not pay attention to it at all, even though the health hazards are similar to those associated with phosgene, such as potential lung edema after several hours.

Some procedures/processes have been developed to produce isocyanates by *phosgene-free* routes (see Section 4.3.1), citing the avoidance of dangerous **phosgene** for reasons of safety. In this connection, it is remarkable that the toxicities of alkyl isocyanates, such as *methyl isocyanate* (leaked from the Union Carbide plant in Bhopal/India in the disastrous accident at midnight, 2–3 December, 1984) with a TLV of 0.005 ppm, far exceed that of phosgene (TLV 0.1 ppm). Another way of substituting phosgene involves reacting rather low-energy molecules, such as ureas, at high temperatures (see Section 6.2.2.2). Such heat-powered reactions are mostly unselective and favor side reactions and the formation of by-products, thus increasing waste. Moreover, the excess thermal energy contributes to the greenhouse effect, and thus these reactions are *environmentally* unfavorable.

The net result of these contradictory factors is that for all phosgenation reactions, by which we mean all reactions that can be achieved by the use of **phosgene**, all relevant intrinsic (*yield*, *reactivity*, *handling*, *work-up*) and extrinsic (*safety*,

Phosgenations – A Handbook. L. Cotarca, H. Eckert

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toxicity, *environmental impact*) criteria (see Chapter 6) have to be weighed against each other, and the best methods and reagents for the desired transformation should be worked out or developed, free of ideological indoctrination. This may or may not point to the use of phosgene itself.

The aim of this book is to present the state-of-the-art on phosgenation chemistry, including all its *phosgene equivalents and substitutes* (some 70 are dealt with in this book), resulting in many novel reactions and processes for improved methods to obtain "phosgenation" products (see Chapters 4 and 5).

A second concern of this book is to show the modern trend of producing **phosgene** *captively*, and *on demand*, thereby minimizing storage (see Section 2.1.2), as well as the efforts to combine safe equivalents with the sometimes superior properties of phosgene in so-called *safety phosgenation*, which involves no storage of phosgene. The **phosgene** is generated *on demand* and immediately consumed, and so the quantity actually present in the reaction system is minimized (see Sections 2.2.2.1 and 7.1.2).

A third, forward-looking concern of this book is the presentation of examples of processes that meet the requirements of "*green chemistry*", which are often syntheses using carbon dioxide, such as the production of **dimethyl carbonate** from methanol (see Section 4.3.3.8). The other class of reactions in this branch of chemistry are smart catalytic reactions, through which the generally high activation energies of phosgenation reactions can be lowered, thus saving energy. Further considerations on trend-setting will be mentioned in Chapter 9 – Outlook.

References

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2 J. S. Tou, B. D. Vineyard, *J. Org. Chem.* **1985**, *50*, 4982–4984.

3 T. R. Kelly, R. A. Silva, H. de Silva, S. Jasmin, Y. Zhao, *J. Am. Chem. Soc.* **2000**, *122*, 6935–6949.

4 SIPRI, *"The Problem of Chemical and Biological Warfare", vol. 1, "The Rise of CB Weapons"*, Almquist & Wiksell, Stockholm, **1971**, p. 125–141.

2
Phosgenation Reagents

Phosgene is a typical highly reactive chemical used since the beginning of the chemical industry. It has been produced on a large scale and used as an intermediate in the dye and polymer (urethane) industries for many years in Europe and the U.S. [1–3]. The compound carries emotional baggage resulting from its use as a warfare agent during World War I.

Among other technologies for the production of fine chemicals, *phosgenation* has attracted much attention. **Phosgene** is currently used to produce *isocyanates* (intermediates for polyurethane resins and pesticides) from amines, *chloroformate esters* and *organic carbonates* from alcohols, *polycarbonates, acid chlorides* from carboxylic acids, *nitriles* from carboxamides, *isonitriles* from *N*-formylated compounds, and *heterocyclic compounds* from difunctional substrates. Several *carbamates* and *ureas* have useful biological activities, and some derivatives thereof have proven to be potent HIV-1 protease inhibitors. These applications produce many important intermediate compounds, including some that are employed in the synthesis of peptides [4–6], and in the activation of poly-*N*-[2-hydroxy-1,1-bis(hydroxymethyl)-ethyl]acrylamide gels for affinity chromatography [7]. The production and use of **phosgene** is under close scrutiny in view of the storage and use of large amounts of chlorine and carbon monoxide, the production of large volumes of waste containing chlorinated by-products, and the high risk of storing and transporting a volatile and very toxic compound. Despite these concerns, 5–6 million tons y^{-1} of **phosgene** are produced and used worldwide.

Because of its highly toxic nature, the handling of **phosgene** *gas*, either on a small scale in the laboratory, or on a medium to large scale in the agrochemical and pharmaceutical industries, needs special expertise. The constant danger in carrying out phosgenation reactions also results from the phosgene storage and from the use of solutions, and it is furthermore associated with the dynamics of external feeding. The *in situ* generation of phosgene would offer greater safety because the high rate of nucleophilic phosgene reactions ensures low stationary concentrations and hence safer reaction conditions.

Both the transportation and storage of **phosgene** pose considerable risks. *Phosgenations* are currently undertaken at the production site of the phosgene. Thus, all other reagents and starting materials have to be brought to the **phosgene**. This entails a high degree of planning, with its associated costs and time.

Phosgenations – A Handbook. L. Cotarca, H. Eckert

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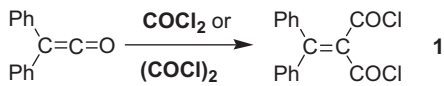
The need to replace phosgene by substitutes not only stems from considerations relating to its high toxicity, but is also due to the fact that its production and use involve chlorine as a raw material and result in the generation of large amounts of halogenated by-products since chlorine is not present in the majority of its end products [8]. A general discussion on the complex criteria for selecting a **phosgenation reagent** is given in Chapter 6.

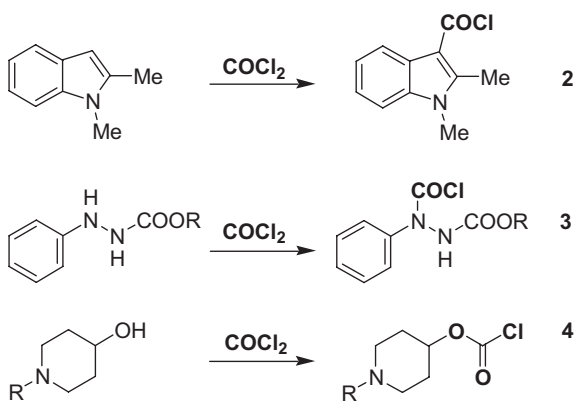
In recent years, **trichloromethyl chloroformate** (**diphosgene**) [4, 9] and **bis(trichloromethyl) carbonate** (**triphosgene**) [10–15] (for reviews, see [16–20]) have frequently been used in organic synthesis as **phosgene** *sources* [11, 21]. These liquid and crystalline *phosgene equivalents*, respectively, have the advantage of being much easier to handle than the *gaseous* **phosgene**.

A long list of *phosgene substitutes* has been proposed and investigated. **Catechol phosphorus trichloride** reacts with compounds containing C=O, P=O, S=O, RO, PO, and SiO groups to give the corresponding chloro derivatives. **Oxalyl chloride** can be an effective alternative chloroformylating agent to phosgene. The reaction of oxalyl chloride with diphenyl ketene, for example, proceeds under milder conditions than that with phosgene to give the identical organic product **1** [22].

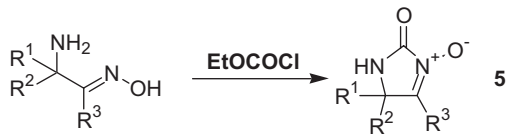


1

Aryl and *alkyl* **chloroformates**, *chlorinated chloroformates* (**diphosgene**), and *chlorinated carbonates* (**triphosgene**) can be used to convert carboxylic acids to the corresponding chlorides. The formation of alkyl chlorides from alcohols using these reagents is also possible. In many cases, however, such derivatives are difficult, or impossible, to prepare, in which case **phosgene** has to be employed. Some examples yielding **2**, **3**, and **4** are given below [23–25].

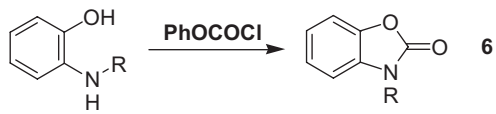


The carbonylating property of **phosgene** can be successfully realized using as substitute reagents lower alkyl chloroformates, such as **ethyl chloroformate**, which is particularly suitable as a ring-closing reagent in the synthesis of imidazoline derivatives **5** [26]; see also Chapter 6.



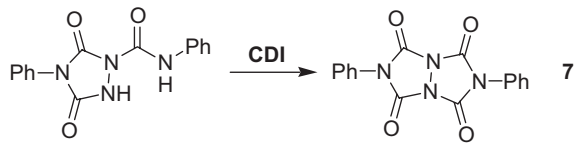
5

Compared to the reaction with **phosgene**, better yields are obtained in this reaction when the R substituents are small alkyl groups, such as methyl or ethyl, although in other cases the reaction was found to be better when phosgene was used. Cyclic carbamic acid derivatives **6** have been similarly prepared using **phenyl chloroformate** [24]; see also Chapter 6.



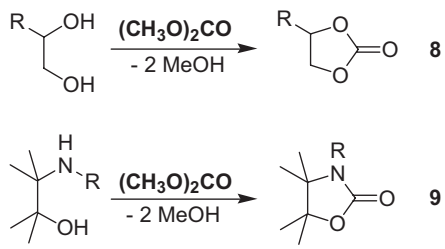
6

1,1-Carbonyldiimidazole (**CDI**) is used as a *phosgene equivalent* for many carbonylations, giving yields of **7** comparable of that achieved with **phosgene** [24]; see also Chapter 6.



7

Dimethyl carbonate is a recognized substitute for **phosgene** in many carbonylation and ring-closing reactions, affording **8** and **9**, respectively [27].

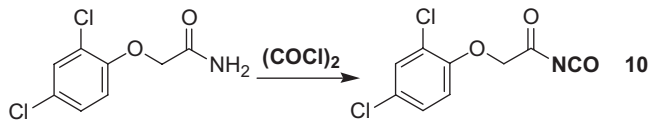


8

9

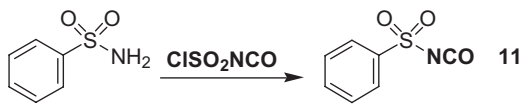
Although there are many alternative routes for the synthesis of isocyanates [24] (see also Chapter 4), none are as simple or as attractive as the carbonylation of primary amines with **phosgene**. This is reflected by the widespread employment of phosgene in the industrial manufacture of isocyanates; the use of **phosgene** continues despite numerous attempts to find suitable alternatives (see Chapter 4). However, **acyl isocyanates** such as **10** cannot normally be prepared by the reaction of **phosgene** with the corresponding carboxylic acid amide, since the phosgene

causes dehydration of the amide group to the corresponding nitrile. In this case, **oxalyl chloride** is effective [24].



10

Chlorosulfonyl isocyanate can be used in place of phosgene to prepare sulfonyl isocyanates **11** [24]; see also Chapter 4.



11

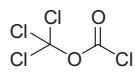
Thionyl chloride, **phosphorus(V) chloride**, and **triphenylphosphine**/**tetrachloromethane** can be used to convert monosubstituted amides into chloro imines. These reagents, as well as **oxalyl chloride**, also transform disubstituted amides into the corresponding imidium chloride salts.

Dehydration is a process for which many phosgene "competitors" have proved useful. **Thionyl chloride**, **phosphorus pentoxide**, **phosphorus oxychloride**, **triphenylphosphine**/**tetrachloromethane**, and **catechol phosphorus trichloride** are the reagents of choice in many dehydration processes.

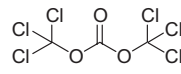
Several methodologies are directed toward the development of mild and safe reagents that can be utilized instead of **phosgene** in organic synthesis [28]. Most of these reagents are themselves prepared from **phosgene**. For example, **bis(4-nitrophenyl)carbonate** [29], **1,1-carbonyl-bis(imidazole)** (**CDI**) [30], **1,1-carbonyl-bis(benzotriazole)** [31], **phenyl chloroformate** [32], and **di-*tert*-butyl dicarbonate**, **(Boc)$_2$O** [33] are prepared from **phosgene**. In a few exceptions, **diphosgene** and **triphosgene** are used instead. In fact, the term **triphosgene** applied to **bis(trichloromethyl) carbonate** is a misnomer, since this compound is not derived from **phosgene** but by exhaustive chlorination of dimethyl carbonate [16]. Scheme 2.1 shows the structures of *phosgene equivalents* and their abbreviations.

There is opinion that employing these reagents is merely a way of circumventing and not of facing and solving the problem of avoiding the use of **phosgene**. However, the question becomes much more complex if process safety is taken into consideration and used as a reagent selection criterion (see Chapter 6). *Phosgenation* is undoubtedly a key step in the synthesis of many pharmaceuticals and agrochemicals. Small- or medium-scale operations require *intrinsic safety*, which must be ensured either by the stabilities of the raw materials (reagents), intermediates, and products, or by hazard minimization during the operation. Consequently, employing *phosgene-free reagents* or *phosgene-like raw materials* with controlled phosgene release during reaction, and the design of safer methods, are important goals with regard to these organic processes.

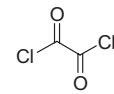
Phosgene



Trichloromethylchloroformate (Diphosgene)



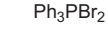
Bis(trichloromethyl)carbonate (**BTC**) (Triphosgene)



Oxalyl chloride

Phosphorus oxybromide

Phosphorus oxychloride



Dibromotriphenyl phosphorane

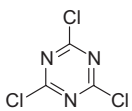
Phosphorus pentoxide

Boron tribromide

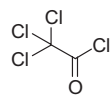
Boron trichloride

Thionyl chloride

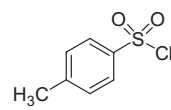
Thionyl bromide



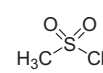
Cyanuric chloride (**CyCl**) 2,4,6-trichloro-1,3,5-triazine



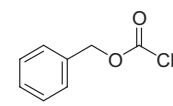
Trichloroacetyl chloride



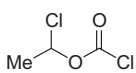
Tosyl chloride (**Tos-Cl**) *p*-Toluenesulfonyl chloride



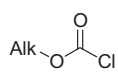
Methanesulfonyl chloride (**Ms-Cl**)



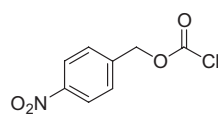
Benzyl chloroformate (**Z-Cl**)



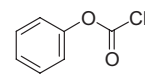
1–Chloroethyl chloroformates



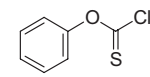
Alkyl (Me,Et) chloroformates



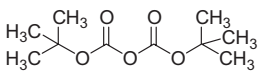
4-Nitrobenzyl chloroformate (**NZ-Cl**)



Phenyl chloroformate

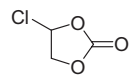


Phenyl chlorothionoformate

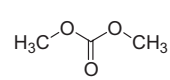


Di-*t*-butyl dicarbonate (**Boc_2O**)

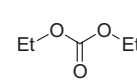
Ethylene carbonate (**EC**)



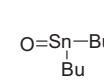
Chloroethylene carbonate



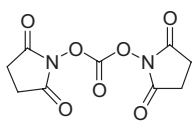
Dimethyl carbonate (**DMC**)



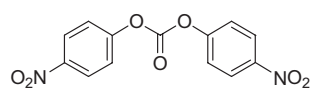
Diethyl carbonate



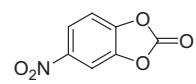
Dibutyltin oxide



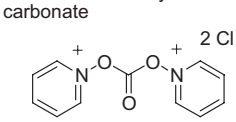
Disuccinimidyl carbonate (**DSC**)



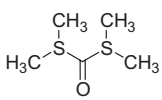
Bis(4-nitrophenyl)carbonate (**DNPC**)



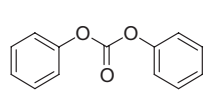
Nitrophenylene carbonate (**NPC**)



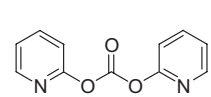
Pyridine N-oxide carbonate



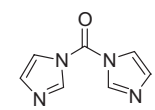
S,S-Dimethyldithio carbonate



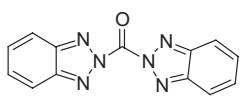
Diphenyl carbonate (**DPhC**)



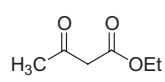
Di-2-pyridyl carbonate (**DPC**)



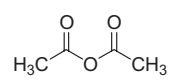
1,1-Carbonyldiimidazole (**CDI**)



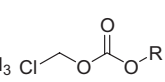
1,1-Carbonylbisbenzotriazole



Ethyl acetoacetate



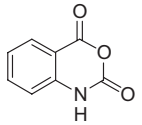
Acetic anhydride



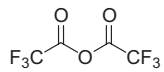
α-Chloroalkyl alkyl carbonates

Diphenylphosphoryl azide

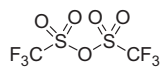
Scheme 2.1. **Phosgene equivalents** and **substitutes**: structures and abbreviations; order according to Table 7.2, Section 7.2.



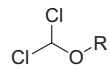
Isatoic anhydride



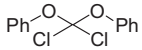
Trifluoroacetic anhydride (**TFAA**)



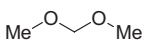
Trifluoromethanesulfonicanhydride (Triflic anhydride) (**Tf_2O**)



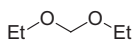
1,1-Dichloromethyl Me or Et ether



Dichlorodiphenoxy methane



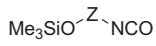
Formaldehyde dimethylacetal (methylal)



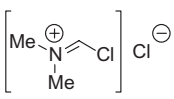
Diethoxymethane

Carbon monoxide

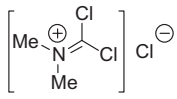
Carbon dioxide



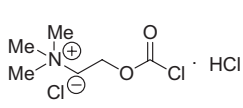
Trimethylsiloxane isocyanates



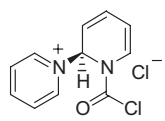
(Chloromethylene) dimethylammonium chloride (**Vilsmeier reagent**)



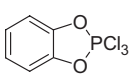
(Dichloromethylene) dimethylammonium chloride (**Viehe's salt**)



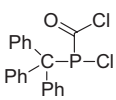
Choline chloroformate hydrochloride



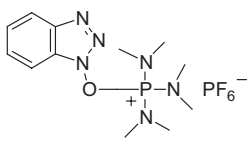
Pyridine-phosgene adduct (**2-DHPP**)



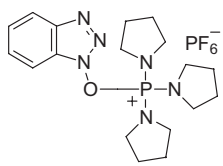
Catechol phosphorus trichloride



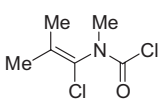
Chlorocarbonyl-chloro-triphenylmethane phosphine



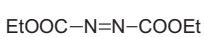
Benzotriazol-1-yloxytris (dimethylamino)-phosphonium hexafluorophosphate (**BOP**)



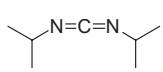
Benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (**PyBOP**)



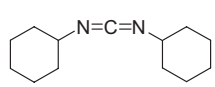
Phosgene-imine adduct



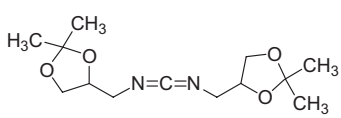
Diethyl azodicarboxylate (**DEAD**)



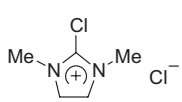
Diisopropylcarbodiimide



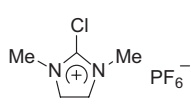
Dicyclohexylcarbodiimide (**DCC**)



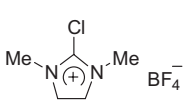
1,3-Bis(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)carbodiimide (**BDDC**)



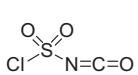
2-Chloro-1,3-dimethyl-imidazolium chloride (**CDC**)



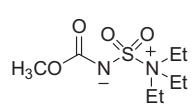
2-Chloro-1,3-dimethyl-imidazolium hexafluorophosphate



2-Chloro-1,3-dimethyl-imidazolium tetrafluoroborate



Chlorosulfonyl isocyanate



(Methoxycarbonylsulfamoyl) triethylammonium-N-betaine (**Burgess reagent**)

Scheme 2.1 *(continued)*

Procedures employing *phosgene equivalents* can also be applied to the large-scale preparations of those carbamates, ureas, or heterocyclic compounds that are difficult to synthesize efficiently by other and safer methods, mainly compounds bearing different functionalities and incorporating chiral carbons in the side chains. In this regard, a first crucial step towards more environmentally friendly approaches to ureas was taken with the use of **bis(4-nitrophenyl)carbonate**, ***S,S*-dimethyldithiocarbonate**, **1,1-carbonyl-bis(imidazole)**, **di-*tert*-butyl dicarbonate**, and **phenyl chloroformate** [28].

The most appealing and promising strategy, however, is the *carbonylation* of amines and/or nitro compounds with **carbon monoxide** over transition metal complexes, which permits the use of safer raw materials. These reactions are catalytic and do not produce large amounts of saline by-products [34, 35].

A further important improvement, which allows the manufacture of **ureas** with concomitant reduction of waste at source (i.e. avoiding the production of large amounts of saline by-products, which represent the main constituent of chemical waste) has been the application of **carbon dioxide**. This strategy combines the use of a non-toxic reagent with the benefit of reducing the emission of $\mathbf{CO_2}$ in a direct way by fixation of the molecule into other molecules [36–38].

2.1 Phosgene

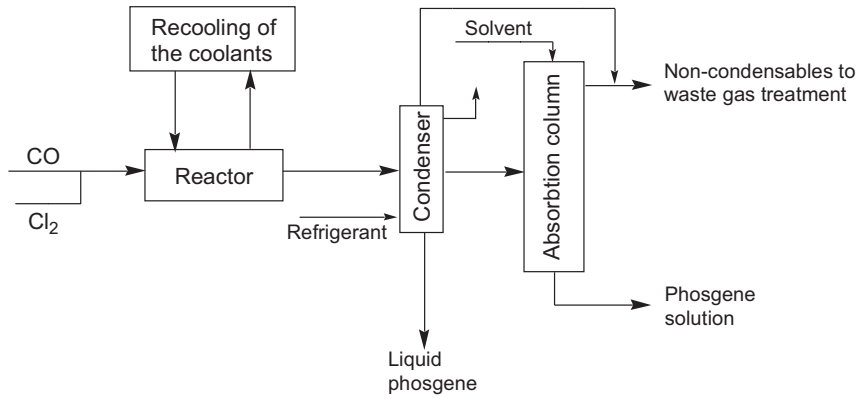
Phosgene (carbonyl dichloride) is a colorless reactive gas with a bp of 8.2 °C, a vapor pressure at 20 °C of 162,000 Pa or 1215 mmHg, and a vapor density of 3.5. Phosgene was first prepared by John Davy in 1812 by the action of light on a mixture of chlorine and carbon monoxide.

The current scale of world phosgene consumption is $5–6 \times 10^6$ tons y^{-1}. The vast majority of phosgene is utilized at its site of production: only very small quantities are shipped. Only *Van De Mark* (now part of *SNPE*), located in Lockport, N.Y., sells **phosgene** on the merchant market. Traditionally, small-scale consumers of **phosgene** had little choice but to buy it from *Van De Mark*. Because of its toxicity, small or zero inventories of **phosgene** are usually maintained, although it is easily liquefied.

Phosgene can be prepared from carbon monoxide, from halogenated hydrocarbons, from carbonaceous materials, from carbon dioxide, carbonyl sulfide or carbon disulfide, and from other oxygenated compounds [39]. The method based on the chlorination of carbon monoxide is by far the most important and has been scaled-up for the commercial manufacture of phosgene.

2.1.1 Conventional Manufacturing Processes

Phosgene is produced commercially by the highly exothermic vapor-phase reaction of anhydrous chlorine gas with high-purity carbon monoxide in the presence of an



Scheme 2.2. Simplified flow chart for the production of **phosgene**.

activated carbon catalyst [1]. The enthalpy of formation is -107.6 kJ mol^{-1}, hence efficient heat removal is required.

$$CO(g) + Cl_2(g) \longrightarrow COCl_2(g)$$

The basic manufacturing process for phosgene has not changed significantly since the 1920s and comprises the preparation and purification of the raw materials, carbon monoxide and chlorine, the metering and mixing of these materials, the reaction of the mixed gases over activated charcoal, and the purification and condensation of the phosgene product. A flow diagram of the process is illustrated below (Scheme 2.2).

The process is normally operated on a continuous basis, employing a high degree of automation. Owing to the toxicity of phosgene, extensive safety features are an integral part of the plant design. The reaction is rapid and nearly quantitative with respect to both raw materials. Traditionally, **phosgene** is produced from large-scale units running at a steady state, and the product requires downstream storage. The plants are provided with a safety absorption system, whereby any surplus **phosgene** is absorbed and destroyed with a circulating caustic solution. This kind of process is only well-suited for large users and it engenders a lot of environmental concerns.

Detailed descriptions of the *basic manufacturing processes* are given in several important references [40–43].

A summary of recently filed patent applications and granted patents regarding **phosgene** preparation is presented in Table 2.1.

Phosgene produced by the traditional processes will typically contain 400–500 ppm by weight tetrachloromethane (the major world producers claim a CCl_4 content of 50–400 ppm). The amount of tetrachloromethane needs to be evaluated on the basis of the total worldwide production of phosgene. In relation to the cumulative effect of recycling *polycarbonates* (the major polymeric material for which phosgene is a raw material), tetrachloromethane has been shown to have both

Tab. 2.1. Recently disclosed processes for the preparation of **phosgene**.

Patent/Application Number	*Authors*	*Owner*	*Main Claims of the Patent*
DE 19916856 A1 23/09/**1999**	H. Eckert, B. Gruber, J. Auerweck	Dr. Eckert GmbH, Hallbergmoos, DE (D-85399)	Phosgene manufactured from CO, Cl_2, and metal (Al, Ga) halide (Cl) catalyst. Low CCl_4 contents of <1 ppm in batch process.
US 5891319 06/04/**1999**	F. J. Freiere, K. B. Keating, E. K. Sakata	DuPont, USA	Electrochemical, low-temperature, uncatalyzed process for the production of carbonyl halides (not specific to phosgene).
WO 9914159, **1999** EP 1017623 B1, **2002** US 6399822 B1, **2002** JP 2001516692, **2001** DE 1974057, **1999** (15/09/**1997**)	H. Eckert, B. Gruber, N. Dirsch	Dr. Eckert GmbH, Hallbergmoos, DE (D-85399)	Method and device for preparing phosgene from diphosgene and/or triphosgene, by reaction on a catalyst comprising compounds with one or several N atoms with a pair of deactivated electrons.
PCT WO 9828227 02/07/**1998**	W. Cicha, L. E. Manzer	DuPont, USA	Process for producing phosgene from CO and Cl_2 using a carbon catalyst having an active metal content of $\geq$1000 ppm.
JP 10120410 A2 12/05/**1998**	S. Nakano	Teijin Chem. Ltd., Japan	Phosgene manufactured in the presence of an activated C catalyst, by the reaction of Cl_2 and CO containing $\leq$6.0 mol% H. Yellowing of the phosgene obtained is prevented by reducing the H content in CO.
PCT WO 9800364 08/01/**1998**	W. Cicha, L. E. Manzer	DuPont, USA	Process for producing phosgene having a low CCl_4 content from CO and Cl_2 at $\leq$300 °C using a silicon carbide catalyst prepared by contacting silicon monoxide with finely divided carbon.
JP 9059012 A 04/03/**1997**	T. Hosomi, T. Takada	Mitsubishi Gas Chem. Co., Japan	Crude phosgene having a CCl_4 content of $<$100 ppm (v/v) is produced from CO and Cl_2 using active carbon as catalyst. The crude phosgene is liquefied at

Tab. 2.1 *(continued)*

Patent/Application Number	*Authors*	*Owner*	*Main Claims of the Patent*
			−40 to +7 °C, and optionally further evaporated at 9–25 °C to obtain purified product. $COCl_2$ of purity >99 wt% and with a CCl_4 content of <10 ppm (*w*/*w*) can be produced by this process. The methane content of the CO used as raw material is preferably <100 ppm.
PCT WO9730932 A1 28/08/**1997**	W. Cicha, L. E. Manzer	DuPont, USA	Process for producing phosgene from CO and Cl_2 using a carbon catalyst having an active metal content of ≤1000 ppm.
EP 796819 A1 24/09/**1997**	N. Kunisi, N. Murai, H. Kusama	Idemitsu Petrochem. Co., Japan	Reaction of CO with Cl_2 by passing both through a catalyst layer comprising active carbon as main component, which is diluted with a material (ceramic and/or metal material) that is largely inert to CO_2 and Cl_2.
WO 9719205 29/05/**1997** DE 19 543 678 28/05/**1997**	F. Gestermann, J. Dobbers, H. Rindfleisch	Bayer A.-G., DE	Process for direct electrochemical gaseous phase $COCl_2$ synthesis using a conducting membrane probe.
US 4764308 16/08/**1988** EP 0134506 B1 22/03/**1989**	H. Sauer, H. F. Porkert, D. Liebsch	Bayer A.-G., DE	Phosgene is produced by reacting Cl_2 and an excess of CO in the presence of activated charcoal in a two-stage process. In the first stage, the chlorine and CO are reacted in a tubular reactor containing activated charcoal at a temperature above 250 °C until 95–98% of the chlorine has reacted. The reaction gases are cooled to 50–120 °C, and then introduced into a second reactor maintained at 5–100 °C, where the

Tab. 2.1 *(continued)*

Patent/Application Number	*Authors*	*Owner*	*Main Claims of the Patent*
			phosgene-forming reaction is completed. The phosgene leaving the second reactor has a residual chlorine content of <50 ppm. The heat generated during phosgene formation is used to produce steam.
US 4231959 04/11/**1980** EP 003530 A1 22/08/**1979**	R. Obrecht	Stauffer Chem. Co., USA	Reaction of Cl_2 and excess CO in the presence of an activated carbon catalyst by recovering unreacted CO and recycling it to the reaction zone (contaminants: <10 wt% each of N_2 and HCl; trace amts. <1 wt% each of O_2 and CCl_4, and <100 ppm Cl_2).

significant ozone depletion and global warming potentials. Therefore, there is an interest in developing phosgene processes in which the amount of tetrachloromethane impurity is minimized.

In the production of *polycarbonates* from dihydroxylic compounds and **phosgene**, tetrachloromethane also causes a yellowing of the material, which is disadvantageous for optical applications of the polymers; a colorless product can only be achieved when the **phosgene** has a CCl_4 content <150 ppm [44].

Thus, the development of a process for producing highly pure phosgene has been one goal of research in this field. On the other hand, extensive industrial research has been dedicated to the quest for new phosgene-free routes to polycarbonates. **Diphenyl carbonate** (**DPhC**) is used as the key reagent for incorporating the carbonate functionality into polycarbonates by the so-called non-phosgene route. One of the difficulties associated with this process, however, is making the **DPhC**. Currently, **DPhC** is made from **dimethyl carbonate** (**DMC**) by transesterification with phenol (see, for example, the *Enichem* process). This reaction is equilibrium-constrained and requires a fairly complicated processing scheme. The **DMC** is in turn prepared by oxidative methylation of carbon monoxide with methanol (as in the *Enichem* process) as a preferred alternative to obviate the need for phosgene.

Several efforts have been made to lower the *tetrachloromethane* content of phosgene to below 150 ppm [44–48]. Examining the patent literature, the major tech-

nical improvements have been focussed on the catalyst; indeed, substitution or modification of the catalyst should have a minimal impact on the existing manufacturing process and should therefore require the least investment.

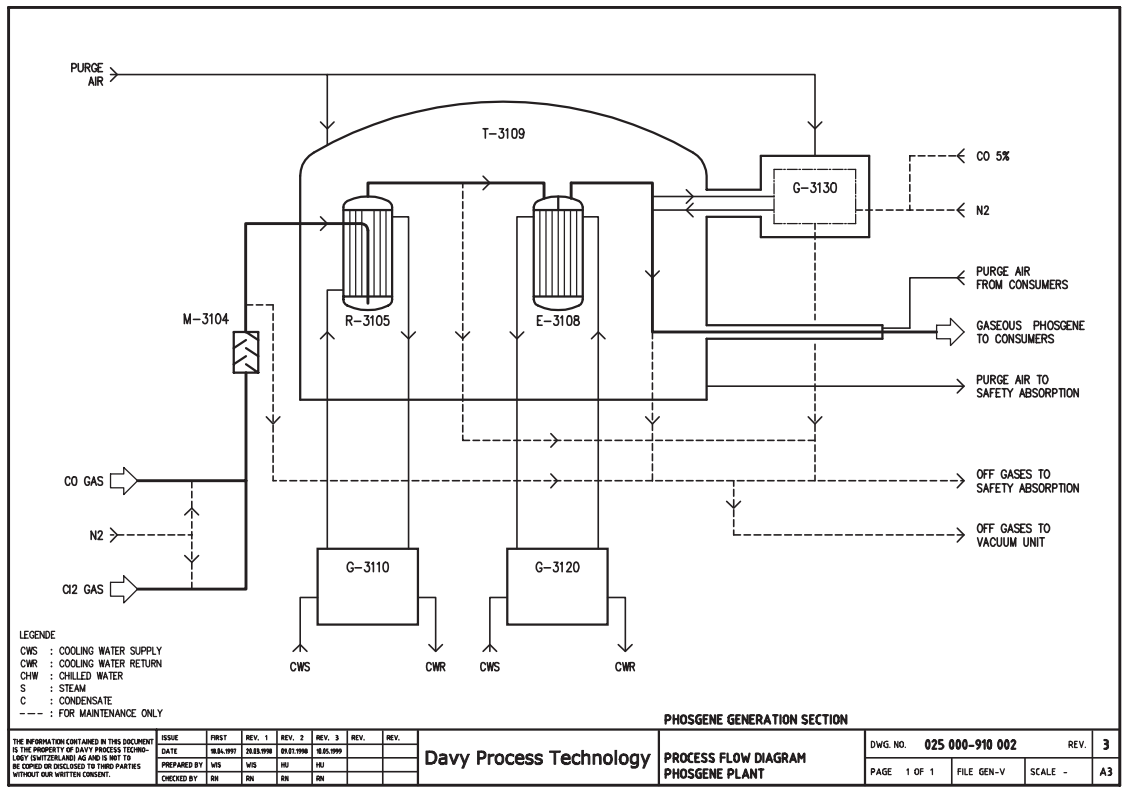
In a recent contribution to this field, a process was reported whereby **phosgene** is manufactured from chlorine and carbon monoxide under catalysis by a Group III metal halide [47]. The key feature of this process is that it uses a *carbon-free catalyst*, principally based on Group III metal (Al or Ga) halides, which avoids the formation of chlorinated carbon products. The carbon-free catalysts were applied in the production of nearly *CCl_4-free* **phosgene**, which contained as little as 1 ppm of the contaminant. The reported reaction times for a batch reaction system using $GaCl_3$ and $GaCl_2$ (3.7 mol%) as catalyst, e.g. 1.5 h and 1 h, respectively, at 1200 kPa, generating **phosgene** in 100% yield, are very promising. *Aluminum chloride* can also be used as catalyst, but reaction times are significantly longer. The reaction temperature is very low (below room temperature to 100 °C) compared to those of traditional process. An elegant feature of the process is that the catalyst is continuously regenerated and activated by resublimation. The process seems to be well-suited for scale-up and may be operated in either continuous or batch mode. The described process has important advantages considering the low level of tetrachloromethane contamination (<1 ppm) of the product, the very mild and highly versatile conditions of operation based on established chemistry, and the ready availability of the high turnover catalyst.

A further Bayer process yields **phosgene** with a CCl_4 content below 150 ppm by reacting carbon monoxide and chlorine in the presence of *elemental carbon* at 30–80 °C at a pressure of 120–400 kPa [44]. Companies such as DuPont [45] and Idemitsu [46] pursue the same approach by treating charcoal catalysts with 0.1–2.3% of active metals, thereby also producing **phosgene** with CCl_4 levels <150 ppm. **Phosgene** manufacture generally takes place in special equipment and plants.

2.1.2
Manufacturing Processes "*On Demand of Consumer*"

Another way of providing consumers on location with **phosgene** *"on demand"* is through the use of *Modular Phosgene Generators*, which are available in several output sizes ranging from 3–10,000 kg h^{-1} from *Davy Process Technology (DPT)*, Switzerland [49]. These *Modular Generators* produce **phosgene** from carbon monoxide and chlorine, and consist of two sections, the intrinsic *phosgene generator* (Scheme 2.3) and a *safety absorption* module (for commercial availability, see Section 7.1.1).

A recent publication [50] details the new *Novartis Crop Protection Inc.* plant (at Monthey, Switzerland) for the manufacture and use of **phosgene** in equipment that is considered *intrinsically safe*. Indeed, the implementation of "dynamic reactors" for the production of phosgene, which manufacture and deliver the phosgene to the users on demand as required, without intermediate storage, has made it possible to strongly reduce the quantities of phosgene contained within the plant. Furthermore, confinement of the phosgene production, supply, and utiliza-



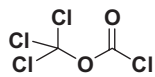
Scheme 2.3. Process flow diagram of the phosgene generation section of a *phosgene generator* from Davy Process Technology (DPT) [49].

tion equipment within a double envelope makes it possible to collect and destroy any leakage of the phosgene in dedicated installations [50].

2.2
Phosgene "Oligomers"

2.2.1
Diphosgene

Trichloromethyl chloroformate (**diphosgene**) **12** is a dense liquid, d_{15} 1.65, bp 128 °C, and vapor pressure at 20 °C of 1370 Pa or 10.3 mmHg (see Chapter 3 and [51]). The compound was used as a warfare agent during World War I and has also been called *Supralite* or *Superpalite*.



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Kurita systematically investigated the reactivity of **diphosgene** and compared its reactions with those of phosgene [52]. Ugi proposed **diphosgene** as the reagent of choice for the synthesis of isocyanides [53].

Some of the safety hazards associated with phosgene could be circumvented by the general availability of diphosgene [1, 54]. It is readily available from the regular commercial suppliers; for sources, see Section 7.2.

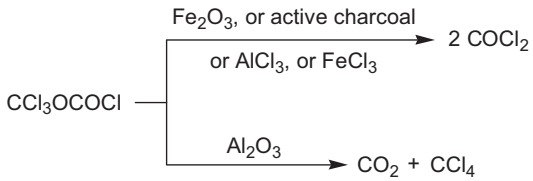
The catalytic decomposition routes of **diphosgene** are extremely interesting. The compound is stable at room temperature, but decomposes to **phosgene** when heated above 300 °C [55–57], or on contact with iron(III) oxide, iron(III) chloride, or aluminum(III) chloride (less active) or activated charcoal (very active) [51].

The kinetics of the thermal decomposition of **diphosgene** has been studied over a temperature range of 260–310 °C and a pressure range of 4–17 mmHg. The reaction has been found to be first order and homogeneous, with catalysis by the glass walls of vessels having only a slight influence [56]. The rate constant is given by the expression: $k_1 = 1.4 \times 10^{13} e^{-14.500/RT}$.

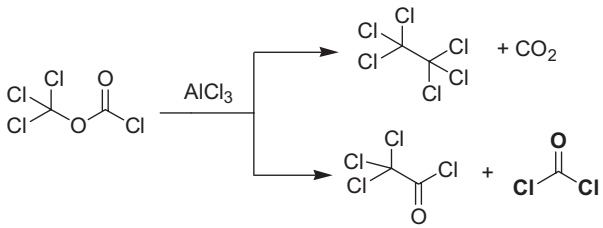
The possible equilibrium between phosgene, carbon monoxide, and chlorine was not found to arise as a result of the reaction, the sole product of decomposition being **phosgene**.

The formation of *N*-carboxy α-amino acid anhydrides with diphosgene is usually unsuccessful without prior decomposition of the diphosgene to phosgene [58]. **Diphosgene** decomposes instantly to give phosgene under catalysis by *active charcoal*, making the method as rapid as the phosgene stock solution method [58] (see Section 4.3.5).

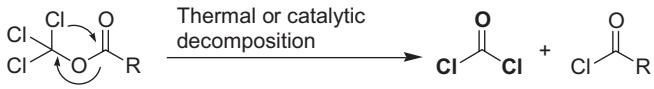
Decomposition to *tetrachloromethane* and *carbon dioxide* occurs on exposure to alumina [51, 55, 57, 60].



Two different **diphosgene** decomposition routes have also been noted in the presence of aluminum(III) chloride, one giving *hexachloroethane* and *carbon dioxide* and the second giving *trichloroacetyl chloride* and **phosgene** [61].

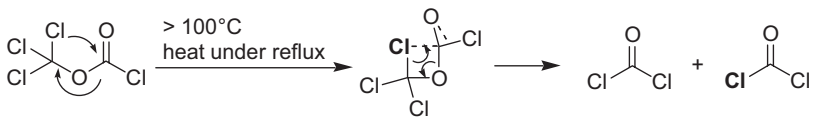


The *thermal decomposition* of a series of compounds containing the trichloromethyl group, generating two or three moles of **phosgene** per mole of starting material, has been reported [55, 57, 59, 62].



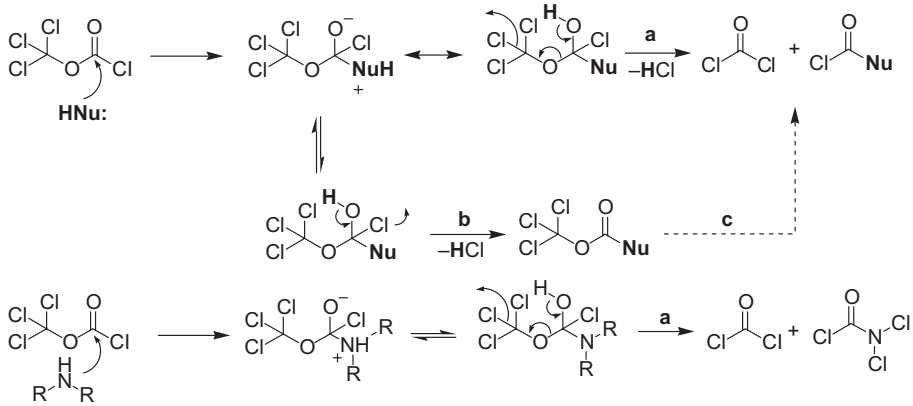
R = alkyl, Cl or $OCCl_3$

Therefore, **diphosgene** can be regarded as being equivalent to two molecules of **phosgene**, into which it is slowly decomposed when pure [58]. One of the internal trichloromethyl chlorine atoms probably plays the **Nu** role in a four-membered cyclic transition state. A continuous stream of **phosgene** is also emitted when **trichloromethyl chloroformate** is simply heated under reflux [55].



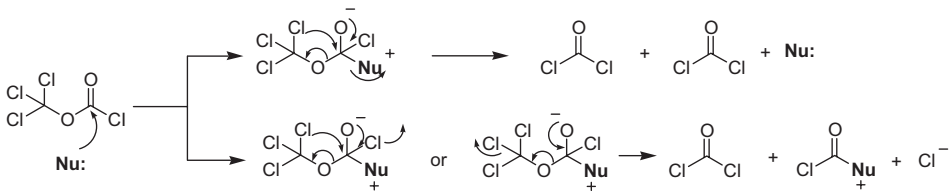
Nucleophilic reactions of **diphosgene** highlight its reactivity as a tricoordinated carbonic acid derivative. Its phosgene equivalence can be rationalized in terms of the mechanistic scheme shown below (e.g. route **a** with a dialkylamine as **HNu**), whereby a mole of **phosgene** is released during the nucleophilic substitution. Several examples of route **b** have also been reported. From the reaction of **diphosgene**

with oximes (**HNu** is HO–N=CR_2), mixtures of products arising from routes **b** and **a**/**c** have been recovered [63].



Diphosgene has been used as a **phosgene** *source* in many applications. The chlorination of carboxylic acids in the presence of dimethylformamide as catalyst is an efficient route to highly pure acid chlorides [64]. In a practical method for the chlorination of carboxylic acids, diphosgene is conveniently converted into phosgene by dissolving it in tetrachloromethane containing a basic catalyst (**diphosgene** in CCl_4:pyridine, 400:1, for 30 min; yields 90%) [65]. Several *nitrogen compounds*, e.g. pyridine, quinoline, tetramethyl urea, or tertiary amines, have also been reported to catalyze the quantitative decomposition of **diphosgene** into **phosgene** [66, 67].

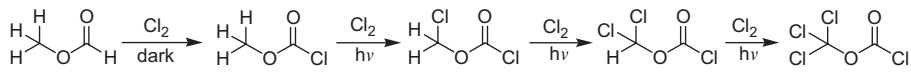
Diphosgene decomposes very rapidly and quantitatively in the presence of a nucleophile such as a ''naked'' chloride anion [68, 69]. Nucleophilic attack at the carbonyl atom, which is the origin of the molecule-catalyzed ''decomposition'' and of phosgene release, can be generalized according to the scheme below. In many cases, in situ generated phosgene reacts very rapidly with the nucleophile, which acts as a ''phosgene scavenger'' affording chlorocarbonyl or nucleophilic disubstituted derivatives, respectively, as the reaction products.



The stability of **diphosgene** in the presence of various metal (Fe, Al, V) oxides and chlorides has been extensively investigated in order to find practical routes for quantitative decomposition or to establish the compatibility of the reagent with various materials [51].

Diphosgene was first prepared by Hentschel, who obtained a mixture of chlori-

nated methyl chloroformates, but it was subsequently proved that **diphosgene** was the final product of the chlorination of methyl formate [55, 56].

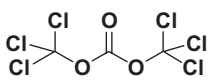


The process of chlorination takes place in a stepwise manner, methyl chloroformate being formed first and then, successively, the monochloro-, dichloro-, and trichloromethyl chloroformates. Methyl formate reacts readily with chlorine in the dark, giving methyl chloroformate. Further chlorination in the dark without the aid of a catalyst gives some chloromethyl chloroformate, but the reaction is slow and the yield is poor. Complete conversion can only be achieved by photochlorination at near the boiling point of the liquid [51, 70].

Photochlorination of methyl chloroformate has been reported as a practical laboratory procedure for preparing **diphosgene**, as recently as 1980 [9]. This reaction has been successfully scaled-up by *Schering Agrochemicals Ltd.* (now part of *Aventis*) to about 500 kg batch size as part of a process for a commercial fungicide [71]. The chlorination of methyl chloroformate occurs in three sequential steps as shown above. The two intermediates (monochloro-**MCMCF** and dichloro-**DCMCF** species) can clearly be seen to sequentially build up and then decrease as the final **PCMF** (diphosgene) product is formed.

2.2.2
Triphosgene

Bis(trichloromethyl)carbonate (**triphosgene**) **13**, also known as **hexachlorodimethylcarbonate** or **trichloromethyl carbonate**, was surprisingly "rediscovered" in the last decades of the 20th century.



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In the laboratory, or when other small-scale quantities are required, **triphosgene** can provide a degree of handling convenience. As a reagent, **triphosgene** can offer many advantages over phosgene. It is safer and more convenient to handle, transport, and store. Exact, stoichiometric amounts may be weighed easily and used to perform desired chemical transformations. Reactions typically require only one-third of an equivalent of triphosgene. **Triphosgene** is now produced on a commercial scale at a level of hundreds of tons y^{-1} (see Chapter 7), and hence it has become more cost-competitive.

The compound was first prepared by Councler [72]. The first data on its physical and chemical properties were reported as early as 1887 [55], but details of its solid-state structure were only published in 1971 [73]. Various applications of **triphosgene** were reported in the early 1900s, in particular its reactions with amines,

alcohols, phenols, and aldehydes [74–77]. In the entire period up to 1980, only a dozen papers and patents appeared, whereas in the last decade their number has grown exponentially. Several literature contributions have reviewed the synthetic possibilities of this reagent, and have thereby opened up many synthetic opportunities for pharmaceutical and agrochemical applications [10–19, 78, 79].

2.2.2.1 Triphosgene as a Phosgene Equivalent or Phosgene Source

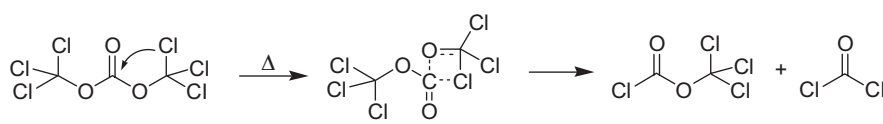
Triphosgene is used as a phosgene equivalent [10–19, 78, 79] or as a source of phosgene [3, 69, 80, 81].

Triphosgene may have an important role to play in evaluating the use of phosgene in a synthesis. One of the recent developments in current use, tested some years ago in various laboratories, is the pre-packaged cartridge for "intelligent" phosgene production based on triphosgene "depolymerization" using a solid catalyst containing one or several nitrogen atoms with a pair of deactivated electrons. *Dr. Eckert GmbH* have designed a process based on downstream demand, in which **triphosgene** is employed as a **phosgene** *source* [3, 80–84] (see also Chapter 7).

The method may be classified within the group of "*methods using compounds as in situ* ***phosgene*** *source (precursor)*" (see Chapter 3) and has important advantages over the traditional methods of phosgene manufacture in small- and medium-scale phosgenations, considering the very mild and highly versatile conditions of operation based on established chemistry, and the ready availability of the high turnover catalyst (owner *Dr. Eckert GmbH* [82]).

2.2.2.2 Stability: Thermally and Chemically Induced Decomposition

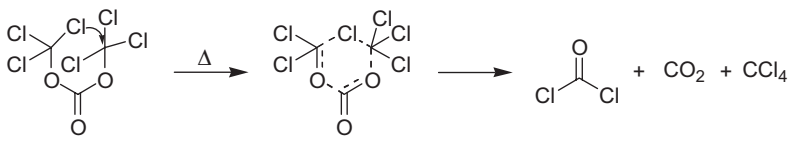
In spite of the growing interest in synthetic applications, no systematic investigation on triphosgene stability has yet been reported. Since its first preparation, bis(trichloromethyl)carbonate has been regarded as a stable solid compound. However, Hood [51] noted a marked decomposition into **diphosgene** and **phosgene** when the product was distilled. A decomposition route via a four-membered transition state, akin to that depicted for diphosgene in Section 2.2.1, can be envisaged.



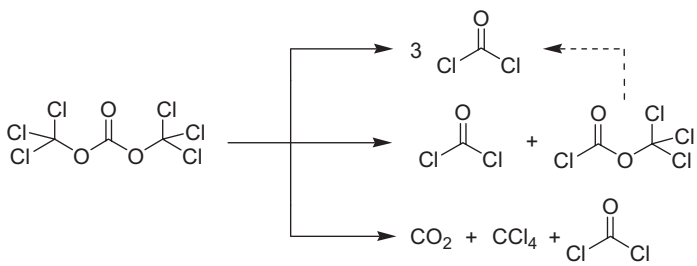
Grignard [70], Kling [85], and Marotta [86] have studied the thermal decomposition of triphosgene, and, although their results were somewhat divergent, high thermal stability up to 300 °C was claimed.

The thermogram obtained by differential scanning calorimetry (DSC) shows a melting peak at 82.4 °C and an exothermal decomposition peak starting at 160 °C ($\Delta H_{dec} = 200$ J g^{-1}). Tests on an accelerating rate calorimeter (ARC) showed the onset of decomposition at 130 °C, with $\Delta H_{dec} = 278$ J g^{-1}, and a final temperature of 179 °C. The accumulated data do not support the originally claimed stability

below the boiling point, although there is no evidence of its decomposition below 130 °C [16]. To identify the gases produced from the decomposition of **triphosgene**, an experiment was performed on a thermogravimetric analyzer interfaced to a Fourier transform infrared spectrometer (TGA-FTIR) [16]. The simultaneous presence of phosgene, diphosgene, carbon dioxide, and tetrachloromethane among the thermal decomposition products suggested another decomposition mechanism, which would be favored by a six-membered transition state, as shown below.



Therefore, three distinct decomposition pathways have been identified in the published literature. **Triphosgene** decomposes into *three molecules* of **phosgene** below its boiling point (206 °C) in the presence of initiators [69, 80, 81]. At lower temperatures, such as during its distillation under reduced pressure, triphosgene decomposes into **phosgene** and **diphosgene**, but when mixed with powdered activated carbon (or with Lewis acids [57]) and heated to the melting temperature, rapid decomposition to **phosgene** occurs [59]. Finally, a decomposition to carbon dioxide, tetrachloromethane and **phosgene** can take place.



A very interesting debate on the safe handling and shipping of **triphosgene** has been provoked by earlier articles in authored journals [87, 88] and relevant monographs [89, 90]. The comments concerned the potential danger from research-size cans of triphosgene, supplied by a chemical reagents producer, and the "unpredictability" of decompositions of triphosgene into phosgene on heating and upon reaction with any nucleophile [88]. Even a trace of moisture was claimed to lead to phosgene formation. It was supposed that phosgene formation is either due to self-decomposition of triphosgene or due to reaction with trace amounts of moisture in the air [88].

Refering to triphosgene and diphosgene, the generalization was made that, effectively, "in any transportation or handling accident, both compounds are phosgene" [3].

Considering such hazard warnings, the tremendous growth of phosgene-free methods, including triphosgene chemistry, during the last decades has been surprising, offering to the research laboratories milder and more easily controllable conditions for phosgenations [16]. Recently, some important contributions to the control of **triphosgene** *stability* have been brought to the attention of the chemical community [80]. Quantitative experimental data, that have allowed hazard and safety guidelines on **triphosgene** usage in organic processes to be drawn up, are available [11–20, 69, 80, 90].

When solid crystalline **triphosgene** is immersed in water, no significant change of pH (HCl release) and hence no decomposition into phosgene is observed. This is due to the very low solubility of triphosgene in water. The behavior and consequences are different when solvents such as THF or dioxane are used. These are significantly miscible with water, and hence the reaction between triphosgene and nucleophilic water can take place in a homogeneous liquid–liquid system. In this case, temperature and basic catalysts play important roles in accelerating the decomposition. For this reason, in processes involving the handling of triphosgene in an organic solvent, the reaction mixture must be rigorously protected from accidental contact with water or NaOH solution (e.g. that in the scrubber).

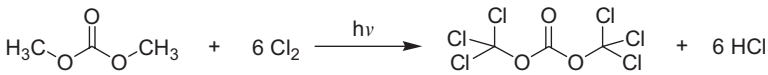
Nucleophilic substitution at **triphosgene** starts with a solvation process [14]. It is supposed that, before any nucleophilic attack, several molecules of the nucleophile first have to become associated with triphosgene in the transition state. In evaluating triphosgene hydrolysis, the effect of moisture on the reactivity must be evaluated. One has to estimate the amount of water present (i.e. water dissolved in the reaction solvent containing triphosgene) during those steps of the process in which triphosgene can generate phosgene. Theoretically, 18 g of water can react with 297 g of triphosgene. Therefore, operation in an open reactor must always be avoided and standard operating procedures must always include nitrogen atmosphere and moderate flushing (with control of the water content in the nitrogen flow).

For example, *Ubichem*, UK, developed a novel process for producing **triphosgene** several years ago, and carried out extensive tests to *determine its stability* in the presence of various impurities [91, 92]. Such studies are, of course, imperative to identify the appropriate materials for plant construction, the appropriate packaging, and the appropriate handling in use.

It was found that triphosgene is indeed unstable in the presence of partially chlorinated intermediates, metal ions, charcoal, and nucleophiles (the source of its reactivity). *Detailed analyses of several marketed products have been carried out and significant levels of partially chlorinated dimethyl carbonate have been found. The compound was also shipped in metal drums. The effect on stability was obvious: HCl and phosgene were immediately detected in the head space of the drum.* The same company now has **triphosgene** made under contract in an entirely glass/poly(tetrafluoroethylene) system, and packs the material in a PTFE container that is then overpacked in a sealed heavy-duty foil laminate sachet. This sachet is designed to withstand high temperatures, and it is specifically employed to minimize the release of triphosgene breakdown products in the event of a transport accident [91, 92].

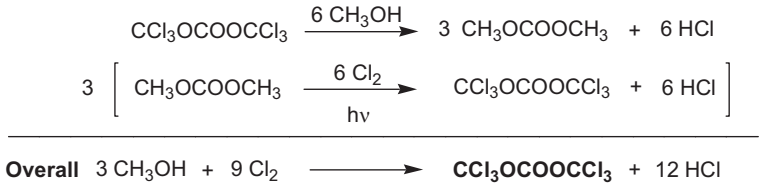
2.2.2.3 Preparation

The compound is prepared by the liquid-phase photochlorination of dimethyl carbonate (a potential large-scale gasoline anti-knock additive); see, for example, [11, 70, 78, 79, 93–95].



Small- and macrolab-scale procedures have also been published [16]. Furthermore, variations on the basic radical chlorination method [96, 97] and data concerning a scaled-up process [91, 92, 98, 99] have been published.

A cyclic process for producing **triphosgene**, in which dimethyl carbonate chlorination is coupled with triphosgene methanolysis (i.e. a manufacturing process essentially based on methanol and chlorine as raw materials), has been claimed in the past [78, 79]. The cost of manufacturing the product in this way is considerably lower than that using the traditional liquid-phase photochlorination of DMC.



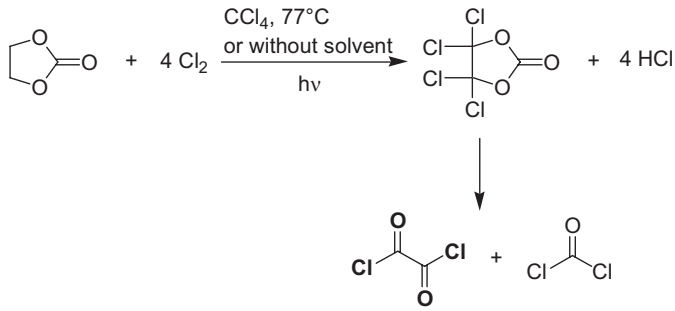
2.3 Other Phosgene Equivalents and Substitutes

2.3.1 Oxalyl Chloride

Oxalyl chloride is a colorless liquid with a bp of 63–64 °C. It is quite stable and can be stored for several months without appreciable decomposition. Nevertheless, it is a very reactive compound and should be handled with extreme care, particularly on a large scale. It fumes in moist air and reacts violently with water with the liberation of hydrogen chloride, carbon dioxide, and carbon monoxide [100].

Oxalyl chloride has often been produced by the direct chlorination of oxalic acid with phosphorus pentachloride [101, 102]. The product is distilled off in 30–50% yield [101], but the applicability of the reaction is limited to the laboratory because it is difficult to control (solid–solid reaction) and a large amount of phosphorus oxychloride is produced.

Alternative approaches starting from **ethylene carbonate** (itself a phosgene equivalent), better suited to the large-scale production of oxalyl chloride, have been developed according to the scheme below [103]:



The above process was improved by carrying out the photochemical chlorination of ethylene carbonate in the presence of an initiator, with a high-pressure Hg lamp at 70–100 °C, and with continuous circulation of the liquid through an illuminated side-arm. It has been found that ethylene carbonate can be photochemically converted to the tetrachloro derivative in the absence of a solvent, and the process has been performed on a 200 L scale.

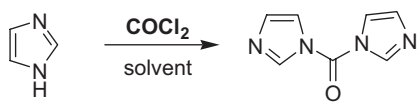
The reagent is used as a mild substitute for **phosgene**, **thionyl chloride**, or phosphorus pentachloride. The by-products resulting from the reactions involving oxalyl chloride are usually gases (HCl, CO, and CO_2).

The main applications of **oxalyl chloride**, as described in Chapter 4, are the formation of aryl isocyanates and chloroformates (by reactions with amines and hydroxylic substrates, respectively), and the formation of acyl chlorides from carboxylic acids under very mild conditions. **Oxalyl chloride** reacts with amides to give acyl isocyanates, and it is used with dimethyl sulfoxide as a mild reagent for the oxidation of alcohols (Swern-type oxidation). It is also used with *N*,*N*-dimethylformamide as a mild reagent for chlorination and formylation. **Oxalyl chloride** is widely used in commercial formulations of speciality polymers, antioxidants, photographic chemicals, X-ray contrasting agents, and chemiluminescent materials. Other physical properties are presented in Chapter 3.

2.3.2
1,1-Carbonyldiimidazole

1,1-Carbonyldiimidazole (**CDI**) is a crystalline **phosgene** substitute (mp 117–122 °C) and a preferred reagent for carboxyl activation. Salts (triflate or sulfate) of **CDI** are also used as activating agents in peptide and ester formation with retention of optical activity [104, 105].

CDI is prepared by the phosgenation of 1*H*-imidazole with **phosgene** in tetrahydrofuran [106] or aromatic solvents [107, 108], or in the presence of tributylamine [109].



Methods for the manufacture of carbonyldiimidazoles from imidazoles and **phosgene** in the presence of tertiary amines have recently been reported [109, 110].

Carbonyldiimidazoles (e.g. **CDI**) are prepared in high yield with little by-product formation by the reaction of imidazoles [(un)substituted in the 4- and/or 5-positions] (e.g. imidazole) with **phosgene** in the presence of a tertiary amine (e.g. tributylamine), which acts as an HCl scavenger. This amine has a lower pK_b value than the imidazole. The reaction is performed in an aromatic hydrocarbon solvent (e.g. xylene), from which the product is crystallized. The tertiary amine hydrochloride salt is extracted into water, neutralized with an aqueous solution of an inorganic base (e.g. NaOH), and the free amine is re-extracted into an organic solvent (EtOAc).

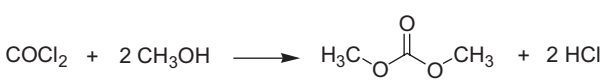
Phosgenation of azolide salts (alkali metal, ammonium, phosphonium, etc.) with **phosgene** in an aromatic or ethereal solvent gave **CDI** in 87% yield [111].

Phosgene-free preparations of **CDI** from silylazoles [112], or by reaction of imidazole and **triphosgene** [113], have also been reported.

1,1-Carbonyldiimidazole is a very useful and commonly employed reagent in many pharmaceutical and agrochemical syntheses (see Chapters 4 and 6). Several prodrugs and active pharmaceutical ingredients are prepared with **CDI**. Among the many recently reported applications, we cite here the chemical development of the commercial route to *Sildenafil* (Pfizer) using **CDI** [114], and the new, recently developed, highly selective synthesis of dialkyl carbonates, which relies on the previously unknown selectivity of imidazole carboxylic esters synthesized by the reaction of **CDI** with alcohols [115]. The imidazole carboxylic esters of secondary or tertiary alcohols form carbonates through exclusive reaction with the primary alcohol functions in polyols bearing mixtures of primary, secondary, and tertiary hydroxyl groups, without the need for protection. The controlled synthesis of asymmetric dialkyl and cyclic carbonates using the highly selective reactions of imidazole carboxylic esters prepared with **CDI** has also been reported.

2.3.3
Dimethyl Carbonate (DMC)

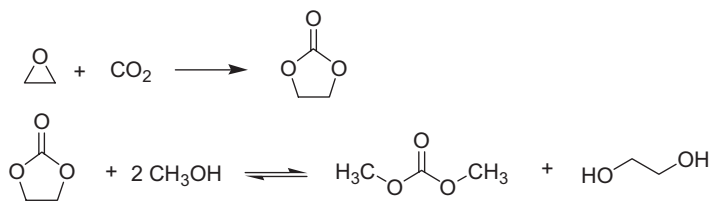
Dimethyl carbonate (**DMC**) is a liquid equivalent of **phosgene** (mp 2–4 °C; bp 90 °C). Reported toxicity and ecotoxicity data lead to the classification of **DMC** as both a non-toxic and environmentally benign chemical [116, 117] (see also Chapter 3). The areas in which **DMC** serves, or can serve, as an actual or potential *phosgene substitute* correspond to the main areas of **phosgene** industrial applications, e.g. the production of *aromatic polycarbonates* and *isocyanates*, leading the production of these important chemicals out of the chlorine cycle [117]. However, one major aspect has to be considered in this context, i.e. the production of **DMC** itself, since the traditional process for **DMC** production has involved **phosgene** as a raw material [118].



Non-phosgene alternative routes for **DMC** production have basically relied on the reaction of methanol with **carbon monoxide** (oxidative carbonylation) or with **carbon dioxide** (*direct carboxylation* with **CO_2**, or *indirect carboxylation* using **urea** or **alkylene carbonates** as CO_2 carriers).

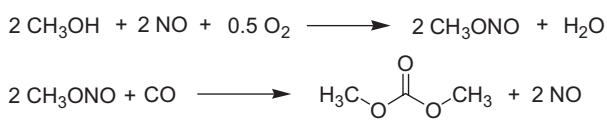
The *oxidative carbonylation* of methanol to **DMC**, which takes place in the presence of suitable catalysts, has been developed industrially.

Carboxylation/transesterification of ethylen oxide to **DMC** via **ethylene carbonate** has also been found to be an attractive route, even though burdened by the complexity of the two-step process, the co-production of ethylene glycol, and the use of toxic ethylene oxide.



Carbonate formation from an alcohol and carbon monoxide is known to take place in the presence of a number of metal and non-metal redox couples, e.g. palladium, platinum, cobalt, copper, nickel, rhodium, mercury, selenium, and bromine. Most of these are also active in the oxidation of CO to CO_2 in water, due to the similarity of the reaction pathways for CO_2 and carbonate formation, which involve intermediate hydroxy carbonyl and alkoxy carbonyl species, respectively. Competition between carbon dioxide and carbonate formation is a major factor that has to be considered when catalyst re-oxidation is carried out by oxygen, as in most technical developments, since in this case water is co-produced in the reaction system.

There are two competitive processes for the manufacture of **DMC**. In the *UBE* process, developed on an industrial scale in Japan, methyl nitrite is exploited as an intermediate, which is generated in a separate step by reaction of methanol, NO, and O_2. Then, a fixed bed, palladium-catalyzed carbonylation of methyl nitrite takes place in the gas phase. $PdCl_2/CuCl_2$ on active carbon is believed to be used in the actual industrial operation.



Copper compounds, besides being the most widely used co-catalysts for palladium re-oxidation, are themselves active in DMC formation. Amine–copper(II) complexes are very efficient in producing DMC from the methanol/CO system, even at room temperature. However, their exploitation on a technical scale failed, mainly due to water-sensitivity and ligand instability under oxidative reaction conditions. On the contrary, the use of a simple copper salt such as CuCl was found to be suitable to set up a commercial process based on direct oxy-carbonylation [119].

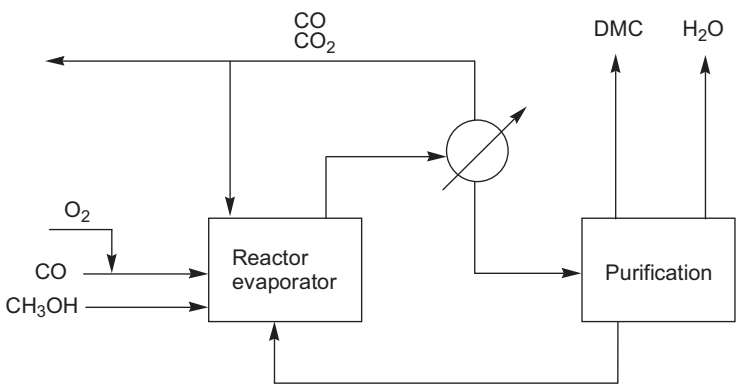
Exploiting the catalytic properties of CuCl, *EniChem* developed its DMC production process, based on one-step oxy-carbonylation of methanol, on an industrial scale. This process, operated industrially since 1983, currently accounts for more than 70,000 T y^{-1} of the **DMC** produced worldwide, with a further 100,000 T y^{-1} production capacity having been scheduled for 2002.

The one-step oxy-carbonylation of methanol to **DMC** is carried out in the liquid phase, in a continuous reactor fed with methanol, carbon monoxide, and oxygen. Reaction conditions are in the range 120–140 °C and 2–4 MPa. The CO/O_2 ratio is kept outside of the explosion limits through the use of a large excess of carbon monoxide and the high oxygen conversion per pass.

As depicted in Scheme 2.4, the concept of the reactor–evaporator is adopted: the catalyst is kept inside the reactor, from which the products are vaporized, largely taking advantage of the heat of reaction ($\Delta H_r = -74$ kcal mol^{-1}), and are removed from the reaction system together with the excess gas leaving the reactor [120].

This design allows the use of high catalyst concentrations and greatly simplifies catalyst separation from the product. High **DMC** productivity is achieved under optimized reaction conditions: up to 250 g L^{-1} h^{-1} has been obtained during pilot trials.

The use of CuCl as a catalyst minimizes the formation of by-products and ensures high purity of the product; it has a practically unlimited catalyst life. The only co-products are water and CO_2, the latter being produced in a substantial amount due to the presence of water in the reaction system. Through adopting a suitable process, the co-produced CO_2 can be re-utilized as a carbon source in the



Scheme 2.4. Conceptual scheme of the *EniChem* one-step **DMC** production process [117].

CO generation. All these features characterize this **DMC** production process as a clean technology [116–118].

Since a halide-free, non-corrosive catalyst for **DMC** production would represent a further improvement of the process, alternative catalytic systems have been investigated. Co(II) complexes with N, O ligands, such as carboxylates, acetylacetonates, and Schiff bases, have been shown to produce **DMC** with good reaction rates and selectivities [121].

Applications of **DMC** as a phosgene substitute are described in Chapter 4.

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3
Evaluation of Phosgenation Reagents

The traditional classification of organic compounds, according to the nature of functional groups and their preparations [1], emphasizes **phosgene** (the dichloride of carbonic acid) as a carbonic acid derivative. Indeed, the reactivity of phosgene in nucleophilic reactions is best understood by *considering the electronic structure of carbonic acid and the electronic and steric effects of the substituents in its derivatives.*

3.1
Definition

A **phosgene** *equivalent or substitute* is a compound able to replace **phosgene** as a building block or reagent in organic syntheses, or able to specifically bring about the basic **phosgene** *functions* as a (cyclo)carbonylating, chlorocarbonylating, chlorinating or dehydrating agent. The general structure **1** below illustrates the main structural characteristic of **phosgene** *equivalents*, i.e. the presence of the carbonyl (or carbonyl precursor) group flanked by two leaving groups.

1

Z^1, Z^2 = halo, alkoxy, aryloxy, midazolyl, triazolyl, etc.)

The groups Z^1 and Z^2 can be identical or different, thus generating symmetrical or unsymmetrical phosgene equivalents, respectively.

3.2
Reactivity

Many **phosgene** *equivalents* have been designed in order to have the reactivity of **phosgene** and the leaving group ability of various organic substituents. Formally, and often essentially, they belong to the family of *carbonic acid derivatives* and, therefore, their chemical behavior and reactivity toward nucleophiles has to be interpreted in terms of this classification [1].

Phosgenations – A Handbook. L. Cotarca, H. Eckert

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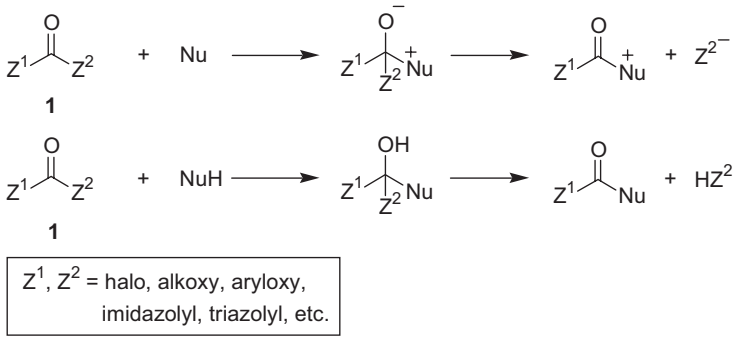


Many **phosgene** *substitutes* **1**, such as **1,1-carbonyldiimidazole**, **thionyl chloride**, **bis(nitrophenyl) carbonate**, **di-*tert*-butyl dicarbonate**, etc., react according to the scheme above and the intermediates can be isolated and characterized.

The various methods in which **phosgene** is substituted by a structurally different organic compound may be classified into the following two categories:

a) methods in which the specific organic compound acts as a phosgene substitute (e.g. mimicking phosgene as a chlorine, chlorocarbonyl or carbonyl source), and
b) methods using the organic compound as an *in situ* phosgene source (precursor).

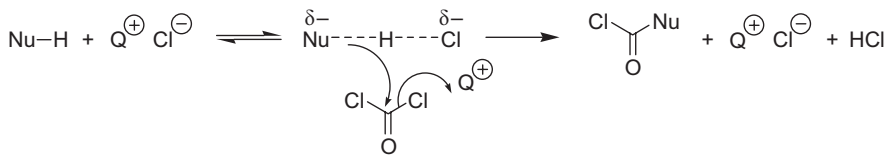
For example, regarding the *nucleophilic processes* involving **triphosgene** and **diphosgene**, two main routes of application have been identified (see also Chapter 2):

a) as a *tricoordinated carbonic acid derivative* with two leaving groups (Cl, $OCCl_3$); the stability of intermediates (e.g. chloroformate, carbamoyl chloride, carbonate, carbamate, *N*-carboxy anhydride, urea) and catalysis play important roles in completing the nucleophilic process; and
b) as an *in situ* or *external phosgene source*, because very clean and quantitative "depolymerization" methods are available [2–4].

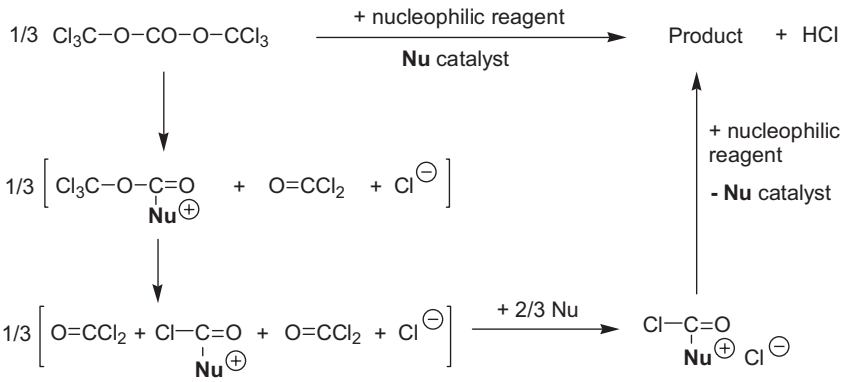
Many simple carbonic acid derivatives are highly reactive, providing useful reagents in synthesis and a rich and interesting chemistry [5]. For example, several novel substituted trioxanes, such as the geminal dichlorotrioxane ($C_3H_4O_3Cl_2$), tetrachlorotrioxane ($C_3H_2O_3Cl_4$), and trioxanone ($C_3H_4O_4$), should be kinetically stable and are likely candidates for use in synthesis. Recently, their thermodynamic and kinetic stabilities were explored computationally [6]. Concerted ring opening provides the most likely path for dissociation to the building-block molecules **carbon dioxide**, formaldehyde, and **phosgene**.

As regards **phosgene** reactions with active hydrogen substrates, mechanistic studies were indicative of substrate activation as a result of the nucleophilicity of chloride anion in the case of Q^+Cl^- type catalysts (e.g. quaternary ammonium chloride). The mechanism of nucleophilic assistance by these catalysts can be ra-

tionalized in terms of an increase of the nucleophilicity of the substrate by proton abstraction, followed by attack of the promoted anion on the electrophile (**phosgene**) [7]:



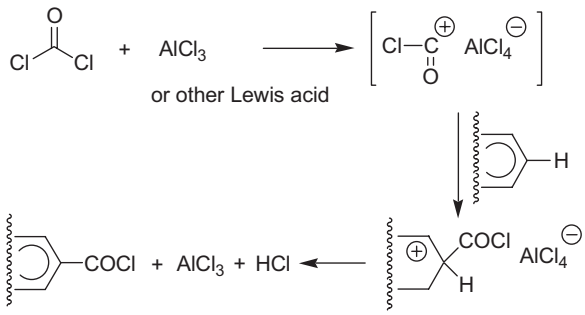
Eckert proposed the following mechanism for *phosgenation* by **triphosgene** [8]:



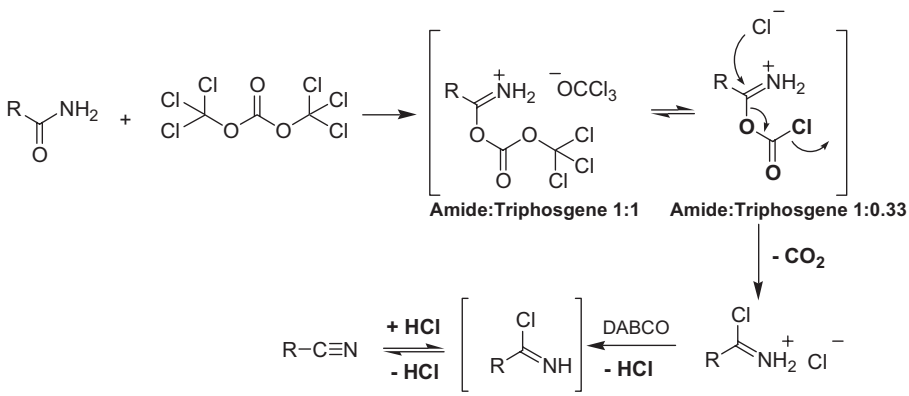
The rate constants for the two steps of the reaction of **triphosgene** with substituted anilines have been determined by conductometric measurements [9]. The first relatively fast step of the reaction is the nucleophilic attack of the amine on **triphosgene** leading to a (trichloromethyl)urethane through *a six- or four-center transition state*, in which the carbon–nitrogen bond is formed concomitantly with the transfer of the proton. A phosgene molecule is also produced in this reaction, which reacts very rapidly with the amine to form an *N*,*N*′-diarylurea. The second, much slower step, is the nucleophilic attack of the amine on (trichloromethyl)-urethane. Through a similar transition state, in which the proton transfer has an even higher importance, an *N*,*N*′-disubstituted urea and another molecule of phosgene are formed.

By the same experimental method, the rate constants for hydrolysis and alcoholysis of **triphosgene** in dioxane have been determined. The effects of the water and alcohol concentrations, and of the temperature, as well as deuterium isotope effects, have been studied [10]. The complex reaction scheme of triphosgene alcoholysis has also been reported and discussed [11].

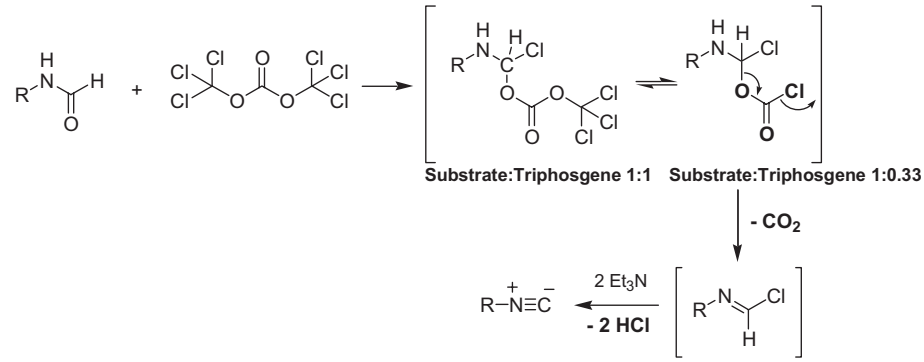
The second type of phosgene reactivity is represented by electrophilic reactions [12]:



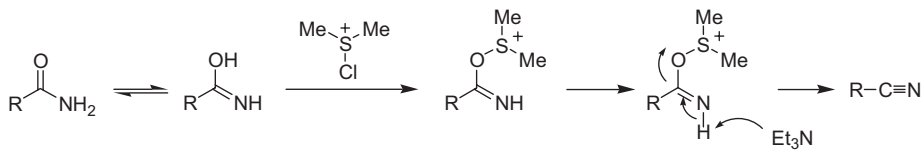
On analyzing the reactions of **phosgene** and phosgene equivalents, the stepwise nature of phosgenation processes becomes apparent. It is observed that the initial step of most of these processes involves **COCl** (chlorocarbonyl) transfer to the appropriate reaction center of the molecule, with formation of the corresponding derivative, i.e. chloroformate, carbamoyl chloride, etc. This **COCl** transfer is usually followed by a nucleophilic attack to give tricoordinated derivatives, or by **CO_2** and/or **HCl** elimination to give dicoordinated derivatives of carbonic acid. The scheme below illustrates the reaction of amides with the phosgene equivalent **triphosgene**. The dehydration of primary amides starts with chloroformylation of the substrate. Further elimination of CO_2 and HCl assisted by an appropriate amine affords the nitrile.



In the case of *N*-substituted formamides, the preferred dehydrating procedure is that of Ugi, utilizing **phosgene** in the presence of a tertiary amine. **Triphosgene** adds to the carbonyl group in exactly the same way as it does in the case of the synthesis of α-chloroalkyl chloroformates (see Chapter 4.4 "Chlorination"). If **triphosgene** is catalytically decomposed by the tertiary amine, the reaction can also be interpreted as a simple phosgenation.



The above mechanism is similar to that proposed by Nakajima [13] for the dehydration of primary amides under Swern conditions. There is an obvious analogy between a sulfoxonium salt and chloroformate:



Therefore, the formation of **chloroformate**, or compounds of similar structure, as key intermediates of limited (low) stability is the driving force behind many processes involving **phosgene** or phosgene equivalents.

Triphosgene is quantitatively converted to **phosgene** by catalysts such as chloride ion [2–4]. The reaction course has been monitored by IR spectroscopy (React-IR), which showed **diphosgene** to be an intermediate. The methanolysis of triphosgene in deuterated chloroform, as monitored by ^{1}H NMR spectroscopy, gave as primary products **methyl chloroformate** and **methyl 1,1,1-trichloromethyl carbonate** in about a 1:1 ratio. The reaction carried out in the presence of a large excess of

Tab. 3.1. Pseudo-first-order rate constants for the reactions of **phosgene**, **diphosgene**, and **triphosgene** (0.01 M) with methanol (0.3 M) in $CDCl_3$ at 25 °C, calculated from the initial rates [4].

Substrate	k_{obs}, s^{-1}	*MeOH, 0.3 M*	*MeOH, 0.3 M*
	MeOH, 0.3 M	*Cl^- 5%*[a]	*Cl^- 10%*[a]
Phosgene	1.7×10^{-2}	[b]	[b]
Diphosgene	9.1×10^{-4}	1.0×10^{-3}	1.1×10^{-3}
Triphosgene	1.0×10^{-4}	2.3×10^{-4}	2.3×10^{-4}

[a] added as $Bu_4N^+Cl^-$; [b] too fast to be measured by NMR

Tab. 3.2. Physical properties of **phosgene** and phosgene equivalents and substitutes [15].

Phosgene Equivalent or Substitute	*CAS Reg. no.*	*Mp [°C]*	*Bp [°C] (mmHg)*	*Risk (R) and Safety (S) Phrases*
Phosgene	75-44-5	−118	8.2	R: 26-34 S: 26-36/37/39-45
Diphosgene (Trichloromethyl chloroformate)	503-38-8		128	R: 26-34 S: 26-36/37/39-45
Triphosgene (Bis(trichloromethyl) carbonate)	32315-10-9	79–83	203–206	R: 20/21/22-36/37/38 S: 23-26-27-38
Oxalyl chloride	79-37-8	−10 to −8	63–64 (763)	R: 14-23/24/25-34 S: 26-36/37/39-45
Boron tribromide	10294-33-4	−46	90	R: 14-26/28-35 S: 9-26-28-36/37/39-45
Boron trichloride	10294-34-5	−107	12.5	R: 14-26/28-34 S: 9-26-28-36/37/39-45
Phosphorus oxychloride	10025-87-3	1.25	105.8	R: 14-22-26-35-48/23 S: 7/8-26-36/37/39-45
Phosphorus oxybromide	7789-59-5	56	192	R: 14-34-37 S: 7/8-26-36/37/39-45
Thionyl chloride	7719-09-7		79	R: 14-20/22-29-35 S: 26-36/37/39-45
Thionyl bromide	507-16-4	−52	48 (20)	R: 14-34-36/37 S: 26-28-36/37/39-43-45
Phosphorus pentoxide	1314-56-3	340		R: 35 S: 22-26-45
Triphenylphosphine dibromide (Dibromotriphenyl-phosphorane)	1034-39-5	235 (dec.)		R: 34 S: 26-28-27-36/37/39-45
Cyanuric chloride (**CyCl**), (2,4,6-trichloro-1,3,5-triazine)	108-77-0	145.5–148.5	190	R: 36/37/38 S: 28
Trichloroacetyl chloride	76-02-8	−146	114–116	R: 14-22-26-35 S: 23-26-36/37/39-45
p-Toluenesulfonyl chloride, (tosyl chloride, **TsCl**)	98-59-9	67–69		R: 34 S: 26-27-28-36/37/39-45
Benzyl chloroformate	501-53-1		103 (20)	R: 34-50/53 S: 26-45-60-61

Tab. 3.2 *(continued)*

Phosgene Equivalent or Substitute	*CAS Reg. no.*	*Mp [°C]*	*Bp [°C] (mmHg)*	*Risk (R) and Safety (S) Phrases*
Ethyl chloroformate	541-41-3	−81	93	R: 11-22-26-34 S: 9-16-26-28-33-36/37/39-45
1-Chloroethyl chloroformate	50893-53-3		118–119	R: 23/24/25-34 S: 26-27-36/37/39-45
Phenyl chloroformate	1885-14-9	38	74–75 (13)	R: 26-34 S: 26-28-36/37/39-45
Phenyl chlorothionoformate	1005-56-7		81–83 (6)	R: 34 S: 26-27-28-36/37/39-45
Bis(4-nitrophenyl) carbonate	5070-13-3	136–138		R: 36/38 S: 26-36
Di-*t*-butyl dicarbonate	24424-99-5	23	56–57 (0.5)	R: 10-36/37/38 S: 16-26-36
Ethylene carbonate	96-49-1	37–39	243–244 (740)	R: 36 S: 26-37/39
Chloroethylene carbonate	3967-54-2	121–123 (18)		R: 34 S: 26-36/37/39-45
Dimethyl carbonate	616-38-6	2–4	90	R: 11 S: 9-16
Diethyl carbonate	105-58-8		126–128	R: 11 S: 9-16
Diphenyl carbonate	102-09-0	79–82	301–302	R: 21/22 S: 36
1,1-Carbonyldiimidazole (**CDI**)	530-62-1	117–122		R: 34-20/21/22 S: 26-27-36/37/39-45
1,1-Carbonylbis(2-methylimidazole)	13551-83-2	218–220		R: 36/37/38 S: 26-37/39
Ethyl acetoacetate	141-97-9	−43	181	R: 36/37/38 S: 26-36
Acetic anhydride	108-24-7	−73	140	R: 10-20/22-34 S: 26-36/37/39-45
Isatoic anhydride	118-48-9	233 (dec.)		R: 36-43 S: 24-26-37
Trifluoroacetic acid anhydride (**TFAA**)	407-25-0	−65	39.5–40	R: 34-14-20/21/22 S: 23-26-27-36/37/39-45
Trifluoromethanesulfonic anhydride (triflic anhydride, $\mathbf{Tf_2O}$)	358-23-6		81–83 (745)	R: 14-34 S: 26-27-36/37/39-45

Tab. 3.2 *(continued)*

Phosgene Equivalent or Substitute	*CAS Reg. no.*	*Mp [°C]*	*Bp [°C] (mmHg)*	*Risk (R) and Safety (S) Phrases*
1,1-Dichlorodimethyl ether	4885-02-3		85	R: 10-23/24/25-36/37/38-40 S: 16-26-36/37/39-45
Dimethoxymethane (formaldehyde acetal, methylal)	7149-92-0	−105	41–42	R: 11-19-36/37/38 S: 16-33-26-36
Diethoxymethane	462-95-3		87–88	R: 11-19-36/37/38 S: 16-26-36/37/39
Phosgene iminium chloride (Dichloromethylene)-dimethylammonium chloride (Vilsmeier reagent/Viehe's salt)	33842-02-3	183–187 (dec.)		R: 14-34 S: 26-28-36/37/39-45
(Chloromethylene)-dimethylammonium chloride (Vilsmeier reagent)	3724-43-4	132 (dec.)		R: 61-20/21-36 S: 26-36/37/39-45-53
Pyridine–phosgene adduct 1-[2-(Chloroformyl)-2-azacyclohexa-3,5-dienyl]pyridinium chloride (**2-DHPP**)	117371-69-4	84–87 (dec.)		
Benzotriazol-1-yloxytripyrrolidino phosphonium hexafluoro-phosphate (**PyBOP**)	128625-52-5	154–156 (dec.)		R: 36/37/38 S: 26-37/39
Benzotriazol-1-yloxy tris(dimethylamino)-phosphonium hexafluoro-phosphate (**BOP reagent**)	56602-33-6	>130 (dec.)		R: 20/21/22-36/37/38 S: 26-36
Carbon monoxide, **CO**	630-08-0	−205	−191.5	R: 61-12-23-48/23 S: 53-45
Carbon dioxide, **CO_2**	124-38-9	−78.5 (sublim.)		R: 61-23-48/23 S: 38
Trimethylsilyl isocyanate	1118-02-1		90–92	R: 10-20/21/22-36/37/38 S: 23-38-16-36/37/39
Chlorosulfonyl isocyanate	1189-71-5	−44	107	R: 14-23/24/25-35 S: 3/7-26-36/37/39-45

Tab. 3.2 *(continued)*

Phosgene Equivalent or Substitute	*CAS Reg. no.*	*Mp [°C]*	*Bp [°C] (mmHg)*	*Risk (R) and Safety (S) Phrases*
(Methoxycarbonyl-sulfamoyl) triethylammonium betaine (**Burgess reagent**)	29684-56-8	76–79		R: 36/37/38 S: 26-37/39
1,3-Dicyclohexyl-carbodiimide (**DCC**)	538-75-0	34–35	122–124 (6)	R: 22-24-41-43 S: 24-26-37/39-45
1,3-Diisopropyl-carbodiimide	693-13-0		145–148	R: 10-26-36/37/38-41-42/43 S: 16-23-26-36/37/39-45
1,3-Bis(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)-carbodiimide [Bis-4-(2,2-dimethyl-1,3-dioxolyl)methyl carbodiimide (**BDDC**)]	159390-26-8			R: 36/37/38 S: 26-36
2-Chloro-1,3-dimethylimi-dazolium chloride (**CDC**)		95–100 (dec.)		See [14]
2-Chloro-1,3-dimethylimi-dazolium hexafluoro-phosphate	101385-69-7	231–233		R: 36/37/38 S: 26-36
2-Chloro-1,3-dimethyl-imidazolium tetra-fluoroborate	153433-26-2	175–177		R: 36/37/38 S: 26-36
Diethyl azodicarboxylate (**DEAD**)	1972-28-7		106 (13)	R: 20/21/22-36/37/38-40-44 S: 15-23-26-36
Diphenylphosphoryl azide	26386-88-9		157 (0.17)	R: 23/24/25-36/37/38 S: 26-28-36/37/39-45

methanol (0.3 M, 30 equiv.) was found to be a pseudo-first-order process with a k_{obs} of 1.0×10^{-4} s^{-1}. Under the same conditions, values of k_{obs} of 0.9×10^{-3} s^{-1} and 1.7×10^{-2} s^{-1} for the methanolysis of diphosgene and phosgene, respectively, were determined. The experimental data suggest that, under these conditions, the maximum concentration of **phosgene** during the methanolysis of triphosgene and diphosgene was lower than 1×10^{-5} M. Methyl 1,1,1-trichloromethyl carbonate

Tab. 3.3. Vapor pressures of **phosgene** and some important substitutes [15–19].

Phosgenation reagent	*Vapor pressure (Pa)*	*Vapor pressure (Torr)*	*Temp. (°C)*	*Ref.*
Phosgene	162000	1215	20	15
Diphosgene	1370	10.3	20	16
Triphosgene	20	0.15	20	16
Diethyl carbonate	1100	8.3	20	15
Dimethyl carbonate	13300	100	37	17
Acetic anhydride	500	3.8	20	15
Triflic anhydride	1060	8	20	18
Phosphoryl chloride	5300	40	27	15
Thionyl chloride	12900	97	20	19

has also been synthesized independently and characterized by the APCI-MS technique.

3.3 Physical Properties

Phosgene equivalents are gaseous, liquid or solid compounds. The main physical properties of **phosgene** and some phosgene equivalents are presented in Table 3.2.

The potential danger in the *handling* of the phosgene equivalents is associated with the *vapor pressures* of the compounds. Very few specific data are available. In the case of the chlorinated phosgene substitutes, diphosgene and triphosgene, the vapor pressures are significantly lower and a value as low as 0.15 Torr has been reported for triphosgene (Table 3.3).

3.4 Physiological Data

While searching for significant data to describe the potential workplace health hazards associated with the use of phosgene equivalents, we were surprised by the lack of quantitative data for monitoring exposure to these compounds. The reason for this is definitely the still limited use of phosgene equivalents in industrial processes. The best approach to prevent erroneous and hazardous use of these materials is to first gain thorough knowledge of the *material data sheets*, which are easily accessible and available [18]. Some *threshold limit value/time-weighted average* (TLV-TWA) data are collected in Table 3.4. The class representative, phosgene, has a TLV of 0.1 ppm, but other phosgene equivalents have values ranging from 0.005 ppm (hexamethylene diisocyanate) to 5000 ppm (**carbon dioxide**). It should be noted that aliphatic isocyanates have even lower TLVs and that suitable safety measures have to be taken before working with these reagents [20].

Tab. 3.4. TLV-TWA[a] data for **phosgene** and some important substitutes [20].

Phosgene Substitute	*CAS Reg. No.*	*TLV-TWA[a] (ppm)*
Phosgene	75-44-5	0.1
Phosphorus oxychloride	10025-87-3	0.1
Thionyl chloride	7719-09-7	1[b]
Ethyl chloroformate	541-41-3	0.1
Benzyl chloroformate (**Z-Cl**)	501-53-1	1
Acetic anhydride	108-24-7	5
Methyl isocyanate	822-06-0	0.005
Isophorone diisocyanate	4098-71-9	0.005
Dimethyl carbonate (**DMC**)	616-38-6	200
N,*N*′-Dicyclohexylcarbodiimide (**DCC**), in solution	538-75-0	50
Diethyl azodicarboxylate (**DEAD**)	1972-28-7	50
Carbon monoxide, **CO**	630-08-0	25
Carbon dioxide, **CO_2**	124-38-9	5000

[a] *Threshold Limit Value/Time-Weighted Average* (TLV-TWA) is the time-weighted average concentration for a conventional 8-hour working day and a 40-hour working week, to which it is believed that nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[b] *Threshold Limit Value/Time-Weighted Average-Ceiling (TLV-C)* is the concentration that should not be exceeded during any part of the working exposure.

3.5 References

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4
Phosgenation Reactions

4.1
Classification of Phosgenation Reactions

Phosgenation (**reaction**) in this book is defined as a method for inserting a chlorocarbonyl, carbonyl, or chlorine group into an organic compound or for dehydrating amidic groups forming cyanide, isocyanide, or carbodiimide groups using **phosgene** or a **phosgene equivalent** or **substitute** (for definitions, see Chapter 2) as reagent.

There are several areas of uncertainty regarding the literature classification of phosgene chemistry. The most common classification is based on the nature of the **reaction center** and usually lists the reagents, or the products of reaction (isocyanates, carbonates, carbamates, ureas, chloroformates, acid chlorides, isonitriles, nitriles, carbodiimides, etc.) [1, 2].

A recent monograph [3] classifies phosgene reactions into *two main categories*: those that introduce the building block *"**carbonyl**"* as a structural unit and those involving **phosgene** and its derivatives as ***reagents***. This classification focuses on the formal reaction product structure and defines phosgene as a *"carbonyl"* unit carrier or, more simply, emphasizes the role of phosgene as a *"dehydroxylating"* agent. An alternative criterion starts from the traditional classification of *functional groups* and their preparation [4], and emphasizes **phosgene** as a ***carbonic acid derivative*** (dichloride of carbonic acid).

Every classification is somewhat arbitrary. The key factors are its *accuracy* and its *meaning* in a wider context. This book is a handbook, which emphasizes its usefulness for both the chemist who is strongly interested in phosgene chemistry planning syntheses and the chemist working in the laboratory. When searching for a method or procedure to perform a certain synthetic strategy, both need a simple way of finding it. Therefore, the contents of this chapter, the main chapter of the book, are arranged in terms of the building or transforming of functional groups that appear in the resulting products. The four main reactions of phosgene, namely *chloroformylation*, *carbonylation*, *chlorination*, and *dehydration*, forming the functional groups *chlorocarbonyl*, *carbonyl* (*isocyanate*, *carbonate*, *carbamate*, *urea*), *chloro*, *cyano*, *isocyano*, and *carbodiimide*, constitute the backbone of our classification of phosgene reactions, and allow the simplest application of the logic of synthetic planning by means of the methodology of *retrosynthesis* [5–7], which works

Phosgenations – A Handbook. L. Cotarca, H. Eckert

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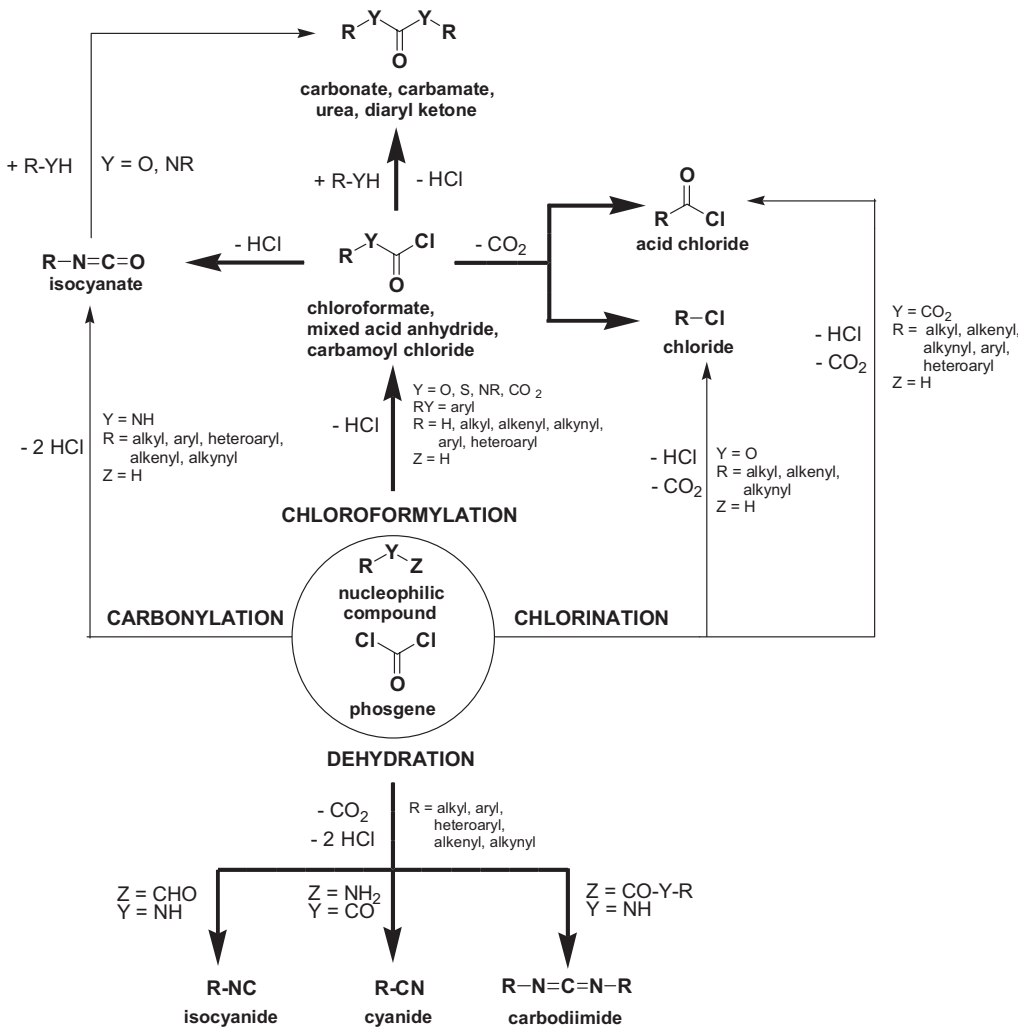


Scheme 4.1. Main phosgenation reactions and functional groups that can be formed.

with idealized molecular fragments, called ***synthons***, and reactions thereof leading to their ***synthetic equivalents***. When a formal *chloroformylation*, *carbonylation*, *chlorination*, or *dehydration* is desired, a phosgenation reaction is appropriate. The reader can then refer to the relevant chapter and choose the best suited **phosgene equivalent** or **phosgene** itself. The various phosgene reactions and the functional groups that they form are presented in Scheme 4.1.

Looking at Scheme 4.1, one can see that in *chloroformylation*, *carbonylation*, and *chlorination reactions*, **phosgene** reacts with nucleophilic groups Y–Z of monovalent type: Z is always H, and Y is represented by the classical nucleophilic elements; the reactivity (nucleophilicity) of the nucleophiles increases according to: thiols <

phenols < alcohols < aromatic amines < aliphatic amines. When Y = CO_2 and Z = H, acid chlorides are formed. In dehydration reactions, multivalent groups are involved; Y–Z is effectively an unsubstituted or substituted amidic group.

R–Y–COCl plays the key role in *phosgenation reactions* that are of a stepwise nature; the major part of these processes is **COCl** (chlorocarbonyl) transfer to R–Y–H generating *chloroformates*, *carbamoyl chlorides*, etc. R–Y–COCl is of limited (low) stability and this is the driving force behind its intermediacy in the synthesis of *chlorides* and *isocyanates* under elimination conditions (eliminating CO_2 and/or HCl), and also determines the character of a reactive substrate in further nucleophilic substitutions to form symmetrical and unsymmetrical substituted carbonic acid derivatives (*carbonates*, *carbamates*, *ureas*) or *diaryl ketones*. Commonly, chloroformylation and isocyanate formation are independent of the nature of R. Obviously, the reactivity is very different due to the relative basic/nucleophilic ratio. For example, Ar–Cl cannot be prepared through a chloroformate intermediate nor by direct *phosgenation*, but the reaction does work well in the aliphatic series.

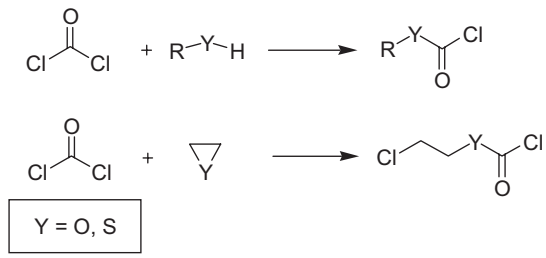
Special reactions of $COCl_2$ with R–Y–Z are also known. When Y = CO and Z = H (aldehyde), an *α-chlorochloroformate* R–CHCl–O–CO–Cl is formed in an addition reaction to the aldehydic C=O double bond. When R = NR^1R^2, Y = CO, and Z = H, a *Vilsmeier salt/reagent* is formed.

4.2 Chloroformylation (Chlorocarbonylation)

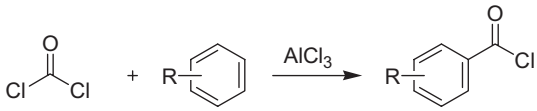
4.2.1 Chloroformates (Chlorocarbonylation of Alcohols)

Phosgene is a source of the chlorocarbonyl group, –COCl, in reactions with many and various nucleophilic species. Depending on the nature of the nucleophilic reaction center (carbon, oxygen, nitrogen or sulfur), a wide variety of useful and, in general, highly reactive products are formed. The reactivity of phosgene is typical of that of acyl halides and the mechanism can be S_N1 or tetrahedral. The scheme below compares chlorocarbonyl group transfers to various nucleophilic reaction centers (oxygen, carbon, and nitrogen, respectively).

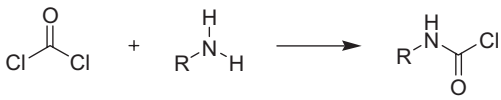
Oxygen or sulfur nucleophiles:



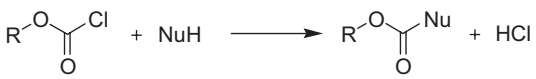
Carbon nucleophiles:



Nitrogen nucleophiles:

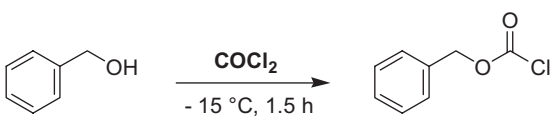


Substrates containing oxygen or sulfur nucleophiles react with phosgene to give chloroformates or chlorothioformates, and the reaction is named *chloroformylation (chlorocarbonylation)*. High selectivities in the chloroformylation and long-term storage of chloroformate for further applications are sometimes hampered by the fact that their formation is often (see Scheme 4.1) accompanied by subsequent nucleophilic substitution of the reactive chlorine leaving group to give symmetrical or unsymmetrical tricoordinated derivatives of carbonic acid.



Phosgene reacts readily with *aliphatic alcohols* at room temperature or below to afford the corresponding *aliphatic chloroformates* in good yields, but *phenols* are much less reactive toward phosgene. Elevated temperatures (>100 °C) and scavengers or specifically designed catalysts (*N*,*N*′-dimethylpropyleneurea, 2-undecylpyridine) are required to prepare aryl chloroformates [8, 9].

An early review on the chemistry of chloroformates (''esters of chloroformic acid'') covered the methods of synthesis, physical and chemical properties and highlighted the possibility of polymer synthesis from chloroformates [10]. An example of a classical chloroformate preparation by phosgenation of benzylic alcohol with phosgene gas is given in [11]. An improved procedure for the synthesis of *benzyl chloroformate* (**1**, *Z-Cl*) in 97% yield is given in [12].



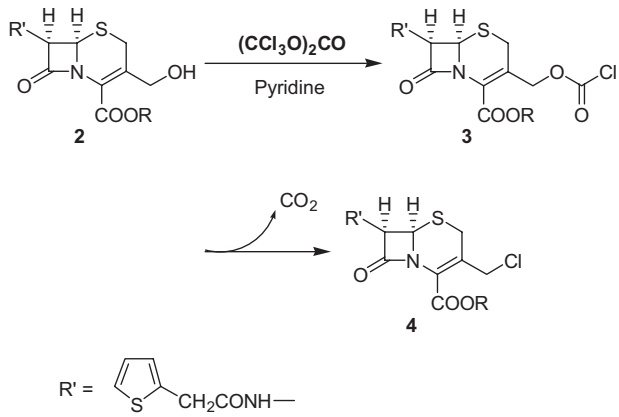
97%

1, Z-Cl

Typical procedure. *Benzyl chloroformate* **1** [12]: In a three-necked, 1 L round-bottomed flask equipped with a magnetic stirrer, gas inlet, dry-ice-cooled reflux

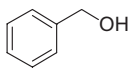
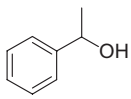
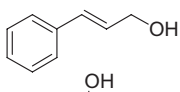
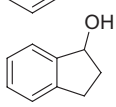
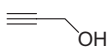
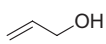
condenser with gas outlet (HCl!), and thermometer, cooled by immersion in a dry-ice/ethanol bath, **phosgene** (for a *safe source*, see Chapter 7) (100 g, 1.01 mol) was condensed at −50 °C. The gas inlet was then replaced by a dropping funnel and benzyl alcohol (108 g, 1.00 mol) was added dropwise at −20 to −10 °C over a period of 1.5 h. The reaction mixture was stirred for a further 12 h at 0 °C (ice bath), with monitoring of the reaction by TLC. Thereafter, the cooling bath was replaced by an oil bath and the flask was fitted with a distillation apparatus. The crude product was distilled in vacuo to afford 165.1 g (97%) of colorless *benzyl chloroformate* **1**, bp 41 °C (0.03 Torr). Analyses (^{1}H and ^{13}C NMR, IR, TLC) were indicative of a pure product (free from benzyl chloride). **Important:** During the course of the distillation, the temperature of the oil bath must be kept below 65 °C! At higher temperatures, benzyl chloride will be increasingly generated. The dry-ice/ethanol bath also serves as a safety device (accidentally overflowing phosgene reacts immediately with the ethanol).

In a study of the chlorination of the cephem nucleus at the C-3 position using **triphosgene**, a clean conversion to cephem chloride **4** has been observed [13]. The reaction is thought to proceed through an unstable cephem chloroformate **3**.



Typical procedure. *Methoxybenzyl-7β-(2-thienylacetamido)-3-(chloromethyl)-3-cephem-4-carboxylate* **4** [13]: A solution of *p*-methoxybenzyl 7*β*-(2-thienylacetamido)-3-(hydroxymethyl)-3-cephem-4-carboxylate (750 mg, 1.6 mmol) and **triphosgene** (160 mg, 0.54 mmol) in dry THF (20 mL) was stirred at room temperature. The progress of the reaction could be conveniently monitored by measuring CO_2 evolution. Subsequently, dry pyridine (270 μL, 3.2 mmol) was added over a period of 30 s; pyridinium hydrochloride precipitated immediately. The mixture was stirred for 30 min, concentrated to dryness, and the residue was purified by column chromatography on silica gel (10% ethyl acetate in benzene). *p-Methoxybenzyl-7β-(2-thienylacetamido)-3-(chloromethyl)-3-cephem-4-carboxylate* **4**, was isolated as a white solid (640 mg, 81%).

Tab. 4.1. Chloride substitution of activated alcohols by **triphosgene** [13].

ROH	*Chloride yield %*	*Chloroformate yield %*
(−)-Menthol		98
		74
	90	
	86	
	85	
	80	
	63	
	65	

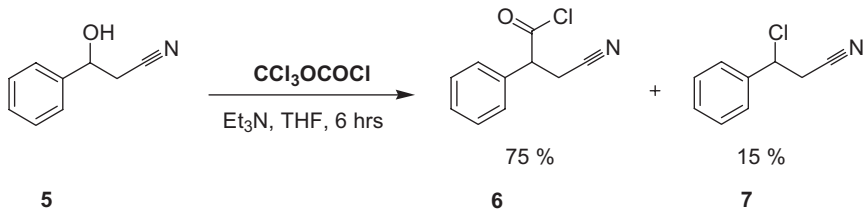
The reaction is applicable to benzylic, allylic, and propargylic alcohols. The chlorides listed in Table 4.1 were each made from the corresponding alcohol in less than 15 min at room temperature, with the exception of propargyl chloride. Although the chloroformate of propargyl alcohol formed in less than 1 min, gentle warming was necessary to drive the reaction to completion.

It is significant that under these conditions, with unactivated alcohols, chloroformates are isolated readily without a trace of the corresponding chloride; (−)-menthol chloroformate and *sec*-butyl chloroformate were prepared in yields of 98% and 78%, respectively.

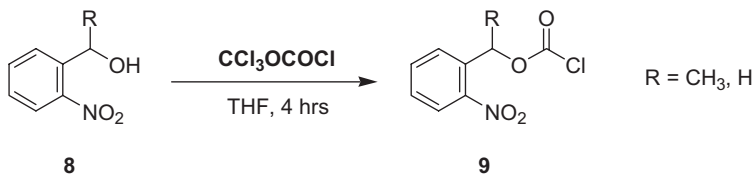
By analogy with the reaction of thionyl chloride with alcohols, which results in the formation of the corresponding chlorides, either an S_N2 or carbonium ion mechanism (such as S_Ni and S_N1) may be invoked for the formation of chlorides from the intermediary chloroformates. The former mechanism would result in inversion, whereas the latter two would give retention and racemization of configuration at the site of reaction, respectively [14, 15]. (*R*)-(+)-1-Phenylethanol ($[\alpha]^{20}_D = +45.7^\circ$ (neat), 99% *ee*) was converted to 1-(chloroethyl)benzene by this procedure. Polarimetric measurement of the product ($[\alpha]^{20}_D = -42.0^\circ$ (neat)) revealed it to be a 3:7 mixture of (*R*)-(+)- and (*S*)-(−)-1-(chloroethyl)benzenes. Thus,

the reaction proceeds primarily by S_N2, with some contribution from S_N1 and/or S_Ni mechanisms.

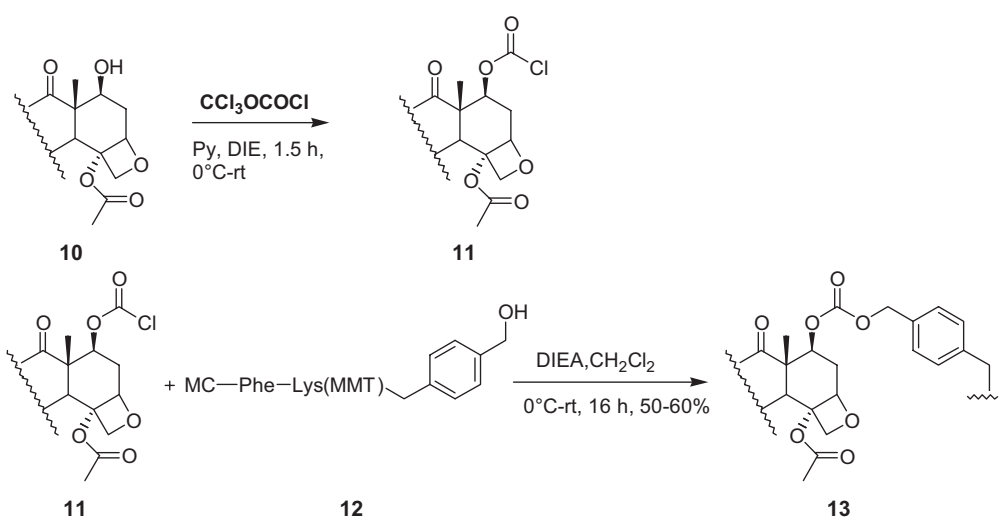
Chloroformates and chlorides are also formed when secondary benzylic alcohols are treated with **diphosgene** in the presence of triethylamine [16]. The distribution of products can be controlled.



Diphosgene has also been used to selectively prepare chloroformates **9** of primary or secondary 2-nitrobenzyl alcohols **8** [17]. A similar conversion has been performed with **triphosgene** and triethylamine in diethyl ether [18].



Protection of the 7-hydroxyl group in *Paclitaxel (taxol®)* **10** as the carbonate **13** of the maleimido-peptide-benzyl alcohol **12** was carried out through the corresponding chloroformate using **diphosgene** in the presence of pyridine/DIE [19].



Highly water-soluble taxol derivatives were prepared by attachment of polyethylene glycol (molecular weight 2–5 kD) at the 7-position of taxol via a urethane or carbonate linkage [20]. The most direct route to accomplish this conversion involves condensation of substituted isocyanates with 2′-*O*-acetyl-taxol. Limitations of this procedure due to a lack of commercial availability of key isocyanates and occasional unexplained variations in yield prompted a search for routes of greater utility, and which would not threaten the integrity of the taxane ring system. The first of these was conversion of 2′-*O*-acetyl-taxol **13** to the 7-chloroformate derivative using **triphosgene** and either *N*,*N*-diisopropylethylamine (DIEA) or pyridine.

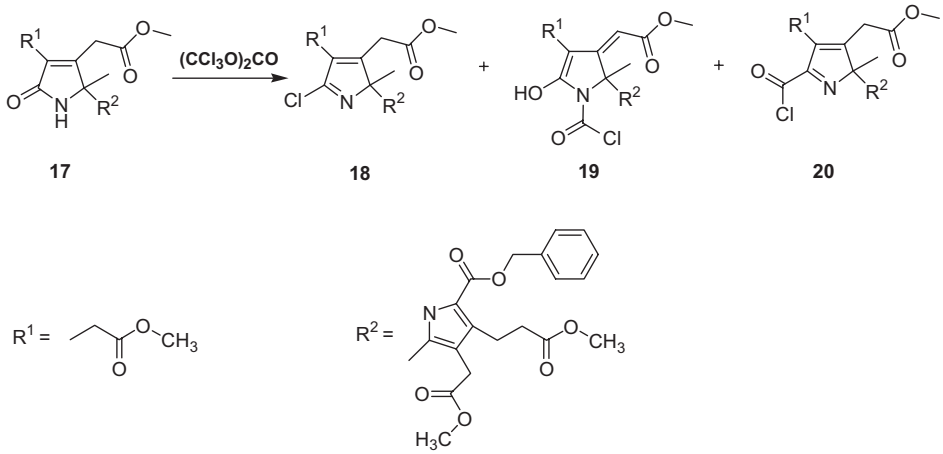
In practice, it was found that approximately 6 equivalents of **triphosgene** and 9 equivalents of base were required to give yields of just 60–70% of chloroformate **15**. Chloroformates are generally water-sensitive; therefore, no attempts were made to isolate the chloroformate, which was reacted directly with excess amine to afford the 7-carbamate derivative **16**. As an alternative to employing triphosgene, it was found that the alcohol reacted smoothly with an excess of ***N,N*-carbonyldiimidazole** (**CDI**) to give high yields of the easily isolated and relatively stable carbonylimidazole derivative. This compound did not react readily with amines in chloroform solution, but in 2-propanol the 2′-*O*-acetyl carbamates **16** were produced in high yield.

Typical procedure. *2′-O-(Methoxyacetyl)-7-O-(imidazolylcarbonyl)taxol* [20]: In a 25 mL round-bottomed flask were placed 2′-*O*-(methoxyacetyl)taxol (102 mg, 0.11 mmol), **CDI** (53 mg, 0.33 mmol), and dichloromethane (5 mL). The resulting clear solution was stirred at room temperature under nitrogen atmosphere for 5 h. The reaction mixture was then diluted with dichloromethane (5 mL), washed with water (2 × 5 mL), dried over anhydrous magnesium sulfate, and concentrated to dryness. The crude product thus obtained (105 mg, 94%) was used without further purification for the preparation of 7-substituted taxol derivatives.

Typical procedure. *2′-O-Acetyltaxol 7-PEG carbamates* [20]: In a 25 mL three-necked, round-bottomed flask equipped with a reflux condenser, a magnetic stirrer, and a guard tube containing NaOH pellets, were placed 2-*O*-acetyltaxol (25 mg, 0.028 mmol) and anhydrous dichloromethane (5 mL). To this solution were added **triphosgene** (17 mg, 0.057 mmol) and pyridine (20 mg, 0.22 mmol), and stirring was continued for 30 min. Dry nitrogen was bubbled through the reaction mixture until all volatiles had evaporated. A solution of PEG-NH_2 (mw 5000, 280 mg, 0.056 mmol) in dichloromethane was added to the residue and the resulting mixture was stirred for 15 min. After standard work-up, the product was purified by preparative HPLC.

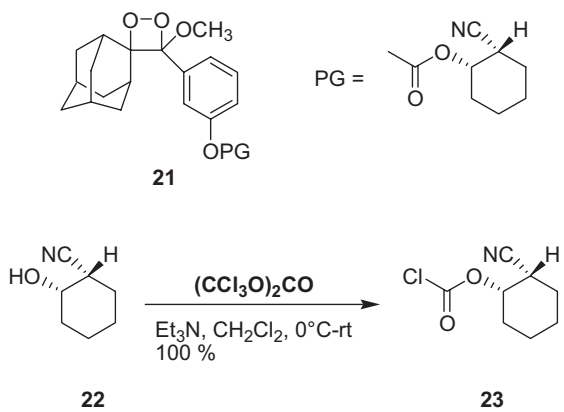
A complex transformation of lactam **17** occurs in the presence of **triphosgene** and 4-dimethylaminopyridine (DMAP) in dichloromethane, as reported in [21]. The reaction was first reported using **phosgene** [22], but **triphosgene** gave identical results and was experimentally preferable. The reaction was not straightforward in that three compounds were formed in differing amounts depending on the conditions. All three materials were unstable but could be separated under argon for

spectroscopic characterization. The rapidly formed kinetic product appeared to be the enolized *N*-chloroformyl lactam **19**, the second product was thought to be the *O*-chloroformyl derivative **20**, and the *2H*-5-chloropyrrol **18** only predominated after heating under reflux in dichloromethane.



Typical procedure. *2H-5-Chloropyrrol* **18** [21]: A suspension of **triphosgene** (50 mg, 160 μmol), DMAP (920 mg, 160 μmol), and lactam **17** (50 mg, 80 μmol) in anhydrous dichloromethane (2 mL) was heated under reflux under argon for 1 h. Thereafter, the mixture was rapidly cooled in ice, filtered through a plug of Celite, and concentrated to dryness under reduced pressure to give the crude *2H-5-chloropyrrol* **18** as an oil (52 mg), which was generally used without further purification.

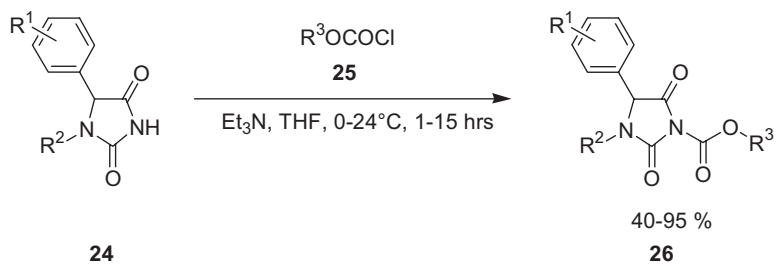
Protection of adamantylphenyl-1,2-dioxetane **21**, used as a substrate source in chemiluminescence reactions, has been realized by reacting it with *cis*-cyanocyclohexyl chloroformate **23**, obtained by treating the corresponding alcohol **22** with **triphosgene** [23].



Tab. 4.2. Hydantoins **26** synthesized from non-commercially available alkyl and aryl chloroformates prepared with **triphosgene** [24].

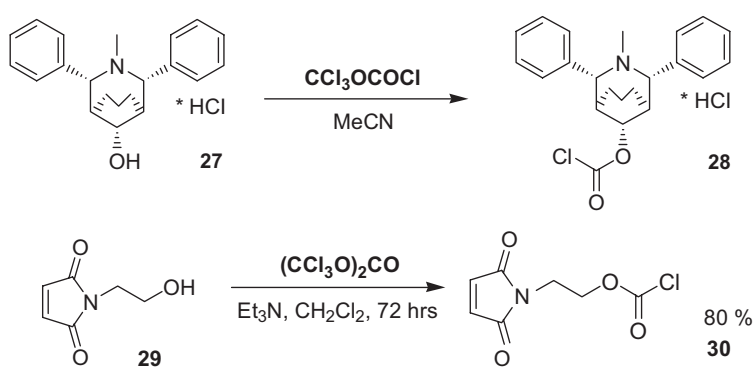
Alcohol (mmol)	*Triphosgene (mmol)*	*Pyridine (mmol)*	*Yield of hydantoins 26 (%)*
2-Adamantanol (1.8)	0.61	2.0	58
1-Octanol (1.77)	0.61	2.0	82
4-Methoxyphenol (1.2)	0.44	1.29	85
4-Trifluoromethanol (1.3)	0.44	1.29	40
3,4-Dichlorophenol (1.3)	0.44	1.29	42
3-Bromophenol (0.9)	0.33	0.9	74
Phenetyl alcohol (2.37)	0.84	2.37	65–85

Phenyloxycarbonyl-hydantoins **26** were synthesized from the corresponding imidazolidine-2,4-diones **24** and chloroformates **25** [24].

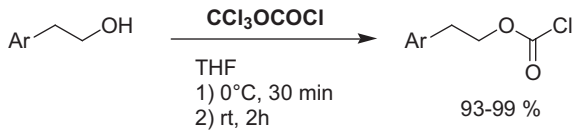


A series of non-commercially available chloroformates (R^3OCOCl) **25** (Table 4.2) were claimed to be synthesized from the desired alcohol and **triphosgene** in the presence of pyridine [24].

Diphosgene reacts with piperidinyl alcohol **27**, which has a protected nitrogen group, to give the corresponding chloroformate **28** [25].



Chloroformates **30** and **32** of 2-substituted ethanols **29** and **31** were prepared with **triphosgene** in 80% yield at ambient temperature [26] and with **diphosgene** in 93–99% yield [27].

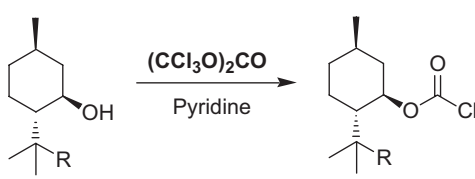


31 **32**

Ar =	2,6-dinitrophenyl 2-bromo-6-nitrophenyl 2,4-dichloro-6-nitrophenyl 2-fluoro-6-nitrophenyl 2-nitrophenyl

Typical procedure. *2-(2,6-Dinitrophenyl)ethyl chloroformate* **32** [27]: A solution of 2-(2,6-dinitrophenyl)ethanol (4.08 g, 19.23 mmol) and triethylamine (2.7 mL, 19.28 mmol) in anhydrous tetrahydrofuran (30 mL) was added to a cold (0 °C) solution of **diphosgene** (3.81 g, 19.28 mmol) in anhydrous tetrahydrofuran (10 mL) over a period of 20 min with stirring. After 30 min, the cooling bath was removed and stirring was continued at room temperature for 2 h. The mixture was then filtered through Celite and the solids were washed with tetrahydrofuran. The solvent was removed from the filtrate and washings in vacuo to give *2-(2,6-dinitrophenyl)ethyl chloroformate* (5.13 g, 97% yield) as a brownish solid, mp 84–85 °C.

Chloroformates **34** of some levorotatory 8-substituted menthols **33** have been prepared with **triphosgene** in the presence of pyridine [28].



33 **34**

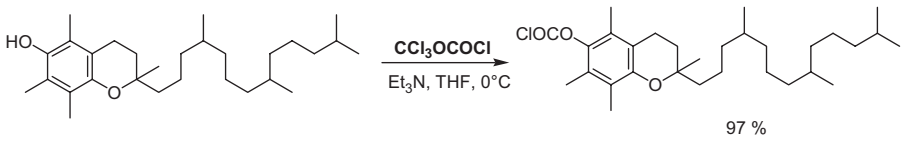
R =	H Ph *m*-$MeOC_6H_4$ *p*-$MeOC_6H_4$ *p*-BrC_6H_4 *p*-$NO_2C_6H_4$ 2-naphthyl cyclohexyl *trans*-4-nitrocyclohexyl

Several analogues of (*Z*)-8-dodecenyl acetate, the major pheromone component of the Oriental fruit moth, *Cydia molesta*, with chloroformate functional groups in place of the acetate moiety, have been synthesized. Thus, chloroformates of dodec-

anol and dodec-8*c*-en-1-ol (obtained in 60% yield and possessing significant inhibitory activity) were prepared with **triphosgene** in THF/pyridine [29].

Typical procedure. *(Z)-8-Dodecen-1-yl chloroformate* **34** [29]: A solution of **triphosgene** (0.367 mmol) in dry THF (1 mL) was cooled in an ice-bath and pyridine (45 μL, 1.2 equiv.) was added. To the preformed white precipitate, a solution of the (*Z*)-8-dodecen-1-ol (85 mg, 0.466 mmol) in THF (2 mL) was added dropwise over a period of 20 min. After stirring for 2 h at ice-bath temperature, the reaction mixture was poured onto ice and aq. HCl (3.7%, 0.4 mL). Subsequent standard work-up and PMPLC afforded the *(Z)-8-dodecen-1-yl chloroformate* (69 mg, 60% yield).

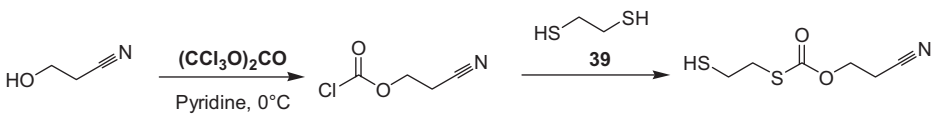
Activation of the hydroxyl group in vitamin E, **35**, to obtain vitamin E modified monomeric conjugates of 3′-deoxyadenosine (cordycepin), which inhibits HIV-1-induced syncytia formation, has been realized with **diphosgene** [30].



35 **36**

Typical procedure. *2-Ambo-α-tocopheryl chloroformate* **36** [30]: 2-*Ambo*-α-tocopheryl chloroformate was synthesized by adding dropwise a solution of 2-*ambo*-α-tocopherol (431 mg, 1 mmol) and triethylamine (0.14 mL, 1 mmol) in anhydrous THF to an ice-cooled solution of **diphosgene** (0.181 mL, 1.5 mmol) in anhydrous THF (4 mL). After stirring for 30 min at 0 °C, a small amount of charcoal was added, and the mixture was kept for a further 15 min. After two filtrations, the filtrate was concentrated to a yellow oil (480 mg, 97%).

The preparation of ethanedithiol mono(*β*-cyanoethyl carbonate) **40** with isolation of the intermediate chloroformate **38** has been described [31].

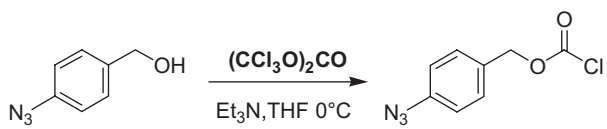


37 **38** **40**

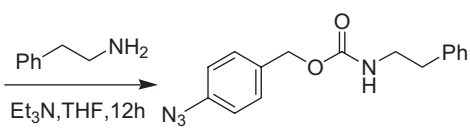
Typical procedure. *Ethanedithiol mono(β-cyanoethyl carbonate)* **40** [31]: **Triphosgene** (24.5 g, 83 mmol) was dissolved in anhydrous toluene (150 mL) and the solution was cooled to 0 °C. Dropwise addition of *β*-cyanoethanol (17.6 g, 248 mmol) was followed by dropwise addition of pyridine at 0 °C. The reaction mixture was then filtered to remove pyridine hydrochloride salt and concentrated to an oil. The crude

β-cyanoethyl chlorocarbonate was dissolved in anhydrous diethyl ether (50 mL), placed in a dropping funnel, and added dropwise to a solution of ethanedithiol (28 mL, 334 mmol) in anhydrous diethyl ether (200 mL) and pyridine (25 mL). The reaction mixture was filtered, and the filtrate was washed with saturated sodium hydrogen carbonate solution (3 × 100 mL) and brine (100 mL) and dried over Na_2SO_4. The organic phase was concentrated to an oil and distilled. The product was collected at 140–150 °C/0.4 mmHg.

Azidobenzyl chloroformate **42**, prepared in good yield by reacting 4-azidobenzyl alcohol **41** with **triphosgene** in the presence of triethylamine, gave a meagre yield of a product identical (TLC, ^{1}H NMR) to 4-azidobenzyl-*N*-(2-phenylethyl)carbamate **43** on treatment with 2-phenylethylamine [32]. Unfortunately, azidobenzyl chloroformate was isolated as an unstable oil, which proved impossible to purify further.



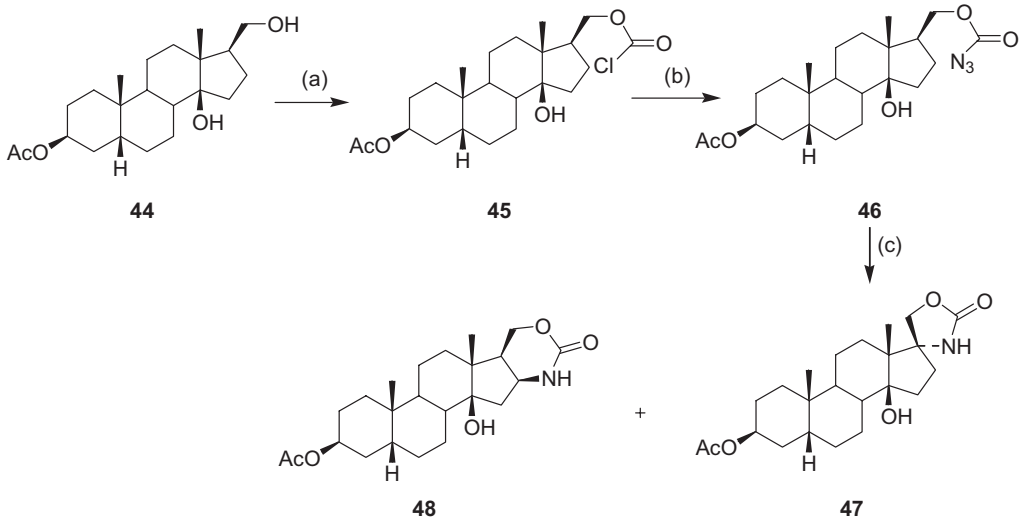
41 **42**



43

Typical procedure. *4-Azidobenzyl-N-(2-phenylethyl)carbamate* **43** [32]: To a stirred solution of **triphosgene** (1.0 g, 3.4 mmol) and 4-azidobenzyl alcohol (1.0 g, 6.7 mmol) in THF (40 mL), a solution of triethylamine (2.0 g, 19.7 mmol) in THF (40 mL) was added dropwise over a period of 1 h. The mixture was stirred under nitrogen in the dark for 72 h at 25 °C and, after removal of the solvent, the residue was partially redissolved in ethyl acetate (25 mL) and filtered through kieselguhr. The filtrate was washed with water (2 × 25 mL), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give the *chloroformate* **42** as a photosensitive viscous yellow oil (0.83 g, 58%), which was used without further purification. Treatment of a stirred solution of the above chloroformate (0.83 g, 3.9 mmol) in THF (20 mL), containing triethylamine (0.4 g, 4.8 mmol), with 2-phenylethylamine (0.54 g, 4.4 mmol) afforded, after 12 h, a product (0.1 g) identical to *4-azidobenzyl-N-(2-phenylethyl)carbamate*.

Acyl azide **46**, a starting material for oxazolidine derivatives **47** and **48** of digitalis steroidal compounds, was prepared by isolating the chloroformate intermediate **45** [33].



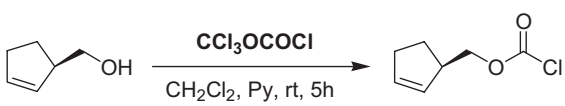
44 **45** **46** **48** **47**

(a) **triphosgene** , pyridine, CH_2Cl_2, room temp
(b) NaN_3, acetone, room temp
(c) tetrachloroethane, 140 °C

Typical procedure. *3β-Acetoxy-17β-azidocarbonyloxymethyl-5β-androstan-14β-ol* **46** [33]: **Triphosgene** (5.7 g, 19.2 mmol) and pyridine (4.7 mL, 5.8 mmol) were added to a solution of the alcohol (14 g, 38.5 mmol) in dry dichloromethane (540 mL). The reaction mixture was stirred for 3 h at room temperature, then a second portion of triphosgene (1.7 g, 5.8 mmol) was added and the reaction mixture was stirred for a further 3 h. The organic solvent was subsequently evaporated under reduced pressure, the residue was redissolved in acetone (540 mL), and then sodium azide (12.5 g, 192 mmol) was added and the resulting mixture was stirred for 2 h at room temperature. The solid was filtered off, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography (cyclohexane/ethyl acetate, 85:15) to give *3β-acetoxy-17β-azidocarbonyloxymethyl-5β-androstan-14β-ol* (12 g, 72%), mp 144–146 °C (dec).

An efficient one-pot synthesis of a series of *azidoformates* (yields 64–90%) from alcohols via chloroformates using **triphosgene** has recently been described [300]. Azidoformates are further reacted forming *N*-carbobenzoxy azetidin-2-ones.

The chloroformate of (*R*)-(2-cyclopent-2-enyl)methanol **49** is obtained in 81% yield using **diphosgene** [34].

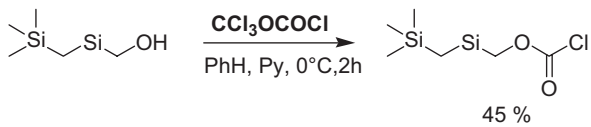


81 %

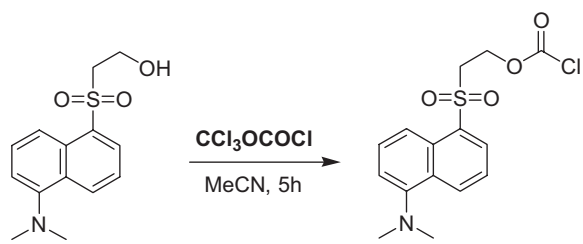
49 **50**

Typical procedure. *(+)-(R)-(Cyclopent-2-enyl)methyl chloroformate* **50** [34]: To a magnetically stirred solution of **diphosgene** (2.42 mL, 20 mmol) in dichloromethane (18 mL), dry pyridine (0.82 mL, 10 mmol) was added at 0 °C, and the resulting suspension was stirred at room temperature for 30 min. Thereafter, a solution of (+)-(*R*)-(cyclopent-2-enyl)methanol (980 mg, 10 mmol) in dichloromethane (8 mL) was added dropwise at 0 °C, and the mixture was stirred at room temperature for 5 h. It was diluted with diethyl ether, resulting in a dark-brown liquid *(+)-(R)-(cyclopent-2-enyl)methyl chloroformate* (1.30 g, 81%).

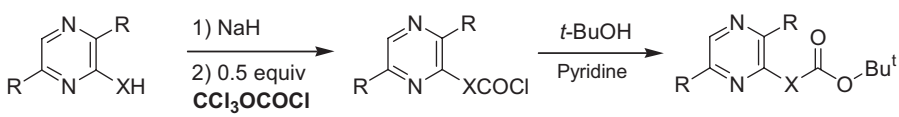
Triphosgene [35] or **diphosgene** [36] have been employed for the preparation of silicon-containing (**52**) [37], sulfur (**54**), and 3,6-disubstituted 2-hydroxy (or thio) pyrazine (**56**) chloroformates [38].



51 **52**



53 **54**



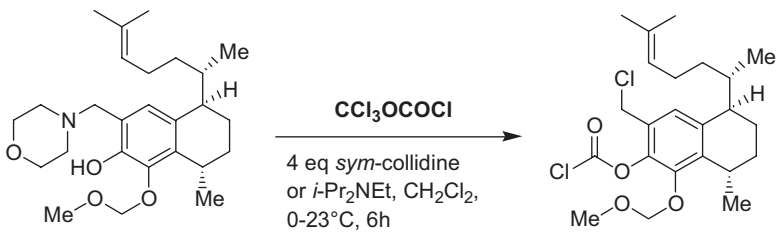
55 **56** **57**

X	R	Yield %
O	Et	43
O	i-Pr	53
O	i-Bu	50
S	Et	75
S	n-Pr	84
S	n-Bu	78

Typical procedure. *t-Butoxycarbonylated pyrazinols* **57** [38]: To a solution of a pyrazinol (10 mmol) or pyrazinethiol (10 mmol) in dioxane (50 mL), sodium hydride (480 mg, 10 mg atom) was added and the reaction mixture was stirred at room

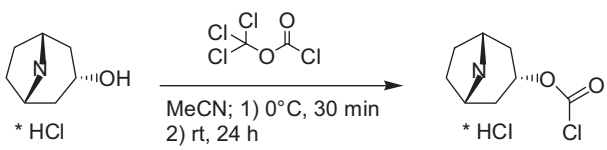
temperature until the evolution of hydrogen had ceased. Under ice-cooling, **diphosgene** (0.9 mL, 7.5 mmol) was added in a single portion to the reaction mixture, which was stirred overnight at room temperature. After the addition of a solution of *t*-butyl alcohol (1.11 g, 15 mmol) in pyridine (2.5 mL) under ice-cooling, the reaction mixture was stirred for 3 h under ice-cooling, and then allowed to stand overnight at room temperature. In order to decompose **diphosgene**, the reaction mixture was stirred with powdered active charcoal (50 mg) for 1 h, and then filtered. After removing the solvent from the filtrate by distillation in vacuo, the resulting oil was dissolved in diethyl ether. The ether layer was washed successively with 10% hydrochloric acid, 10% aqueous potassium hydroxide, and water, then dried over sodium sulfate, and concentrated. The resulting oil was purified by distillation in vacuo to give the product as a colorless oil.

Mannich base **58** was efficiently converted to the chloromethyl compound **59** with **diphosgene** [39].



58 **59**

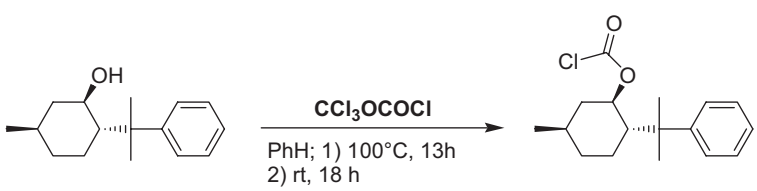
Tropine hydrochloride **60** was transformed into the corresponding chloroformate **61** in 98% yield with **diphosgene** [40].



98 %

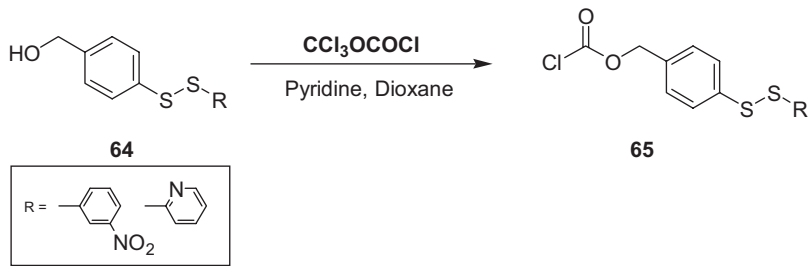
60 **61**

(−)-8-Phenylmenthol **62** gave the corresponding chloroformate **63** upon treatment with **diphosgene** in benzene [41].

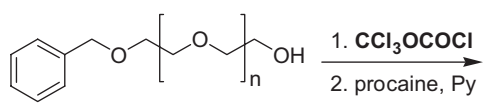


62 **63**

Chloroformates **65** of 4-substituted benzyl alcohols **64**, intermediates for benzyl carbamate disulfide drug derivatives, have been prepared with **diphosgene** in dioxane/pyridine [42].

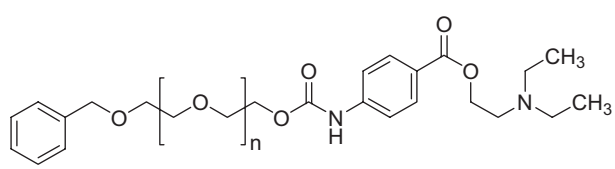


The synthesis of biotinylated local anaesthetics from tetracaine and procaine, having the monobenzyl ether of hexaethylene glycol as a structural fragment, has been realized using **diphosgene** and *N*,*N*-dimethylaniline (DMA) in benzene to give *glycol chloroformates*, which were not isolated but reacted directly with procaine in pyridine solution. The corresponding carbamates *P-3-Bn* and *P-6-Bn* were prepared in yields of 98% and 100%, respectively, by this procedure [43].



66

(n = 5) : 30 %



67

(n = 2) : 98 %

(n = 5) : 100 %

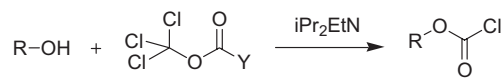
Typical procedure. *P-6-Bn carbamate* **67** [43]: **Diphosgene** (1.01 g, 5.4 mmol) and benzene (5 mL) were placed in a 100 mL round-bottomed flask equipped with a dropping funnel, magnetic stirring bar, and inlet for argon. The solution was cooled in an ice bath, and a solution of hexaethylene glycol monobenzyl ether (H-6-Bn) (1.84 g, 4.94 mmol) and *N*,*N*-dimethylaniline (0.66 g, 5.4 mmol) in benzene (10 mL) was added dropwise over a period of 5 min. The resulting white suspen-

sion was stirred at 4 °C for 12 h. The benzene was then quickly removed in vacuo and the residue was cooled in an ice bath. A solution of procaine (1.17 g, 4.44 mmol) in pyridine (12 mL) was added in a single portion. The resulting yellow suspension was stirred at 0 °C for 20 min and then at room temperature for 3.5 h. The reaction mixture was then stirred with saturated $NaHCO_3$ solution (100 mL) and extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were washed with saturated NaCl solution (30 mL), dried ($MgSO_4$), and concentrated in vacuo (85 °C, 0.1 Torr) to yield *P-6-Bn* (3.14 g, ca. 100% yield) as a yellow oil, which was nearly pure by TLC.

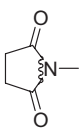
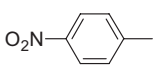
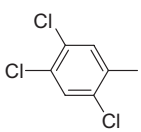
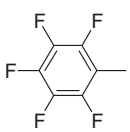
A series of aryl chloroformates **69**, which are very unstable at room temperature, being readily decomposed by amines, acids, protic solvents, and atmospheric moisture, could be prepared with **diphosgene** and **triphosgene** in the presence of ethyl diisopropylamine (Table 4.3) [44].

Typical procedure. *Chloroformates of Table 4.3* [44]: In a dry 200 mL flask equipped with an Ar inlet adaptor, a rubber septum, and a magnetic stirring bar, was placed the alcohol (14.4 mmol) in dry dichloromethane (50 mL). The mixture was cooled

Tab. 4.3. Unstable chloroformates prepared with **diphosgene** and **triphosgene** [44].

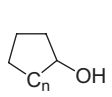


68 **69**

R	*Y*	*Conditions*	*Yield %*
	Cl	0 °C, 0.5 h, reflux, 2 h	81
	Cl	0 °C, 0.5 h, reflux, 2 h	88–90
	Cl	0 °C, 3 h, 0–20 °C, 6 h, reflux, 2 h	97
	$OCCl_3$	0 °C, 3 h, 0–20 °C, 6 h, reflux, 2 h	90
	Cl	0 °C, 0.5 h, reflux, 2 h	45
	Cl	0 °C, 3 h, 0–20 °C, 4 h, 33–34 °C, 1.5 h, reflux, 2 h	79
	$OCCl_3$	0 °C, 3 h, 0–20 °C, 6 h, reflux, 2 h	47

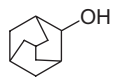
to −30 °C, whereupon **diphosgene** (3.92 g, 19.8 mmol, 1.4 equiv.) and iPr$_2$EtN (1.86 g, 14.4 mmol, 1 equiv.) were slowly added in the order specified. The resultant solution was stirred at 0 °C for 3 h, at 20 °C for 6 h, and then at reflux temperature for a further 2 h. The solvent was subsequently evaporated in vacuo to give a crystalline solid, which was suspended in THF (20 mL). The suspension was decanted to remove the crystalline iPr$_2$EtN·HCl and the supernatant was concentrated to dryness under reduced pressure. The crude product obtained was crystallized from THF.

Chloroformates of the mono- or polycyclic monohydroxylic compounds **70**–**80** were prepared with **triphosgene** and pyridine in dichloromethane within 1 h at ambient temperature [45].



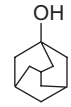
70

n = 0-6, 8



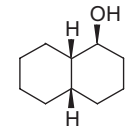
71

adamantan-2-ol



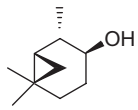
72

adamantan-1-ol



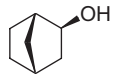
73

(4a*r*, 8a*c*)-decahydro-naphthalen-1*c*-ol (racemate)



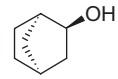
74

(2*exoH)*-pinan-3*exo*-ol



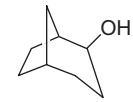
75

norbornan-2*exo*-ol (racemate)



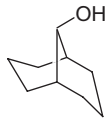
76

norbornan-2*endo*-ol (racemate)



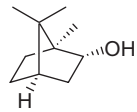
77

bicyclo[3.2.1]octan-2-ol



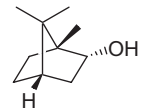
77

bicyclo[3.3.1]nonan-2-ol



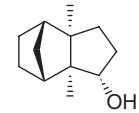
78

(+)-isoborneol



79

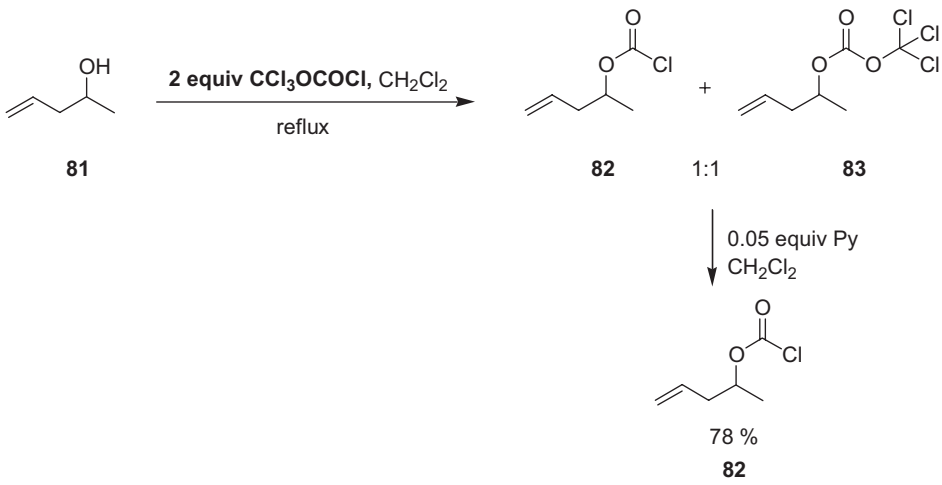
(1S)-borneol



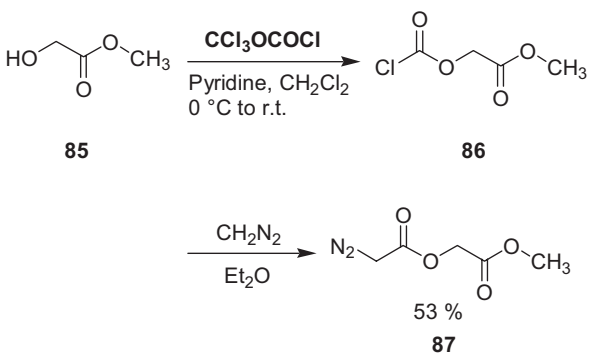
80

albene-racemate

Chloroformylation of unsaturated alcohols has been carried out by treatment with either **diphosgene** or **triphosgene** [46]. A two-step procedure for the preparation of the unsaturated chloroformate **82** was developed. The first step is treatment of alcohol **81** with 2 equiv. of **diphosgene** in boiling dichloromethane to give a 1:1 mixture of chloroformate **82** and trichloromethyl 4-penten-2-yl carbonate **83**. The second step is conversion of the latter into chloroformate **82** by treatment of the mixture with a catalytic amount of pyridine (0.05 equiv.) in dichloromethane. After careful evaporation of the solvent, the residue was soaked in dry pentane and then pyridinium hydrochloride was removed by filtration. Chloroformate **82** was obtained in 78% yield after distillation (bp 75 °C/66 mmHg).



The diazoester of hydroxyacetic acid methyl ester **87** was prepared via the chloroformate **86** using **diphosgene** as chloroformylating agent [47].

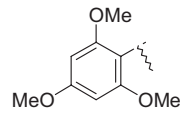
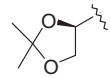
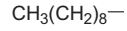
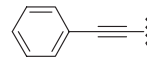
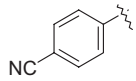


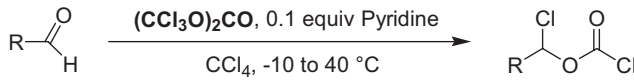
Phosgene, **diphosgene**, **and triphosgene** react readily with a variety of aldehyde substrates under mild conditions thereby affording the corresponding *α-chloro chloroformates* in good yields [48–51].

On a laboratory scale, the best catalyst for the addition of phosgene to aldehydes is benzyl tri-*n*-butylammonium chloride (BTBAC). The most important reagent, α-chloroethyl chloroformate (''ACE-Cl'') is typically isolated in 96% yield after stirring acetaldehyde with neat phosgene (1.1 equiv.) for 1 h in the presence of 3 mol% BTBAC. Even chloromethyl chloroformate can be prepared using this process, but it is essential that the monomeric gaseous formaldehyde is introduced into the reactor already containing the catalyst and phosgene, so that it reacts immediately and is not repolymerized [50, 52].

A method for the preparation of *α-chloro chloroformates* using **triphosgene** was developed by Coghlan (Table 4.4) [51].

Tab. 4.4. Chloroformates **89** prepared from aldehydes **88** and **triphosgene** [51].

R	*Isolated Yield %*	*R*	*Isolated Yield %*
	50		64
	82		66
	93		94
	89		85
	62	Ferrocene Carboxaldehyde	78



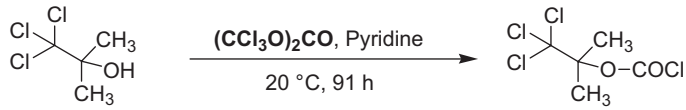
88 **89**

Yields obtained for acrolein and cyclohexane carboxaldehyde (50% and 89%, respectively) are similar to those reported for the phosgene reaction (54% and 87%), but reaction of **triphosgene** with *benzaldehyde* gives a considerably higher yield than that reported (82% *vs.* 68%) [49].

Typical procedure. *Cyclohexyl α-chloro chloroformate* [51]: To a mechanically stirred solution of cyclohexane carboxaldehyde (4.05 g, 36.1 mmol) and pyridine (300 mg, 3.79 mmol) in CCl_4 (40 mL) under a nitrogen atmosphere at −20 °C, solid **triphosgene** (5.37 g, 18.1 mmol) was added at such a rate that the reaction temperature remained between −20 and −10 °C (∼5 min). The resulting viscous slurry was allowed to warm to room temperature over 90 min, and then heated to 40 °C for 1 h. The reaction mixture was allowed to cool and stirred overnight at room temperature. Filtration of the pyridinium salts followed by removal of the solvent in vacuo gave ∼8 g of crude product, which was purified by distillation (bp 90–91 °C at 10 Torr), thereby affording the desired *cyclohexyl α-chloro chloroformate* (6.80 g, 89%).

The chloroformate of the tertiary alcohol 1,1,1-trichloro-2-methylpropan-2-ol **90**, 2,2,2-trichloro-*tert*-butyl chloroformate **91** (*TCBoc-Cl*), is a reagent that can be used to introduce the *TCBoc* protective group, and is stable under acidic and basic con-

ditions. It is prepared with **triphosgene** and pyridine in dichloromethane at 20 °C in 91% yield [53].

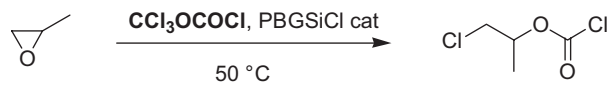


91 %

90 **91**

Typical procedure. *2,2,2-Trichloro-tert-butyl chloroformate* **91** [53]: To a solution of dry **90** (17.8 g, 0.1 mol) (dried from commercial **90**·hemihydrate by passing a solution in dichloromethane through a silica gel column) and **triphosgene** (9.8 g, 0.033 mol) in dichloromethane (80 mL), a solution of pyridine (10.5 mL) in dichloromethane (10 mL) was added dropwise under vigorous stirring at room temperature (by cooling with an ice-bath). The mixture was stirred for a further 12 h at room temperature, and the progress of the reaction was monitored by ^{1}H NMR spectroscopy. The solvent was removed in a rotary evaporator and the residue was taken up in hexane. The red precipitate produced was filtered off (under nitrogen atmosphere) and the solvent was removed from the filtrate in a rotary evaporator. The crude product (97%) was purified by fractional distillation, affording 21.6 g (91%) of pure *2,2,2-trichloro-tert-butyl chloroformate* **91** as a colorless liquid, which subsequently crystallized; mp 28–30 °C, bp 83–84 °C (14 Torr); ^{1}H NMR ($CDCl_3$): $\delta = 1.58$ (s).

Methyl oxirane **92** reacts with **diphosgene** at 50 °C to give the chloroformate of *β*-chloroisopropyl alcohol **93** in 90% yield [54].



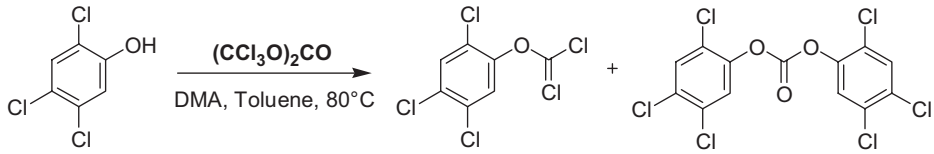
90 %

92 **93**

PBGSiCl cat = silica-supported pentabutylpropylguanidinium chloride

General procedure. *β-Chloro chloroformate* **93** (bulk preparation) [54]: **(Caution: Fumehood! Review phosgene safety precautions before repeating)**. In a flask equipped with a dry ice/dichloromethane condenser was placed a suspension of PBGSiCl (2 g; 0.34 mmol of Cl^-) in the liquid epoxide (34 mmol). **Diphosgene** (2.4 mL, 20 mmol) was then added dropwise at room temperature and in some cases the reaction was slightly exothermic. Following the addition, the reaction mixture was heated at 50 °C and a gentle phosgene reflux was obtained. The reaction was monitored by gas chromatography until complete consumption of the starting epoxide (4–6 h). Excess phosgene was then carefully eliminated under reduced pressure, trapped, and treated with crushed ice. After filtration of the catalyst beads, the crude product was not yet entirely pure and had to be distilled under reduced pressure to yield pure *β-chloro chloroformate* **93**.

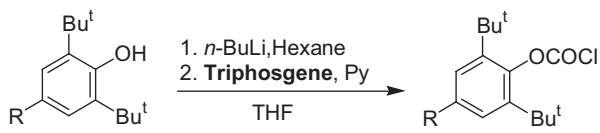
2,4,5-Trichlorophenol chloroformate **95** is prepared from **94** with **triphosgene** and *N*,*N*-dimethylaniline in toluene at 80 °C [55].



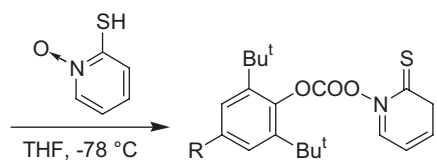
54 % 4 %

94 **95** **96**

N-(Phenoxycarbonyloxy)thiopyridone derivatives **99** are efficient unimolecular photochemical sources for the clean generation of phenoxyl radicals. They are prepared by the reaction of lithium phenoxides with **phosgene** (from **triphosgene** and pyridine in a 1:3 molar ratio) [56].



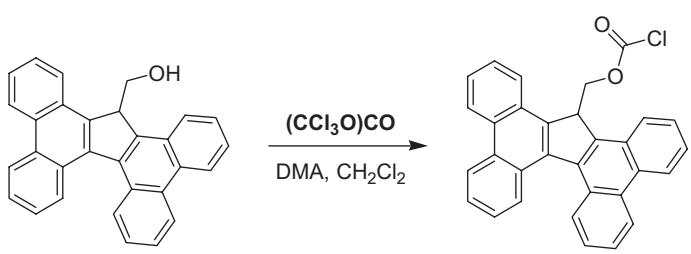
97 **98**



99

R = Bu^t, OMe and Me

Chloroformate **101** of tetrabenzo[*a*,*c*,*g*,*i*]fluorenyl-17-methanol **100** was obtained with **triphosgene** [57].

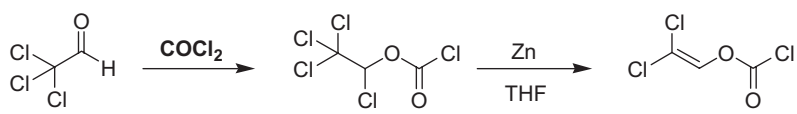


71 %

100 **101**

Typical procedure. *(17-Tetrabenzo[a,c,g,i]fluorenyl)methyl chloroformate* **101** [57]: Tetrabenzo[*a*,*c*,*g*,*i*]fluorenyl-17-methanol (1.0 g, 2.52 mmol) was taken up in dichloromethane (20 mL) along with **triphosgene** (0.5 g, 1.68 mmol), and *N*,*N*-dimethylaniline (DMA) (0.64 mL, 5.04 mmol) was added. The mixture was stirred for 45 min and the precipitated solid was filtered off and recrystallized from dichloromethane/*n*-hexane to give *(17-tetrabenzo[a,c,g,i]fluorenyl)methyl chloroformate* **101** as a pale-yellow solid (0.577 g). A further crop of the product was obtained from the dichloromethane filtrate after adding water, acidifying to pH 1 with 2 M HCl, drying the organic layer ($MgSO_4$), removing the solvent, and recrystallizing the residue from dichloromethane/*n*-hexane. Total yield (0.819 g, 71%).

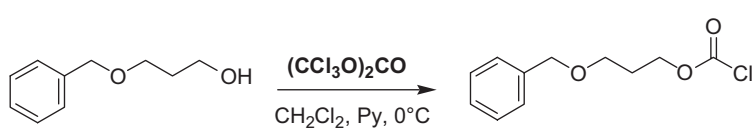
2,2-Dichlorovinyl chloroformate **104**, a stable and active acylating agent (e.g. for the protection of alcohols in acidic media) was prepared for the first time from 1,2,2,2-tetrachloroethyl chloroformate **103** (an α-chloroalkyl chloroformate synthesized by treatment of chloral **102** with phosgene in the presence of a reusable "naked Cl^-" catalyst) by dehalogenation with Zn dust [58].



102 **103** **104**

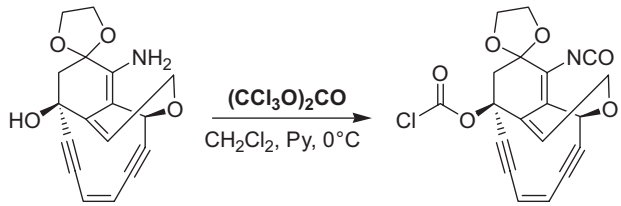
Typical procedure. *1,2,2,2-Tetrachloroethyl chloroformate* **103** [58]: Freshly distilled chloral (4.4 g, 0.030 mol) was added (over 30 min) to a stirred refluxing solution (dry-ice Dewar condenser) of benzyl tri-*n*-butylammonium chloride (BTBAC) (10 g, 0.032 mol) in **phosgene** (for a *safe source*, see Chapter 7) (60 mL). After 1 h, the excess phosgene was removed through a series of five bubble traps (empty, H_2SO_4, empty, aqueous NaOH, NH_4OH to hood exhaust) with the aid of an aspirator, and the *1,2,2,2-tetrachloroethyl chloroformate* was isolated by distillation: bp 76–79 °C/19 Torr, 47.7 g (65% yield). Note: Unless *1,2,2,2-tetrachloroethyl chloroformate* is completely free from the catalyst, it slowly reverts to the reactants.

3-Benzyloxypropyl chloroformate **106**, a useful reagent in the total synthesis of di- and tri-*O*-methyl *Dynemicin A* methyl esters, was prepared by syringe pump addition (over 2 h) of 3-benzyloxypropanol **105** (2.9 equiv.) and pyridine (3.0 equiv.) to a solution of **triphosgene** in dichloromethane at 0 °C [59].

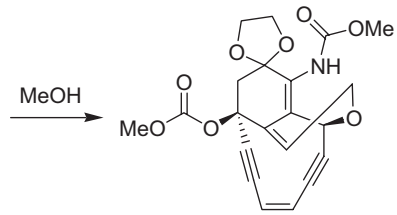


105 **106**

Triphosgene was used in the total synthesis of *Calicheamicinone* for the simultaneous activation of both a hydroxyl and amino group [60].



107 **108**



109

Typical procedure. *Methyl 5′-[(methoxycarbonyl)oxy]-3′-oxospiro{1,3-dioxolane-2,7′-(3′H)-[1,5][3]hexene[1,5]diyno[1H-2]benzopyran}-8′-yl carbamate* **109** [60]: **Triphosgene** (1.01 g, 3.4 mmol) was added under nitrogen to a solution of vinyl amine **107** (365 mg, 1.17 mmol) in dry dichloromethane (80 mL) at 0 °C. Pyridine (1.40 mL, 17.4 mmol) was then added, followed by methanol (10 mL). After 30 min at 0 °C, the reaction was quenched by the addition of pH 7 phosphate buffer (50 mL), followed by ethyl acetate (200 mL). The aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash chromatography on SiO_2 (hexanes/ethyl acetate, 2:3) to give 413 mg (82%) of *methyl 5′-[(methoxycarbonyl)oxy]-3′-oxospiro{1,3-dioxolane-2,7′-(3′H)-[1,5][3]hexene[1,5]diyno[1H-2]benzopyran}-8′-yl carbamate* **109** as a yellow solid; mp > 105 °C (dec.).

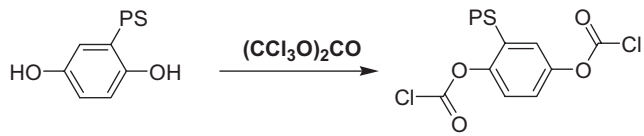
Activation of 2-adamantol as chloroformate **111** using **triphosgene** and subsequent carbamate formation in the synthesis of α-methyltryptophan derivatives **112** as highly selective and orally active gastrin and CCK-B antagonists with potent anxiolytic properties has also been reported [61].

110 **112**

Typical procedure. *2-Adamantyl-α-methyltryptophan derivative* **112** [61]: To a stirred solution of 2-adamantol (912 mg, 5.9 mmol) in anhydrous dichloromethane (15 mL) were added **triphosgene** (653 mg, 2.20 mmol) and pyridine (474 mg, 5.99 mmol) in anhydrous dichloromethane (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was then removed in vacuo at 30 °C, the residue was redissolved in EtOAc (30 mL), and this solution was stirred for 10 min. The precipitate was filtered off and the solvent was removed in vacuo at 30 °C to leave an oil, which solidified upon standing (1.29 g, 100%). To a stirred solution of this solid (965 mg, 4.5 mmol) in anhydrous THF (10 mL) was added a solution of α-methyl-(*R*)-tryptophan methyl ester **110** (928 mg, 4.0 mmol) in anhydrous THF (20 mL), and then a solution of triethylamine (808 mg, 7.98 mmol) in anhydrous THF (20 mL) was added dropwise. After 15 min, the reaction mixture was filtered, the solvent was removed in vacuo, and the residue was subjected to column chromatography eluting with 2% MeOH in CH_2Cl_2 to yield a syrup (1.42 g, 89%).

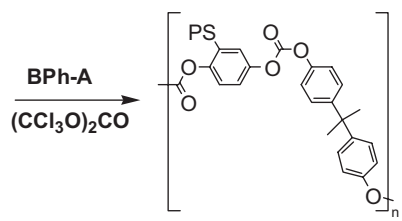
The preparation of *chloroformates of aryl ketones* bearing aromatic hydroxyl functions using the *phosgene equivalents* **diphosgene** and **triphosgene** has been claimed in patent literature [62].

Similar functionalization was described in the synthesis of poly(bisphenol-A carbonate)-*graft*-polystyrene **115** by a macromonomer technique. Pyridine rather than triethylamine was the proton acceptor of choice in the synthesis of the graft copolycarbonate by solution polycondensation [63].



Macromonomer

113 **114**



115

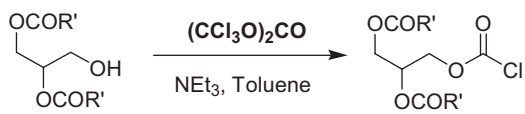
BPh-A = Bisphenol-A

Typical procedure for *polycondensation in demixing solvents* [63]: A solution of **triphosgene** (4 mmol), benzyltrimethylammonium chloride (0.1 mmol), and macromonomer ($M = 1900$) (0.5 mmol) in dichloromethane (40 mL) was added to a cooled (0 °C) solution of NaOH (22 mmol) in H_2O (40 mL) under vigorous stir-

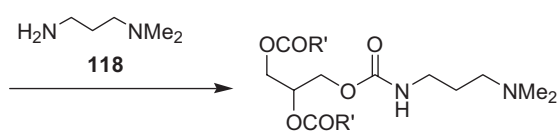
ring. After 5 min, bisphenol-A (9.5 mmol) was added. After a further 20 min, the contents of the vessel were poured into methanol. The solid produced was filtered off and purified by dissolving it in dichloromethane and reprecipitating it from methanol; the product was then dried over P_2O_5 (yield: 86%). The dried polymer was extracted with acetone by stirring for 1 h; the insoluble fraction was collected by filtration and washed with acetone (yield: 57%).

Typical procedure *for solution polycondensation* [63]: The macromonomer (0.26 mmol) and **triphosgene** (1.9 mmol) were placed in a dry vessel under nitrogen atmosphere and dissolved by the addition of dichloromethane (15 mL). Pyridine (7 mL) was then added dropwise, causing the formation of a yellow precipitate. After stirring for 1 h, a solution of *bisphenol-A* (5 mmol) in dichloromethane (20 mL) and pyridine (7 mL) was added dropwise. The yellow precipitate vanished, and a white precipitate formed as the viscosity of the solution increased considerably. After 24 h and 48 h, two drops of water were added. Pouring the solution into methanol (1 L) led to the formation of a fibrous white solid, which was collected by filtration, washed with methanol, water, and further methanol, and dried over P_2O_5 to constant weight (yield: 84%). Washing with acetone gave an insoluble residue (yield: 79%).

Chloroformates **117** of dioleoylglycerol **116**, intermediates in the synthesis of positively charged lipids, were prepared with **triphosgene** in toluene [64].



116 **117**



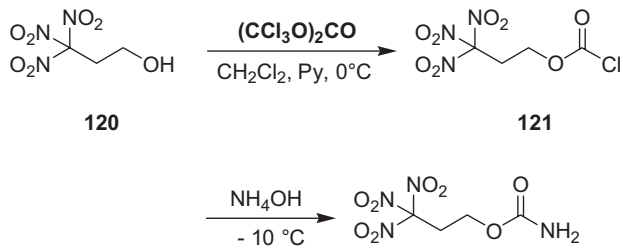
79 %

119

Typical procedure. *3-Dimethylaminopropyl lipid carbamate* **119** [64]: To a stirred solution of **triphosgene** (48 mg, 0.16 mmol) in dry toluene (20 mL), at 0 °C under Ar atmosphere, were added the lipid (200 mg, 0.32 mmol) and triethylamine (36 mg, 0.36 mmol). Stirring was continued for 30 min at 0 °C and for 2 h at ambient temperature. Then, 3-dimethylaminopropylamine **118** (0.164 g, 1.6 mmol) was introduced and the solution was stirred overnight. Thereafter, a mixture of brine (10 mL) and 10% sodium hydrogen carbonate solution (10 mL) was added, and the product was extracted with dichloromethane (3 × 20 mL). The combined extracts

were washed with 0.1 N HCl (10 mL), 10% sodium hydrogen carbonate solution (10 mL), and finally with water. The mixture was then dried over sodium sulfate and concentrated to give 0.19 g of the product (79%).

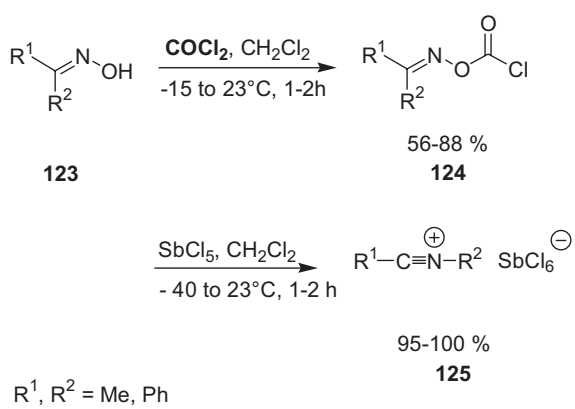
3,3,3-Trinitropropyl carbamate **122** was prepared via the corresponding chloroformate **121** using **triphosgene** [65].



120 **121** **122**

Typical procedure. *3,3,3-Trinitropropyl carbamate* **122** [65]: To a stirred mixture of **triphosgene** (1.8 g, 6 mmol) and 3,3,3-trinitropropanol (3.1 g, 16 mmol) in dichloromethane (10 mL) at 0 °C, a solution of pyridine (1.5 mL, 19 mmol) in dichloromethane (5 mL) was added dropwise. After 24 h at room temperature, the reaction mixture was cooled to −10 °C, whereupon concentrated ammonium hydroxide (30%, 2 mL, 32 mmol) was added dropwise with stirring. The precipitated solid was removed by filtration and the filtrate was extracted with water and dilute hydrochloric acid. The volatiles were removed to give 2.75 g of product, which was chromatographed on silica gel 40 (eluting first with dichloromethane and then with dichloromethane/acetone, 80:20) to yield 0.65 g of solid; mp 82–84 °C.

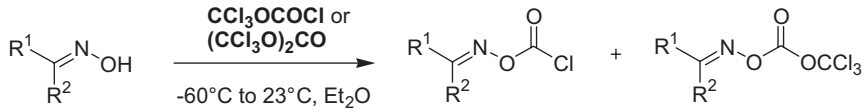
Phosgene reacts with oximes to form *O-(chloroformyl) oximes* **124**, which, on addition of antimony pentachloride, undergo smooth Beckmann rearrangement with loss of carbon dioxide to give the nitrilium salts **125** almost quantitatively [66]. With oxygen or nitrogen nucleophiles, *O-(chloroformyl) oximes* **124** form symmetrical and unsymmetrical oxalyl derivatives.



123 **124** **125**

The preparation of *O-(chloroformyl)oximes* **124** was previously reported by Jumar [67], with the obtained yields being between 56 and 88%.

Oximes react with **diphosgene** or **triphosgene** to form mixtures of the chloroformyl esters and the (trichloromethoxy)formyl esters in variable ratios. With antimony pentachloride, these mixtures give nitrilium salts, which are contaminated with excess $SbCl_5$ as the exact amount of this reagent required is difficult to determine.

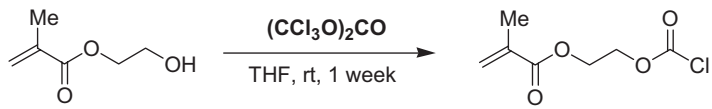


123 **124** **126**

Typical procedure. *Chloroformyl ester* **124** (R^1, R^2 = Me) *and the (trichloromethoxy)-formyl ester* **126** (R^1, R^2 = Me) [66]: A solution of **123** (R^1, R^2 = Me) (0.73 g, 10 mmol) in diethyl ether (10 mL) was added dropwise to a cold (−40 °C) solution of **triphosgene** (4.45 g, 15 mmol) in diethyl ether (10 mL). After stirring at 23 °C for 30 min, the solvent was evaporated. The ^{13}C NMR spectrum of the colorless solid residue (3.33 g) showed signals for **124**, **126**, and unreacted **triphosgene**.

Oxalyl chloride proved to be an interesting reagent for the above transformation; on treating an oxime with 1.5 equivalents of this reagent in diethyl ether at low temperatures, a precipitate (hydrochloride of the oxime) is formed immediately, which dissolves after a few minutes affording *(chlorooxalyl)oximes* in high yields (68–99%) [66].

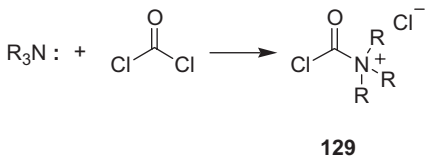
Chloroformate **128** of *2-hydroxyethyl methacrylate* **127**, an intermediate for the synthesis of azo polymers useful for colon-specific drug delivery, was prepared with **triphosgene** [68].



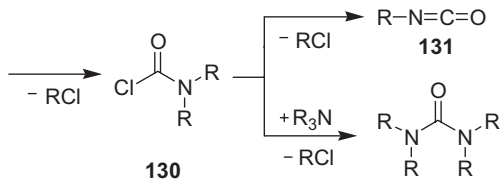
127 **128**

4.2.2
Carbamoyl Chlorides (Chlorocarbonylation of Amines)

The most widely documented aspect of **phosgene** chemistry is the interaction of the reagent with *nitrogen nucleophiles* (for example, R_3N). The intermediate complex **129** formed is unstable and usually collapses, with elimination of RCl, to give a stable carbamoyl chloride derivative **130**. The carbamoyl chloride thus formed can eliminate RCl to create a new site of unsaturation (isocyanate, **131**) and/or react further with another molecule of starting material to afford urea, **132**, a tricoordinated carbonic acid derivative (see Scheme 4.1).



129



130 131 132

The availability of the nitrogen electron pair for bonding and the steric environment about the nitrogen center determine the reactivity of the various nitrogenous functional groups.

This section deals with the reactions of amino compounds with **phosgene** *generated from its common source or phosgene equivalents*, by a direct transfer of the chlorocarbonyl group, giving carbamoyl chlorides. Reactions of imines and other unsaturated (cyclic) nitrogen compounds with phosgene will be discussed later.

4.2.2.1 Reactions with Primary Amines

The preparation of amides by the treatment of amines with acyl halides is a very general reaction. When **phosgene** is the acyl halide, both *aliphatic and aromatic primary amines* or *their salts* give carbamoyl chlorides, which can be regarded as substituted chloroformamides, ClCONHR.

There are numerous *solvent phosgenation* procedures. If an excess of $\mathbf{COCl_2}$ is employed, or if the hydrogen chloride formed is removed as it is produced (for example, by the use of a strong base, such as a tertiary amine), then the final product will be the carbamoyl chloride. Performing the reaction at high temperatures in the presence of an excess of phosgene results in the formation of isocyanate and hydrogen chloride, consistent with the overall stoichiometry [69]; the carbamoyl chlorides are easily dehydrochlorinated to the corresponding isocyanate upon heating [70–73].

This is one of the most common methods for the preparation of isocyanates. Various reported methods for obtaining isocyanates using phosgene or phosgene equivalents are discussed in Section 4.3 of the present chapter.

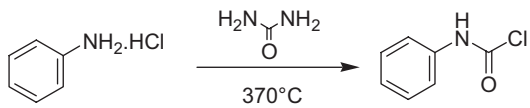
The reactions of *amines* and *amine hydrochlorides* with **phosgene** in the *gas-liquid phase* are reported to be catalyzed by numerous compounds such as morpholine [74], boron trifluoride [75], aluminum chloride [76], *N*,*N*-dialkylcarbamates [77], *N*,*N*-dialkylamides [78, 79], tetraalkylureas and thioureas [78–80], hexamethylphosphoramide [78], as well as activated carbon [81].

Carbamoyl chlorides have been prepared by the *vapor-phase* reaction of phosgene with primary amines [82–85]. The method is widely applicable, and its greatest

utility lies in the preparation of *lower alkyl carbamoyl chlorides* and the corresponding isocyanates. Exposure of these alkyl carbamoyl chlorides to the conditions of the solvent phosgenation procedure and conventional thermal dehydrohalogenation techniques leads to extensive degradation and yield losses due to the formation of by-products (allophanoyl chlorides and isocyanate polymers).

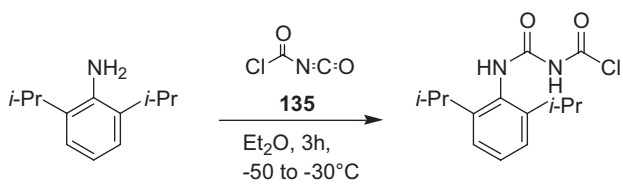
The kinetics of the reaction of phosgene with several aromatic amines has been examined [86–89] using a "quenching-flow" technique. The reactions follow second-order kinetics, and an S_N2 mechanism has been proposed.

One of the first *phosgene-free* transformations for the preparation of carbamoyl chlorides was, surprisingly, accomplished with *urea*. Heating aniline hydrochloride **133** with *urea* at 370 °C resulted in phenylcarbamoyl chloride **134** [90].



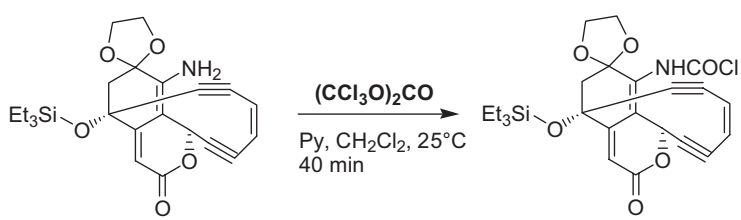
133 **134**

Chlorocarbonyl isocyanate **135** has been employed to obtain a *chlorocarbonyl urea* **137** from 2,6-diisopropyl aniline **136** [91].



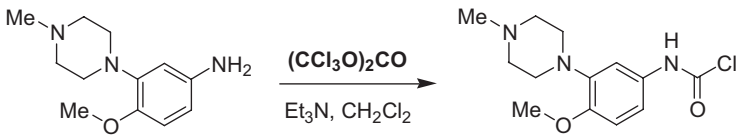
136 **137**

The carbamoyl chloride **139** of enamine **138** has been obtained with **triphosgene** in dichloromethane/pyridine at 25 °C [92].



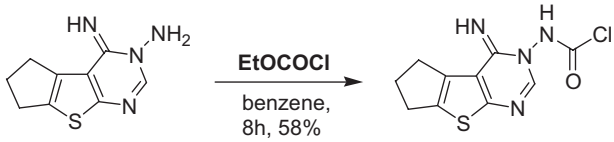
138 **139**

Aromatic carbamoyl chloride **141** has been obtained with **triphosgene** from 3,4-disubstituted anilines [93].

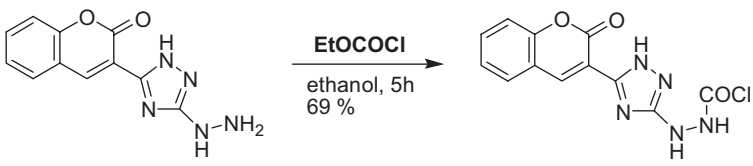


140 **141**

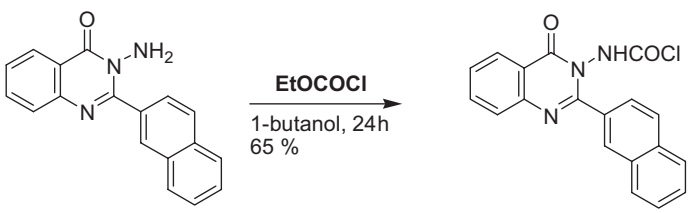
Several *alkyl and aryl chloroformates* have been used to prepare *carbamoyl chlorides*. **Ethyl chloroformate** is a good carbonylating agent for primary amines. Hydrazino carbamoyl chlorides (e.g. **143**, **145**, and **147**) have been prepared with **ethyl chloroformate** in benzene [94], ethanol [95], and 1-butanol [96], respectively.



142 **143**

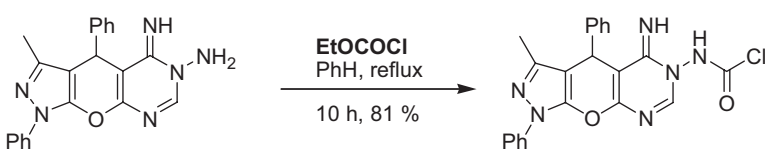


144 **145**



146 **147**

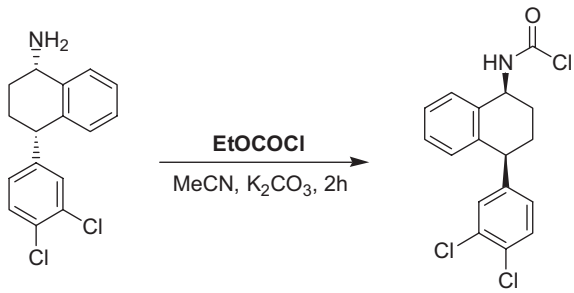
Ethyl chloroformate also reacts with 6-amino-1,4,5,6-tetrahydro-5-imino-3-methyl-1,4-diphenylpyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine **148** to give *6-chlorocarbonylamino-1,4,5,6-tetrahydro-5-imino-3-methyl-1,4-diphenylpyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine* **149** [97].



148 **149**

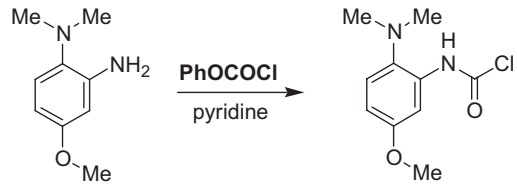
Typical procedure. *6-Chlorocarbonylamino-1,4,5,6-tetrahydro-5-imino-3-methyl-1,4-diphenylpyrazolo[4′,3′:5,6]pyrano[2,3-d]pyrimidine* **149** [97]: To a solution of 6-amino-1,4,5,6-tetrahydro-5-imino-3-methyl-1,4-diphenylpyrazolo[4′,3′:5,6]pyrano[2,3-*d*]pyrimidine (0.37 g, 0.001 mol) in dry benzene (100 mL) was added an excess of **ethyl chloroformate** (0.5 mL) and the mixture was refluxed for 10 h. After cooling, the solid product formed was collected and crystallized from benzene/EtOH (3:1) to furnish white flakes; yield 0.35 g (81%).

Desmethylsetraline **150** has been transformed into the corresponding carbamoyl chloride **151** by **ethyl chloroformate** in acetonitrile [98].

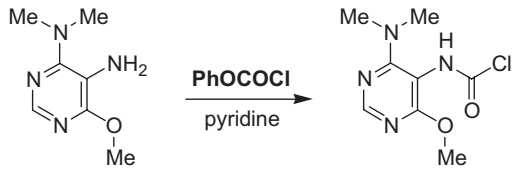


150 **151**

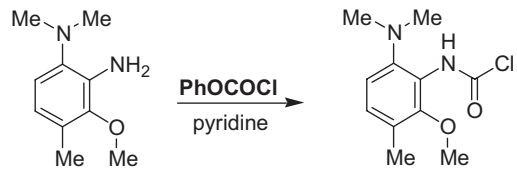
Various carbamoyl chlorides **153**, **155**, and **157** of *ortho*-dimethylamino-substituted anilines **152** and **156** or 6-dimethylamino-5-aminopyrimidine **154** have been prepared with **phenyl chloroformate** [99].



152 **153**

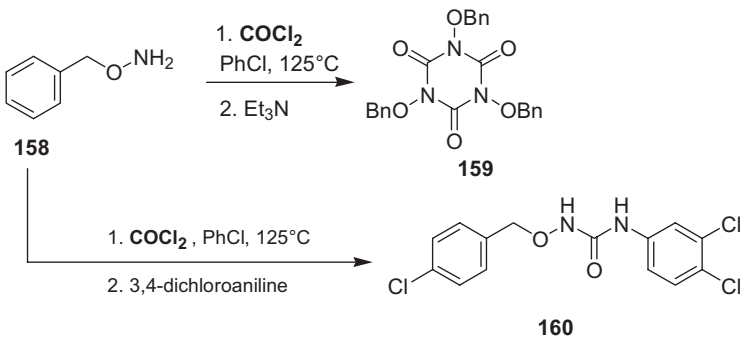


154 **155**

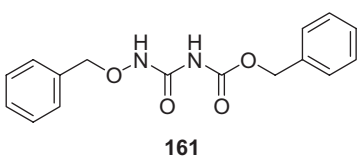


156 **157**

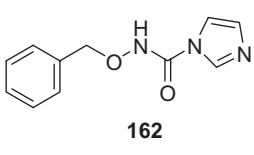
Phosgenation of *O*-benzylhydroxylamine **158** with **phosgene** did not allow the isolation of the desired carbamoyl chloride or the corresponding *N*-benzyloxyurea. More complex transformations occurred depending on the catalyst and conditions. McKay isolated the 1,3,5-tribenzyloxyisocyanuric acid **159** when triethylamine was added to a solution of *benzylhydroxylamine hydrochloride* and **phosgene** in chlorobenzene that had been heated at reflux [100].



In the absence of triethylamine, heating benzylhydroxylamine with **phosgene** under the same conditions, followed by the addition of 3,4-dichloroaniline, gave trichloride **160**; chlorination had occurred under the reaction conditions. Furthermore, it was also found that the reactive intermediate in this process was neither an alkoxy isocyanate nor a chloroformate, but rather the allophanate **161**.

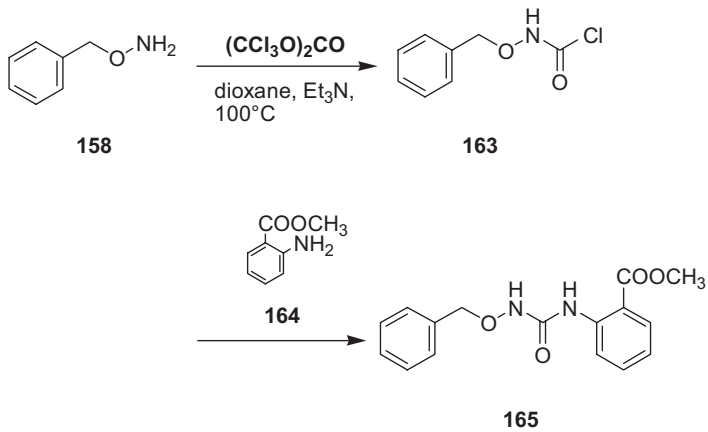


The preparation of *N*-benzyloxyureas *without phosgene* can be accomplished using several coupling agents, including **2(*S*),3-pyridinediyl thiocarbonate** (**PTC**) [101], ***N,N′*-carbonyldiimidazole** (**CDI**) [102, 103], **triphosgene**, **(*p*-nitrophenoxy)carbonyl chloride** [104], and **ethyl chloroformate** [105] (see also Section 4.3 on carbonylation). Experimental studies revealed the imidazolylcarbonyl synthon **162** to be a superior synthetic equivalent [106].



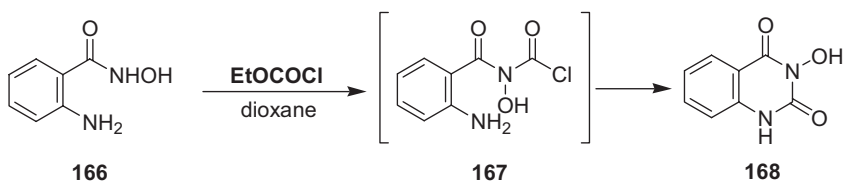
Treating *O*-benzylhydroxylamine **158**, as the free base, with **triphosgene** under nitrogen in dioxane at 100 °C, followed by cannulation of this solution into a mix-

ture of methyl anthranilate and triethylamine, furnished the target benzyloxyurea in 72% yield [106]. These conditions circumvent the complications seen by McKay; the authors reported no evidence of chlorination or isocyanuric acid formation.

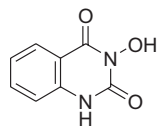
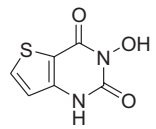
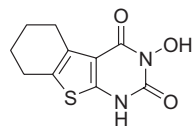
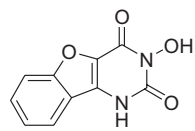


Typical procedure. *N-Benzyloxyureas* **165** *by addition of anthranilate* **164** *to benzyloxycarbamoyl chloride* **163** [106]: **Triphosgene** (600 mg, 2.05 mmol) was added to a solution of *O*-benzylhydroxylamine (500 mg, 4.1 mmol) in anhydrous 1,4-dioxane (25 mL) and, under nitrogen, the reaction flask was immersed in an oil bath heated to 100 °C. After 45 min, the hot solution was cannulated dropwise into a mixture of the anthranilate (3.15 mmol) and Et_3N (12 mL, 12 mmol) at 100 °C. After cooling to 24 °C, the precipitate was filtered off ($Et_3N{\cdot}HCl$), and the filtrate was concentrated. The residual oil was diluted with Et_2O (10 mL), and 1 N anhydrous HCl in Et_2O (10 mL) was added. The resulting HCl salt of unconsumed anthranilate was filtered off, and the filtrate was diluted with EtOAc (50 mL), washed with aq. $NaHCO_3$ (20 mL) and brine (20 mL), and dried (Na_2SO_4). Concentration in vacuo and chromatography of the residue gave *N*-hydroxyureas.

N-Hydroxyureas prepared as described above are valuable intermediates for the synthesis of *N*-hydroxypyrimidinediones **168** by cyclization with one equivalent of potassium *tert*-butoxide in benzene at reflux; yields of 85–95% are obtained (Table 4.5). Alternatively, the latter have been obtained from the *N-o*-aminobenzoylhydroxylamine **166** by chlorocarbonylation and further cyclization [106].

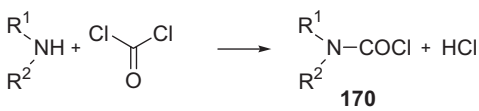


Tab. 4.5. Preparation of 3-hydroxypyrimidine-2,4-diones [106].

Entry	*Yield of BnO-NHCOCl (%)*	*Final product*
1	72	
2	65	
3	59	
4	62	

4.2.2.2 **Reactions with Secondary Amines**

Secondary amines react with **phosgene** to afford carbamoyl chlorides **170** in excellent yields. For example, *tert*-butylbenzylcarbamoyl chloride (R^1 = *tert*-butyl, R^2 = benzyl) can be obtained in 96% yield [107].

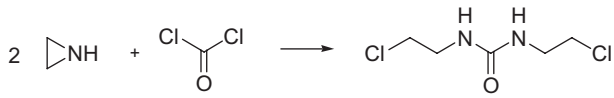


170

Typical procedure. *tert-Butylbenzylamine-N-carbonyl chloride* [107]: A solution of *tert*-butylbenzylamine (48.6 g, 0.3 mol) in toluene (100 mL) was added (over 25 min) to a stirred, ice-cooled solution of **phosgene** (30 g, 0.3 mol) (for a *safe source* and *safety precautions*, see Chapter 7) in toluene (500 mL), while passing in further **phosgene** at a rate of 0.1–0.2 mol/h. The resulting thick suspension was refluxed until clear (100 °C, 16 h) while continuing to add **phosgene**. Evaporation of the volatiles in vacuo afforded a pale-brown to yellow crystalline residue, with a sweet and pungent odor, 66 g (96%), mp 85–89 °C.

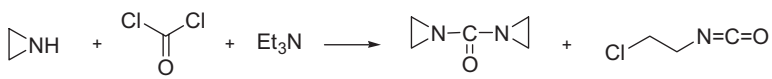
Although most *N*,*N*-dialkylcarbamoyl chlorides are fairly stable, aziridinecarbamoyl chloride has never been isolated [108, 109].

When aziridine **171** is added to an excess of **phosgene**, in the absence of an acid acceptor, *bis(2-chloroethyl)urea* **172** is produced as the major product [109, 110].



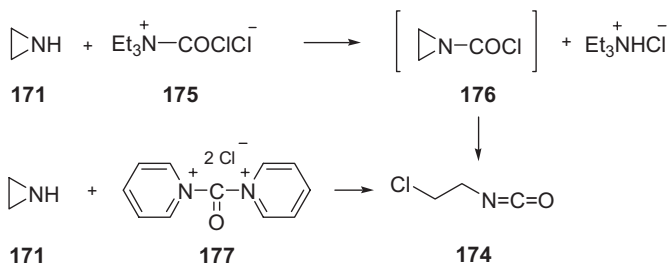
171 **172**

When equivalent amounts of aziridine and triethylamine in tetrachloromethane are added to a solution containing 1 equiv. of **phosgene** at −10 °C, a mixture of *bis(aziridinyl)urea* **173** and *2-chloroethyl isocyanate* **174** is formed, the former being the major product [109].



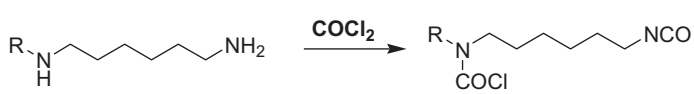
171 **173** **174**

2-Chloroethyl isocyanate **174** is the major product obtained when *aziridine* is allowed to react with an equivalent amount of *1:1 triethylamine*-**phosgene** *complex* **175** [108] or 2:1 *pyridine*-**phosgene** *complex* **177** [109]. *Aziridine carbamoyl chloride* **176** was postulated as a transient intermediate in this reaction. Attempts to trap this elusive species as the triethylammonium or pyridinium salt have been unsuccessful [109].



171 **175** **176** **171** **177** **174**

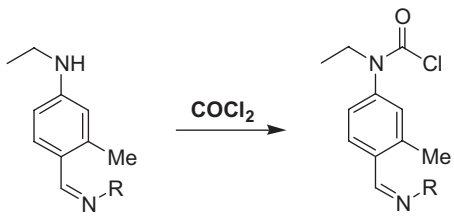
Compounds containing both an isocyanate and a carbamoyl chloride group (for example, **179**) have been prepared by *reacting monoalkyl α,ω-diamines* (for example, **178**) with **phosgene** [111, 112].



178 **179**

High dye-yield linking units having the *N*-alkyl-*N*-aryl carbamoyl chloride structure

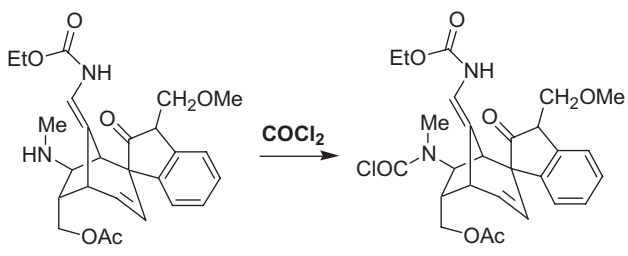
181, obtained by a last-step phosgenation with **phosgene** of protected (as a Schiff base) aryl aminocarbonyl compounds **180**, have recently been described [113].



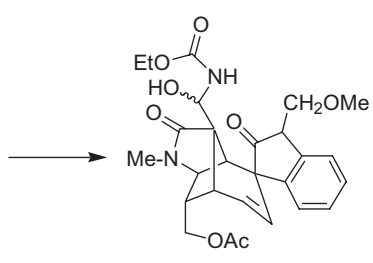
180 **181**

Diferrocenyl amines (which are unexpectedly difficult to derivatize), useful for the preparation of novel diferrocenylamino compounds, including nitrenium salts, amino radicals, transition metal amides, and carbamato ligands, are transformed in a multistep process, with **phosgene**, into the corresponding carbamoyl chlorides [114].

An interesting silver ion mediated lactam formation between the carbamoyl chloride and enecarbamate in **183** has been reported [115]. The starting substrate, **183**, a useful intermediate in the stereocontrolled total synthesis of (+)-Gelsemine, was prepared with **phosgene**.

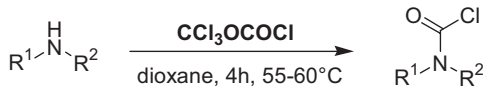


182 **183**



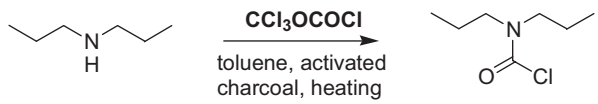
184

Various short-chain dialkylamines (R^1 = Me, Et, R^2 = Me, Et, *i*Pr) **185** react with **diphosgene** in dioxane at 55–60 °C [116] or hexachloroacetone [117] to give the corresponding carbamoyl chlorides **186**.



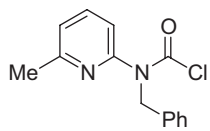
185 **186**

Diphosgene was employed as a phosgene source for the preparation of *diisopropyl* and *di-n-propyl carbamoyl chloride* **188** [118].



187 **188**

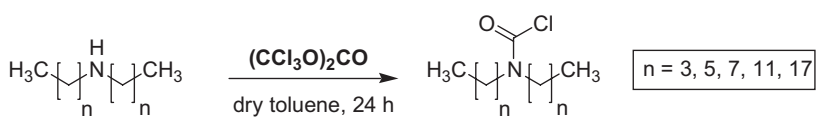
Benzyl (6-methyl-2-pyridinyl)carbamoyl chloride **189** has been used as a useful new reagent for the direct esterification of carboxylic acids and the selective benzoylation of diols at primary OH groups [119]. The reactions were carried out in the presence of Et_3N and DMAP.



189

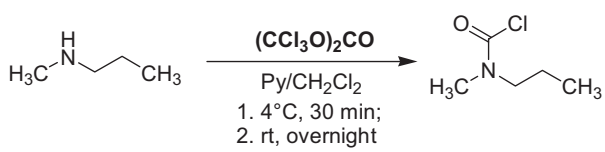
A synthesis of ureas on solid-phase by the formation of *carbamoyl chlorides* from secondary amines and **phosgene** or **triphosgene** has been reported. Intermediate carbamoyl chlorides can be reacted with primary or secondary amines to give urea products in high yield and with high chemical purity [120].

A series of secondary carbamoyl chlorides **191**, each having two chains varying from 4 to 18 carbons in length, has been synthesized with **triphosgene** [121].



190 **191**

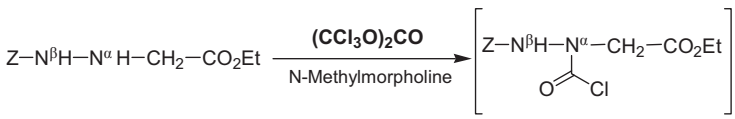
Methyl propyl amine **192** reacts with **triphosgene** in pyridine/dichloromethane to give the corresponding carbamoyl chloride **193** [122].



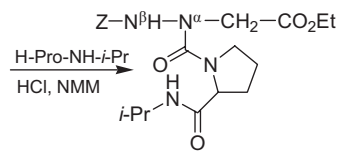
192 **193**

N-Alkyl-*N*-arylcarbamoyl chlorides have been synthesized in >90% yield by the carbamoylation of secondary *N*-alkyl-*N*-arylamines with **triphosgene** for 2–3 h at 0–23 °C in a solvent (benzene, toluene, xylene, or chloroform), and in the presence of an organic base (triethylamine, *N*,*N*-diisopropyl-*N*-ethylamine, or pyridine) [123].

Triphosgene was proposed as a carbonylating agent for coupling the appropriately substituted hydrazide **194** to the proline nitrogen to obtain the AzAsx–Pro or AzAla–Pro aza sequence (Az denotes the N/C$^{\alpha}$H replacement, and Asx stands for asparagine Asn or aspartic acid Asp) [124].

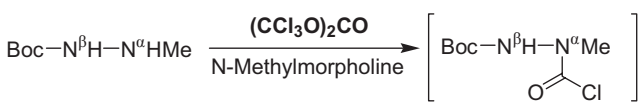


194 **195**

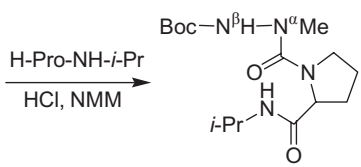


196

Triphosgene reacts with hydrazine ester **194** to give an activated intermediate **195**, probably the carbamoyl chloride, which was not isolated but rapidly coupled to the amino terminus of a peptide to give the desired aza-peptide motif. Coupling of HCl, H-Pro-NH-*i*Pr resulted in the aza-dipeptide **196**, which was transformed into the AzAsn derivatives by the action of ammonia or methylamine. A similar transformation has been observed for Boc-Me hydrazine.



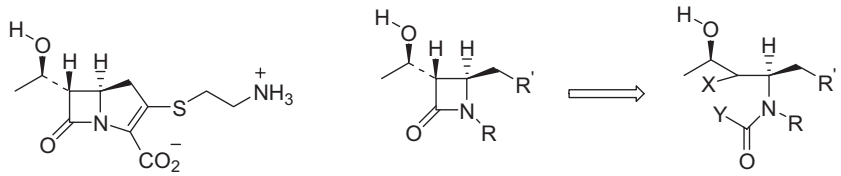
197 **198**



199

A synthetic route to the *β*-lactam moiety in thienamycin **200**, an antibiotic substance produced by *Streptomyces cattleya*, as well as to that in related compounds,

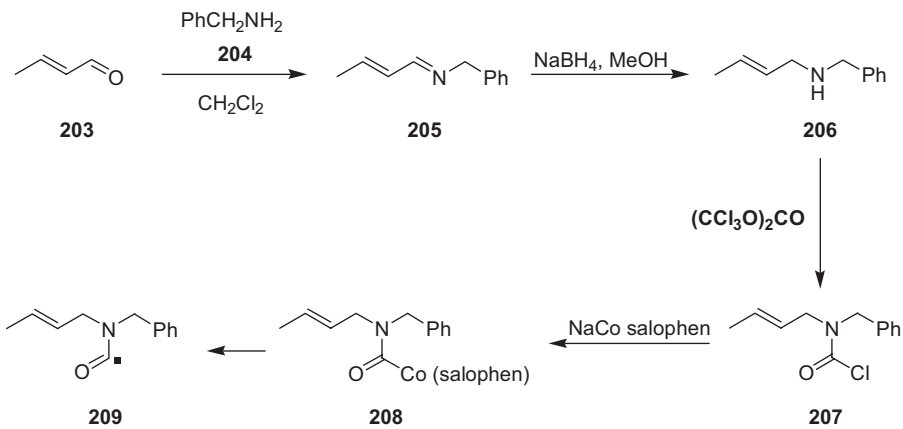
involves a cyclization between the amide carbonyl and C-3 in an acyclic precursor molecule, i.e. disconnection **201** → **202** [125, 126].



200 **201** **202**

An intermediate carbamoyl chloride of type **202** (Y = Cl) has been prepared using **triphosgene**, starting from the imine **205** derived from but-2-enal **203** and benzylamine **204**.

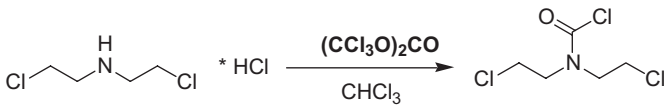
The unsaturated carbamoyl cobalt salophen reagent **208** is a precursor of novel carbamoyl radical intermediates, which undergo facile cyclization to *β*-lactams.



203 **205** **206** **207** **208** **209**

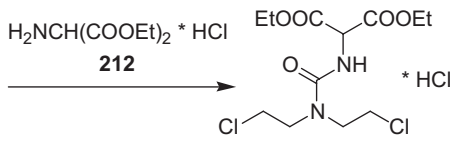
Typical procedure. *N-Benzyl-N-(but-2-enyl)carbamoyl chloride* **207** [126]: A solution of the amine **206** (918 mg, 5.7 mmol) in dry benzene (2 mL) was added dropwise over 0.5 min to a stirred suspension of **triphosgene** (563 mg, 1.9 mmol) and pyridine (450 mg, 5.7 mmol) in dry benzene (30 mL) under an atmosphere of nitrogen. The resulting suspension was stirred under nitrogen for 96 h and then filtered under nitrogen. The filtrate was concentrated to dryness under reduced pressure to leave the carbamoyl chloride (1.27 g, 99.5%) as a yellow liquid.

Carbamoyl chloride **211** of di(2-chloroethyl)amine **210**, a useful intermediate in the preparation of nitrogen mustards and L-phenylalanine mustards as antitumor agents [127], was prepared in 85% yield using **triphosgene** and pyridine as acid scavenger at temperatures below 20 °C [128, 129].



85 %

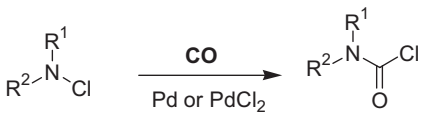
210 **211**



213

Typical procedure. *N,N-Di(2-chloroethyl)carbamoyl chloride* **211** [129]: Under nitrogen atmosphere, *N,N*-di(2-chloroethyl)amine hydrochloride (19.25 g, 0.1 mol) and **triphosgene** (9.98 g, 33 mmol) were stirred in dichloromethane (60 mL), cooled in an ice-bath. A solution of pyridine (25.82 g, 0.2 mol) in dichloromethane (20 mL) was added dropwise at such a rate that the temperature did not exceed 5 °C. The reaction mixture was then allowed to warm to room temperature and was stirred for 3 h. The solvent was then removed in a rotary evaporator, the residue was redissolved in hexane, and the precipitated salt was removed by filtration. The filtrate was rotary evaporated and the remaining liquid was distilled in vacuo to afford 17.44 g (85%) of *N,N-di(2-chloroethyl)carbamoyl chloride* **211**, bp 72 °C (0.1 Torr).

The formation of acid halides from an alkyl halide and **carbon monoxide** in the presence of a Group VIII metal compound is a known process [130]. By analogy, an alternative procedure for preparing carbamoyl chloride by the insertion of **carbon monoxide** into the nitrogen–chlorine bond has been reported [131].



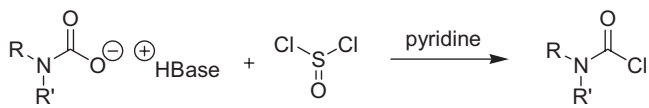
214 **215**

The reaction of chloroamine **214** with carbon monoxide is effectively catalyzed by palladium metal, palladium(II) chloride, or rhodium(III) chloride to produce carbamoyl chloride **215**.

The reaction was carried out in a stainless steel pressure tube (not the best material, since it may catalyze the decomposition of the chloramine or the carbamoyl chloride product) at temperatures below 50 °C for 20 h without stirring or shaking. The yield of dimethyl carbamoyl chloride depends on the reaction temperature, the nature of the solvent, the amount of catalyst, and the carbon monoxide pressure. The reaction still proceeds fairly smoothly under milder conditions. At room temperature in 1,2-dimethoxyethane, a yield of 99% was obtained [131].

The carbonylation reaction can also be applied to various substituted chloramines (*N*-chloro-*N*-methylbenzylamine, *N*-chloropiperidine, *N*-chloromorpholine), but the yields are lower (15–80%). Monochloramine produced *N*-methylcarbamoyl chloride (yield 30%), which was isolated and analyzed as methyl *N*-methylcarbamate.

In analogy to the conversion of carboxylic acids to acyl chlorides, it has been found that *carbamic acid derivatives* **216** can be converted to *carbamoyl chlorides* **218** by chlorination with an electrophilic agent such as **thionyl chloride 217** or **$POCl_3$** [132].



216 **217** **218**

In this case, **carbon dioxide** was used as a carbonyl source and *phosgene substitute*. This reaction was shown to be successful using various bases, including amidines and guanidines (Table 4.6). As was found in the conversion of primary amines to

Tab. 4.6. Conversion[a] of piperidine to piperidine carbamoyl chloride with **CO_2** and a chlorination agent [132].

***Base*[b]**	***Electrophile***	***Solvent***	***Yield of carbamoyl chloride* %[c]**
CyTEG	$POCl_3$	CH_2Cl_2	67
CyTEG	$POCl_3$	Toluene	67
CyTEG	$SOCl_2$	CH_2Cl_2	44
CyTEG	$SOCl_2$	Toluene	72
CyTEG/pyr	$SOCl_2$	Toluene	85
CyTEG/2 pyr	$SOCl_2$	Toluene	87
CyTEG/pyr	$SOCl_2$	CH_2Cl_2	80
CyTMG/pyr	$SOCl_2$	Toluene	79
DBU/pyr	$SOCl_2$	Toluene	89
MTBU/pyr	$SOCl_2$	Toluene	93
$(i\text{-}Pr)_2NEt$/pyr	$SOCl_2$	Toluene	82
Et_3N/pyr	$SOCl_2$	Toluene	45
Piperidine/pyr	$SOCl_2$	Toluene	77
Piperidine/pyr	$SOCl_2$	CH_2Cl_2	75

[a] All reactions run at −10 °C under carbon dioxide at atmospheric pressure; reactions judged to be complete within 15 min;
[b] CyTEG = *N*-cyclohexyl-*N′*,*N′*,*N″*,*N″*-tetraethylguanidine, CyTMG = *N*-cyclohexyl-*N′*,*N′*,*N″*,*N″*-tetramethylguanidine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, MTBU = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene, pyr = pyridine; [c] all yields are GC yields based on biphenyl as internal standard.

isocyanates, the nature of the base is somewhat important, but it is not limited to guanidines and amidines.

Rapid addition of a pre-formed carbamate anion solution (generated from dialkyl amine, *N*-cyclohexyl-*N′*,*N′*,*N″*,*N″*-tetramethylguanidine (1 equiv.), and pyridine (1 equiv.) under a pressure of **carbon dioxide**) to a solution of **thionyl chloride** (1 equiv.) at −10 °C led to an exothermic reaction. Rapid aqueous extraction (to remove salts and "SO_2") of the crude reaction mixture and distillation of the residue gave good isolated yields of the carbamoyl chloride (40–80%). The results obtained using various reagents in this reaction are shown in the table below. It is not yet clear as to why added pyridine improves the yield of carbamoyl chloride (from 72 to 85%). It is possible that pyridine acts as a trap for the sulfur dioxide that is likely to be formed during the course of the reaction.

Typical procedure. *N,N-Dibutyl carbamoyl chloride* [132]: In a 100 mL round-bottomed flask were placed dibutylamine (6.45 g, 0.05 mol), pyridine (4.0 g, 0.05 mol), *N*-cyclohexyl-*N′*,*N′*,*N″*,*N″*-tetraethylguanidine (12.7 g, 0.05 mol), and toluene (40 mL). The resulting solution was cooled to −10 °C using an ice/salt bath and **carbon dioxide** was bubbled into the cooled solution for 30 min. After this period of time, the pre-formed carbamate solution was added in a single portion via a cannula to a cooled (−10 °C) solution of **thionyl chloride** (6 g, 0.05 mol) in toluene (40 mL). The reaction mixture was stirred at −10 °C for 45 min. It was then poured into 0.1 M aq. HCl (100 mL), giving rise to two layers. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and the solvent was removed in vacuo. The residue was distilled in vacuo (1 mmHg) at 95–98 °C to give 7.62 g (79%) of *N,N-dibutyl carbamoyl chloride*.

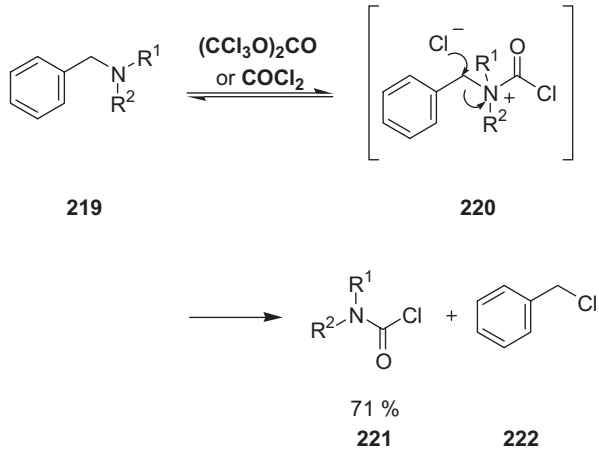
4.2.2.3 Reactions with Tertiary Amines

The reaction between **phosgene** itself and *triethylamine* has been reported to give *diethylcarbamoyl chloride* [133], but, surprisingly enough, when tribenzylamine was used, no C–N bond breaking was observed and no carbamoyl chloride was formed.

It is well established that *N-dealkylation of tertiary amines* can be achieved by reacting them with chloroformate reagents followed by cleavage of the intermediate carbamate [134]. Several *chloroformate reagents* are now available that allow the realization of such transformations, which release the free amine. In analogy with the mechanism proposed for the aforementioned *N*-dealkylation methods, such a direct transformation is possible by replacing the *chloroformate reagent* by a *phosgene substitute*.

A procedure employing **triphosgene** to directly transform *N*-benzyl-protected tertiary amines into *carbamoyl chlorides*, which are versatile intermediates for the direct preparation of amides, ureas, carbamates, and heterocyclic derivatives, has recently been described [135].

Tribenzylamine **219** (R^1, R^2 = Bn) was found to react smoothly with 0.33 equiv. of **triphosgene** in dichloromethane to give 71% of the expected *carbamoyl chloride* together with 27% of recovered starting material.



The reaction most probably proceeds according to the mechanism described for chloroformates. In fact, an equimolar amount of benzyl chloride beside the carbamoyl chloride was obtained in all the reported reactions. The results in Table 4.7 also show that the method is compatible with various functional groups (ketone, ester, amide, unsaturations; entries 1 to 4). However, the presence of a phenyl group on the nitrogen atom seems to inhibit the reaction (entry 5) since, in this particular case, the starting material is entirely recovered. Interestingly enough, the same order of reactivity between benzyl and alkyl groups as with chloroformates is observed (entries 6 and 7): benzyl reacts much more rapidly than ethyl or methyl groups, thus leading to regioselective *N*-debenzylation.

Extension of this method to solid-phase procedures would have the advantage of allowing the removal of benzyl chloride simply by filtration, thus affording polymer-bound carbamoyl chlorides ready for further reactions.

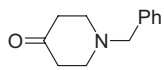
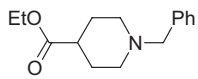
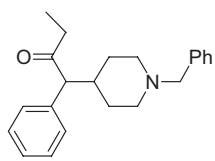
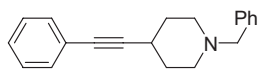
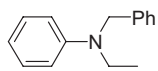
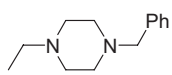
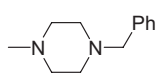
General procedure. *Carbamoyl chlorides* **221** *from tertiary N-benzylamines* **219** [135]: A 0.3 M solution of the *tertiary* benzylamine (1 equiv.) in dichloromethane is added to a 0.1 M solution of **triphosgene** (0.33 equiv.) in dichloromethane at 0 °C under an inert atmosphere. The mixture is then allowed to warm to room temperature and stirred until no further change is seen by TLC. The reaction mixture is then concentrated under reduced pressure and the residue is purified by flash chromatography.

4.2.2.4 Reactions with Amides

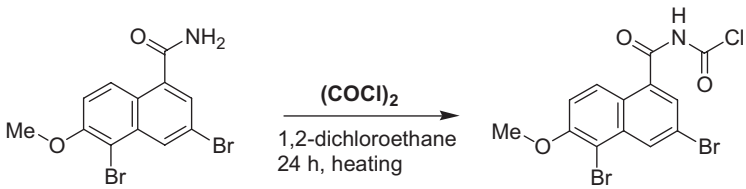
Phosgene and phosgene substitutes, particularly oxalyl chloride, dehydrate amides resulting in various useful phosgene equivalents (see Scheme 4.1). Although dehydration is the most important preparative method when amides are subjected to phosgenation, several accounts of chlorocarbonyl group transfer to amidic nitrogen have also appeared.

Oxalyl chloride has been used for *N*-chlorocarbonylation of the aromatic amide **223** [136].

Tab. 4.7. Transformation of *tert-N*-benzylamines into carbamoyl chlorides [135].

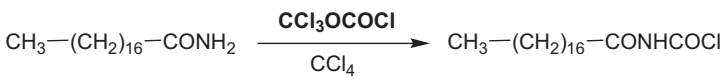
Entry	*Starting compound*	*Reaction time (h)*	*Yield (%)*	*Recovered starting material (%)*
1		7	90	2.5
2		7	70	20
3		6	86	0
4		23	36	26[a]
5		5	0	99
6		24	74	7
7		24	77	13

[a] in this particular case, the low yield can be attributed to product instability



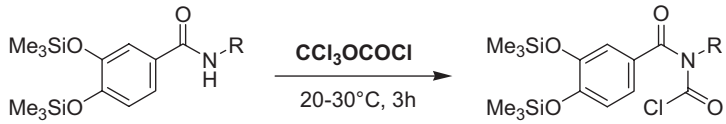
223 **224**

Stearoyl carbamoyl chloride **226** has been obtained from stearamide **225** with **diphosgene** in tetrachloromethane [137].



225 **226**

Diphosgene has been used to prepare carbamoyl chlorides **228** of *N*-substituted 3,4-bis(trimethylsilyloxy)benzamides **227** [138].



227 **228**

R = -CH_3 -$(CH_2)_2CN$
-$(CH_2)_3OH$ -$(CH_2)_2OCH_3$
-$CH_2COOC_2H_5$

4.3 Carbonylation

4.3.1 Isocyanates

4.3.1.1 Introduction

Isocyanates are important commercial precursors for the synthesis of polyurethanes and polyureas. Moreover, they are frequently used as intermediates in the synthesis of biologically active compounds [139, 140].

The most widely utilized method for the synthesis of *isocyanates*, the phosgenation of amines, uses **phosgene** as a reagent.

Isocyanates and *polyisocyanates* are manufactured on a commercial scale by the reaction of gaseous **phosgene** with amines or amine salt precursors [141–143]. As restrictions upon the use of very toxic materials such as **phosgene** and other chlorine-containing compounds within the chemical industry have become more rigorously enforced, there has been increasing interest in developing alternative methods for isocyanate production [144]. Alternative methods, such as the *thermolysis of carbamates (urethanes)*, very often require rather drastic reaction conditions [139, 140].

A unique approach to the synthesis of advanced isocyanate intermediates is the carbonylation of amines with *phosgene equivalents* such as **oxalyl chloride**, **trichloromethyl chloroformate** (**diphosgene**) [146, 251] or **bis(trichloromethyl) carbonate** (**triphosgene**) [53, 147–150]. A variety of phosgene-free syntheses starting from *"non-apriori phosgenated"* isocyanate precursors have also been developed, but many of these methods involving degradation or rearrangements have limitations [152]. The term *non-phosgene* or *phosgene-free route* is primarily used to describe the conversion of amines (or the corresponding nitro precursors) to isocyanates by the use of carboxylation agents (**CO_2** or **CO**) [144].

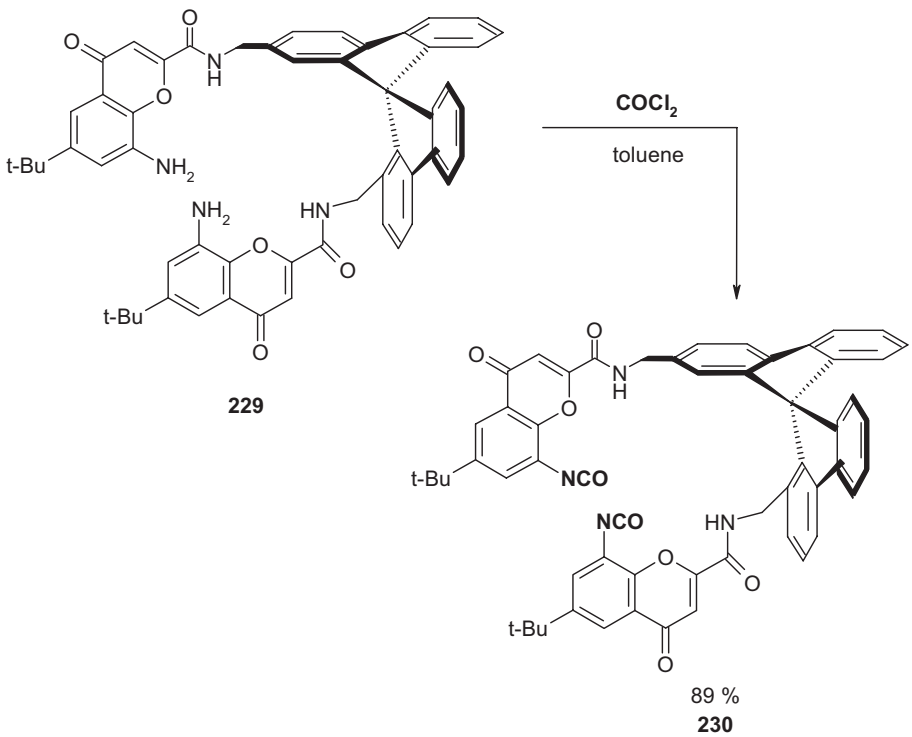
Information on the commercial manufacture of isocyanates or patent literature has been limited. Recently published leading monographs [153–155] cover many aspects of isocyanate synthesis, and therefore we have tried to illustrate only very recent progress in the field. A recently developed technique for ***"safe phosgena-***

tion'' involves the controlled ''depolymerization'' of **triphosgene** and a special catalyst and thus avoids the transportation and storage of phosgene. This method offers a more easy and comfortable handling of phosgene in synthesis [156] (see also Chapter 7).

4.3.1.2 Aromatic Isocyanates

Aryl isocyanates prepared with phosgene

A *macrocyclic receptor* for the chiral recognition of hydroxycarboxylates, such as those of lactic or mandelic acids, has been synthesized from a readily available known bis-chromenylurea and a spirobifluorene linker [157]. The *diisocyanato* intermediate **230** is obtained from the corresponding diamine **229** by carbonylation with **phosgene** in 89% yield.



229 **230**

N-Phenyl-N′-pyridinylureas, which are active as anticonvulsant agents, are prepared via substituted *phenyl isocyanates* by carbonylating the corresponding substituted anilines with **phosgene** [158].

General procedure *for the synthesis of aryl isocyanates* [158]: A refluxing solution of the substituted aniline (0.1 mol) in toluene (100 mL) was saturated with HCl (g). **Phosgene** (for a *safe source* and *safety precautions*, see Chapter 7) was then passed through the mixture until a clear solution was obtained. Careful removal of the toluene by distillation resulted in isolation of the desired *isocyanate*.

A procedure for the synthesis of of *4,4′-diphenylmethane diisocyanate* **264** using **phosgene** has been described [145].

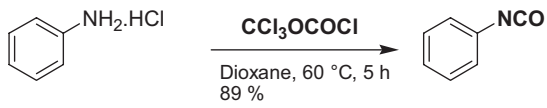
Typical procedure. *4,4′-Diphenylmethane diisocyanate:* **Phosgene** (800 g, 8 mol) (for a *safe source*, see Chapter 7) was dissolved in *o*-dichlorobenzene (2000 mL), and the resulting solution was cooled in an ice-salt bath. To the stirred solution, a hot solution of 4,4′-diaminodiphenylmethane (200 g, 1.01 mol) in *o*-dichlorobenzene (1000 mL) was slowly added through a heated dropping funnel. The rate of addition was regulated so that the temperature of the phosgene solution did not rise substantially above 0 °C. The fine suspension that resulted was slowly heated and additional phosgene (700 g, 7.1 mol) was added at 130 °C until a clear solution appeared. After purging with carbon dioxide, the solvent was removed in vacuo and the product was purified by vacuum distillation. At 156–158 °C (0.1 mmHg), 215 g (0.85 mol, 84%) of *4,4′-diphenylmethane diisocyanate* was obtained.

Several procedures for the preparation of isocyanates with phosgene have been described [153, 159, 160]. Nevertheless, many of them require the delivery of gaseous phosgene from an external source, such as a pressurized cylinder.

Aryl isocyanates prepared with diphosgene

The reaction of **diphosgene** with aniline [161] was carried out under conditions similar to those employed in the phosgene method.

Phenyl isocyanate was obtained in high yields (78–89%) either from the hydrochloride or the free base. It was also confirmed that 0.5 mol of **diphosgene** is sufficient to convert 1 mol of the amine to the isocyanate.

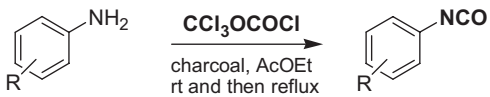


231 **232**

Aryl diamines gave poorer results. Treatment of *p*-phenylenediamine hydrochloride with **diphosgene** in dioxane gave only poor yields (23% or less) of the *diisocyanate*, even though the reaction was carried out under almost the same conditions as used with phosgene. When the free base was used instead of the hydrochloride, the yield of the diisocyanate was improved to 47%.

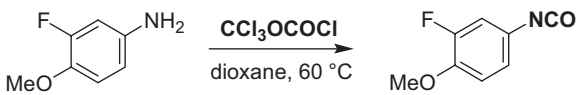
Typical procedure. *Phenyl isocyanate* [161]: To a mixture of aniline hydrochloride (12.95 g, 0.1 mol) and dry dioxane (100 mL) was added **diphosgene** (6.3 mL, 10.4 g, 0.05 mol). The mixture was heated to 60 °C; after stirring for 1.5 h, it became a clear solution. Heating was stopped after 3.5 h and the solvent was removed under reduced pressure. The residue was distilled at 70–73.5 °C (36 mmHg) to give 10.6 g (89%) of *phenyl isocyanate*. It could be redistilled almost quantitatively, bp 75–77 °C (39 mmHg) or 55–57 °C (16 mmHg).

Several *monosubstituted aryl isocyanates* **234** have been prepared from the corresponding anilines **233** with **diphosgene** in presence of *charcoal* [162, 163].

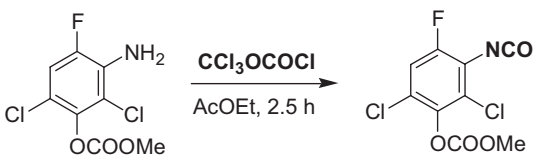


233 **234**

Polysubstituted aryl isocyanates **236** and **238** were obtained with **diphosgene** in dioxane, ethyl acetate, or toluene from 3-fluoro-4-methoxyaniline **235** [164] and 3-amino-2,6-dichloro-4-fluorophenyl methyl carbonate **237** [165], respectively. Table 4.8 summarizes the reported substituted aryl isocyanate preparations with **diphosgene**.



235 **236**



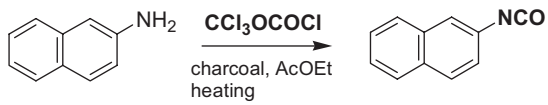
237 **238**

Tab. 4.8. Substituted aryl isocyanates prepared with **diphosgene**.

R in 234	*Reaction conditions*	*References*
H	EtOAc, charcoal, heating	162, 166, 167
	Dioxane, heating	168
2-Me, 3-Me, 4-Me, 2-Et	EtOAc, charcoal, heating	162, 167
	EtOAc, 1) 40–50 °C 1 h, 2) 80 °C, 2 h	169
3,5-dimethyl, 2,4,6-trimethyl	Charcoal, EtOAc, heating	167
	EtOAc, 1) 40–50 °C 1 h, 2) 80 °C, 2 h	169
3-F, 3-Cl, 4-Cl	Dioxane, heating	168
4-F, 4-Cl, 4-Br, 4-I	EtOAc, charcoal, heating	162
2-I, 3-I, 4-I	Charcoal, EtOAc, rt and reflux	163
4-COOEt	EtOAc, 1) 40–50 °C 1 h, 2) 80 °C, 2 h	169
3-Ac, 4-Ac	EtOAc, charcoal, heating	167
2-CF_3, 3-CF_3, 4-CF_3	EtOAc, charcoal, heating	162
	Dioxane, heating	168
4-NMe_2	EtOAc, charcoal, heating	162
4-OCF_3	EtOAc, charcoal, heating	162
4-allyloxy	1,2-DCE, 70 °C, 1 h, 89%	170
4-NH_2	Dioxane	161
	product: 1,4-diisocyanato-benzene	
2-COOH	Dioxane, PCl_5	161
	product: 2-isocyanato-benzoyl chloride	

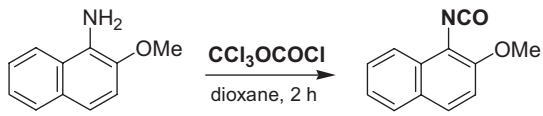
4-(Allyloxy)phenyl isocyanate was synthesized in 89% yield by the reaction of 4-(allyloxy)aniline and **trichloromethyl chloroformate** [171] in ethylene dichloride at 70 °C for 1 h.

2-Isocyanato-naphthalene **240** has been prepared from 2-aminonaphthalene **239** with **diphosgene** and **charcoal** in ethyl acetate [162].



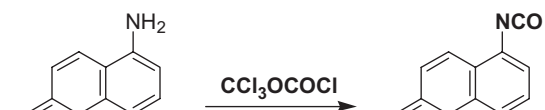
239 **240**

2-Methoxynaphthyl-1-isocyanate **242** was prepared by phosgenating the amine **241** with **diphosgene** in dioxane [172].

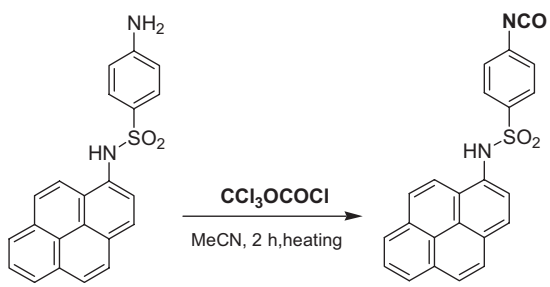


241 **242**

Pyren-1-yl isocyanate **244** and *4-isocyanato-N-pyren-1-yl-benzenesulfonamide* **246** were prepared from the corresponding amines **243** and **245** with **diphosgene** by heating in benzene [173].

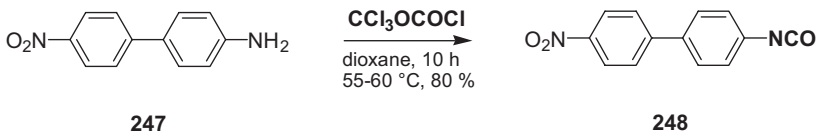


243 **244**

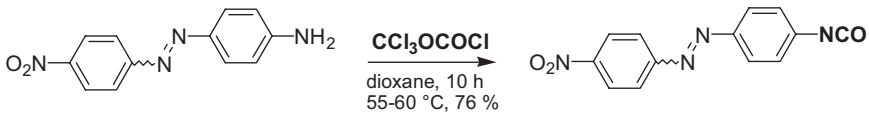


245 **246**

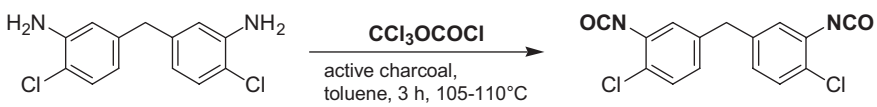
Various substituted *diphenyl diisocyanates* **248**, **250** [174], and *diphenylmethane diisocyanates* **252**, **254**, and **256** [175, 176] have been prepared with **diphosgene**.



247 **248**

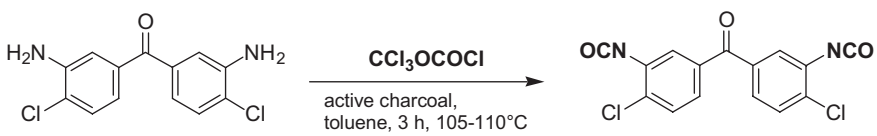


249 **250**



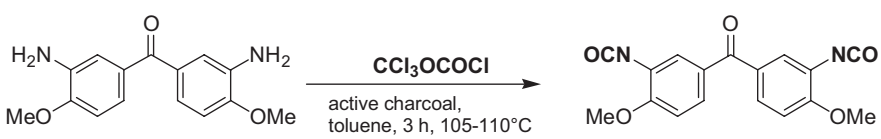
89.4 %

251 **252**



85.6 %

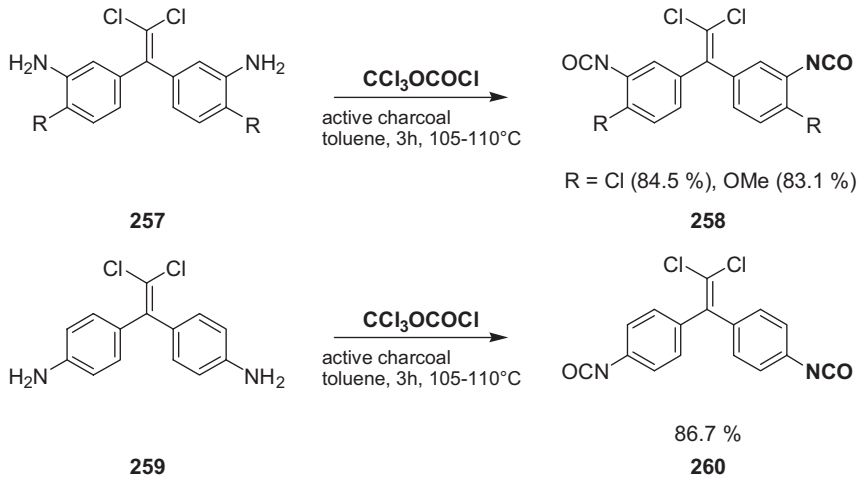
253 **254**



83.3 %

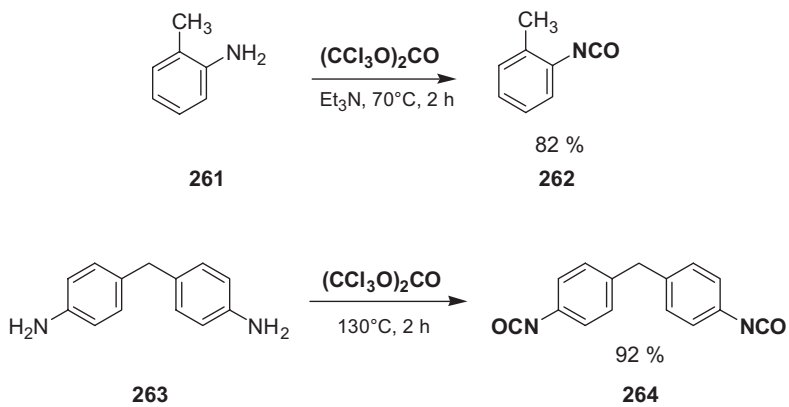
255 **256**

Diisocyanates **258** and **260**, obtained from 1,1-bis(3-amino-4-substituted-phenyl)-2,2-dichloroethenes **257** and from 1,1-bis(4-aminophenyl)-2,2-dichloroethene **259**, respectively, were also prepared with **diphosgene** [175, 176].



Aryl isocyanates prepared with triphosgene

Triphosgene is used as a carbonylating agent in the synthesis of *2-tolyl isocyanate* **262** and in the synthesis of *4,4′-diphenylmethane diisocyanate (MDI)* **264** from the corresponding diamine in high yield (92%) [53].

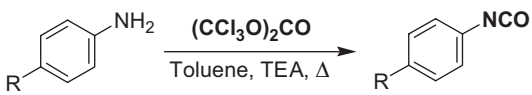


Typical procedure. *4,4′-Diphenylmethane diisocyanate* **264** [53, 177]: A solution of 4,4′-diaminodiphenylmethane **263** (5.95 g, 30 mmol) in 1,2-dichlorobenzene (150 mL) was slowly added dropwise to a solution of **triphosgene** (5.94 g, 20 mmol) in 1,2-dichlorobenzene (20 mL). The mixture was heated to 130 °C for 2 h and then to 180 °C for 1 h. The crude product was purified by fractional distillation in vacuo, after distillation of the solvent fraction, affording 6.91 g (92%) of *4,4′-diphenylmethane diisocyanate*; bp 142 °C (0.05 Torr), mp 37 °C.

4-Substituted phenyl isocyanates **266** have been prepared from the corresponding anilines **265** and **triphosgene** (Table 4.9) [149–151, 178].

Tab. 4.9. 4-Substituted phenyl isocyanates prepared with **triphosgene** [178].

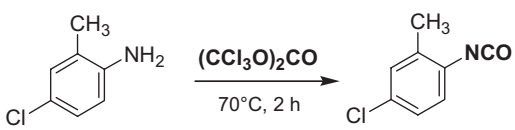
R (265, 266)	*Yield (%)*	*4-Substituent*	*Yield (%)*
H	50.4	-O-$(CH_2)_4CH_3$	51.0
-Me	67.7	-I	45.2
-Et	50.7	-COOMe	63.0
-*n*Pr	46.6	-COOEt	72.5
-*i*Pr	66.2	-COO*i*Bu	47.7
-*n*Bu	55.0	-COO*n*Bu	48.0
-OEt	67.5	-CN	66.0
-O*n*Bu	65.5	4-Tolyloxy	39.0
-OBn	39.0	4-Chlorophenoxy	45.0



265 **266**

Typical procedure. *4-Iodophenyl isocyanate* **266** (R = I) [178]: To a solution of **triphosgene** (3.0 g, 10 mmol) and triethylamine (2.02 g, 20 mmol) in dry benzene (30 mL), a solution of 4-iodoaniline (4.3 g, 20 mmol) in dry benzene (15 mL) was added over 20 min. During the course of the addition, the temperature of the reaction mixture was increased from ambient to reflux temperature. After refluxing for 3 h, the reaction mixture was filtered. The filtrate was concentrated to obtain a residue, which was subjected to distillation under reduced pressure to afford a colorless liquid. Yield 2.21 g (45.2%).

4-Chloro-2-methylphenyl isocyanate **268** was prepared in dioxane at 100 °C [180] and at 70 °C in toluene in 68% yield [53].

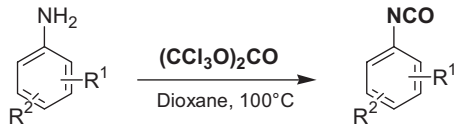


267 **268**

Various *substituted phenyl isocyanates* **270** [179, 180], i.e. 2,3-dichloro-, 2,5-dichloro-, 2,6-dichloro-, 2-bromo-4-methyl-, 2,4-dibromo-, 4-chloro-2-phenoxy-, 4-butyloxy-2-chloro-, 4-chloro-2-(4-chlorophenoxy)-, 4-chloro-2-(4-chlorophenylsulfanyl)-, 4-chloro-2-[2]naphthyloxy-, 2-chloro-4-(4-chlorophenoxy)-, 2-chloro-4-trifluoromethoxy-, 2-chloro-4-phenoxy-, 2-chloro-4-decyloxy-, 2-chloro-4-(4-chlorophenylsulfanyl)-, 2-(4-bromophenylsulfanyl)-4-chloro-, 2,4-bis(4-chlorophenylsulfanyl)-, and 2-chloro-4-methoxy-, have been prepared with **triphosgene** in dioxane at 100 °C starting from the corresponding anilines **269** [180].

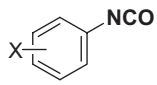
Tab. 4.10. Fluoro- and chlorophenyl isocyanates **271** prepared with **triphosgene** [179].

Substituent X in 271	*Yield (%)*
3-F	29
2-F	32
3-CF_3	42
4-Cl	36
3-Cl	69
2-Cl	54
4-F	38



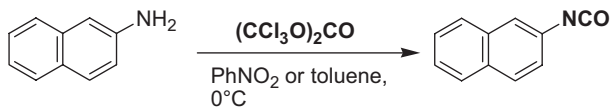
269 **270**

Fluoro- and chloro-substituted phenyl isocyanates **271** have been prepared by heating the anilines with **triphosgene** and triethylamine either in benzene [179] (Table 4.10) or in dichloromethane [181].

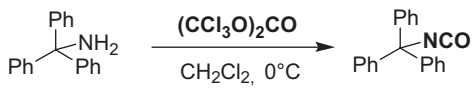


271

Ureas from DL-α-methyltryptophan were obtained by coupling the amino group with *4-chlorophenyl isocyanate*, *2-naphthyl isocyanate* **273**, or *triphenylmethyl isocyanate* **275**, the latter two intermediates being prepared from the corresponding amines and **triphosgene** [182].



272 **273**

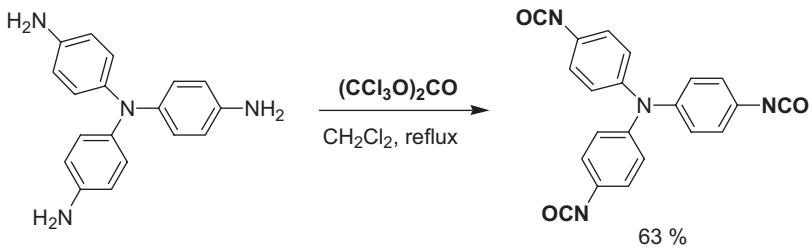


274 **275**

Typical procedure. *Triphenylmethyl isocyanate* **275** [182]: To a solution of **triphosgene** (1.10 g, 3.70 mmol) in dry dichloromethane (15 mL) was added a solution of tri-

phenylmethylamine (2.50 g, 10.0 mmol) and triethylamine (3.84 g, 37.9 mmol) in dichloromethane (10 mL) at 0 °C. After stirring at ambient temperature for 2 h, the organic solvent was removed, EtOAc was added to the residue, and the mixture was filtered. Evaporation of the organic solvent from the filtrate yielded the isocyanate quantitatively (2.85 g).

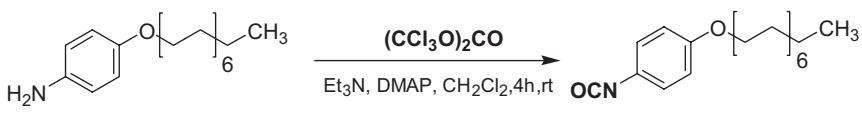
The preparation of *tris(p-isocyanatophenyl)amine* with **triphosgene** has also been reported [183].



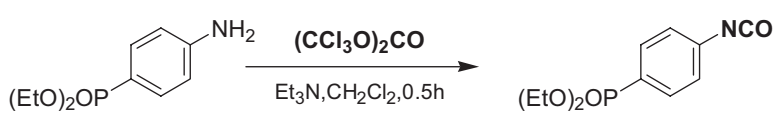
276 **277**

Typical procedure. *Tris(p-isocyanatophenyl)amine* **277** [183]: To a refluxing solution of **triphosgene** in 1,2-dichloroethane, a solution of tris(*p*-aminophenyl)amine in 1,2-dichloroethane was added dropwise and the mixture was heated to reflux under dry nitrogen. *Tris(p-isocyanatophenyl)amine* was obtained in 63% yield after purification by recrystallization from diethyl ether; mp 148 °C.

1-(4-Isocyanatophenoxy)tetradecane **279** [184] and *(4-isocyanatophenyl)phosphonic acid diethyl ester* **281** [185] were prepared with **triphosgene** and triethylamine in dichloromethane.

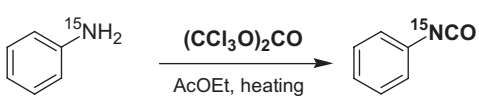


278 **279**



280 **281**

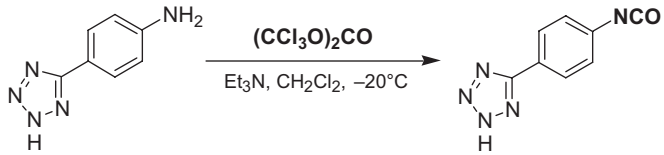
^{15}N-Phenyl isocyanate **283** was prepared in 76% yield by heating the ^{15}N-labeled aniline **282** with **triphosgene** in ethyl acetate [186].



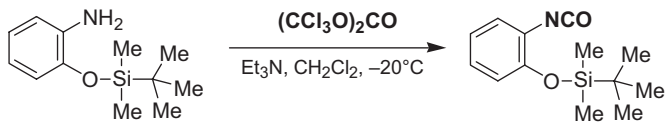
76 %

282 **283**

Triphosgene was used as carbonylating agent to obtain *5-(4-isocyanatophenyl)-2H-tetrazole* **285** and *2-(tert-butyldimethylsilyloxy)phenyl isocyanate* **287** [187].

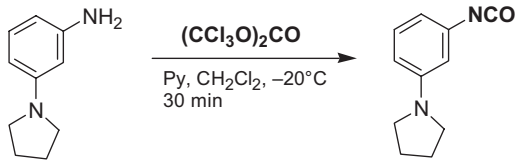


284 **285**



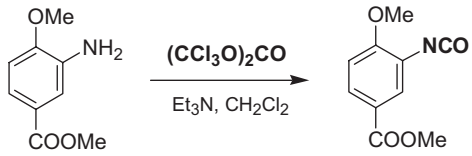
286 **287**

3-Isocyanato-phenyl-pyrrolidine **289** was prepared with **triphosgene** and pyridine at −20 °C in dichloromethane [188].

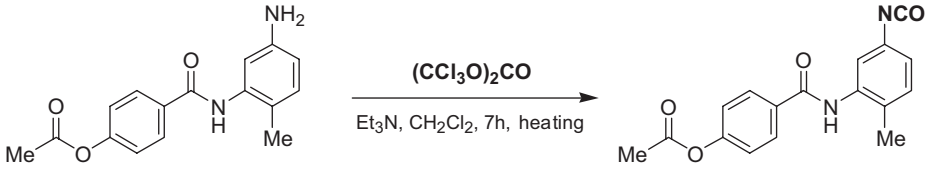


288 **289**

3-Isocyanato-4-methoxybenzoic acid methyl ester **291** [189] and *acetic acid 4-(5-isocyanato-2-methyl-phenylcarbamoyl)phenyl ester* **293** [190] were prepared by heating the corresponding amines **290** and **292**, respectively, with **triphosgene** and triethylamine in dichloromethane.

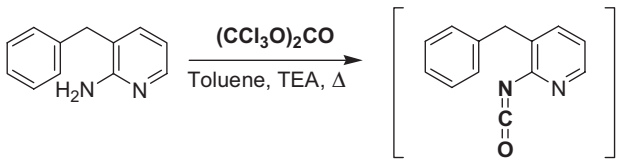


290 **291**

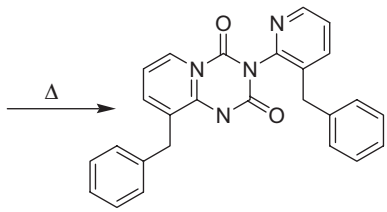


292 **293**

2-Amino-3-benzylpyridine **294** reacts with **triphosgene** to give *2-isocyanato-3-benzylpyridine* **295**. Dimerization/cyclization of this isocyanate intermediate gave 5-benzyl-3-(3-benzyl-2-pyridyl)pyrido[1,2-*a*][1,3,5]triazine-1,3-dione **296** [191].



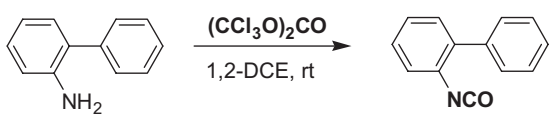
294 **295**



296

Typical procedure. *5-Benzyl-3-(3-benzyl-2-pyridyl)pyrido[1,2-a][1,3,5]triazine-1,3-dione* **296** [191]: To a solution of 2-amino-3-benzylpyridine (0.37 g, 2 mmol) and **triphosgene** (0.20 g, 0.67 mmol) in toluene (10 mL) was added triethylamine (0.40 g, 4 mmol) and the mixture was refluxed for 2.5 h. The cooled mixture was filtered, the filtrate was concentrated in vacuo, and the oily residue was purified by chromatography on silica gel ($CHCl_3$/acetone, 85:15). Evaporation of the solvent from the appropriate fraction left a fluorescent oil, which crystallized on adding petroleum ether to afford **296** as a colorless powder; yield 0.16 g (38%), mp 245–246 °C.

2-Isocyanato-biphenyl **298** was prepared from the corresponding amine **297** and **triphosgene** in 51% yield at ambient temperature in 1,2-dichloroethane [192].

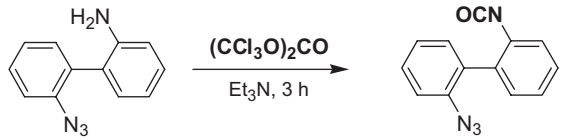


297 **298**

Typical procedure. *2-Isocyanato-biphenyl* **298** [192]: A solution of **triphosgene** (1.48 g, 5 mmol) in 1,2-dichloroethane (20 mL) was slowly added to a stirred solution of *o*-aminobiphenyl (2.55 g, 15 mmol) in 1,2-dichloroethane (50 mL) at room temperature. The reaction is slightly exothermic and the temperature increased to 30 °C. The reaction mixture was then stirred at room temperature for a further 2 h, filtered, and the solvent was evaporated to afford a deep-brown oil (2.4 g). Column

chromatography (SiO_2, CH_2Cl_2/light petroleum, 70:30) afforded **298** as a slightly yellow oil (1.5 g, 51%).

Azido-2′-isocyanatobiphenyl has been prepared in 57% yield with **triphosgene** and triethylamine in benzene [193].

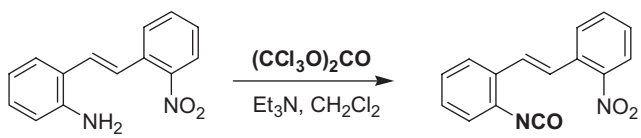


57 %

300 **301**

Typical procedure. *Azido-2′-isocyanatobiphenyl* **301** [193]: Triethylamine (1.0 g, 9.84 mmol) and **triphosgene** (0.33 g, 1.1 mmol) were added to a solution of 2-amino-2′-azidobiphenyl (0.69 g, 3.28 mmol) in dry benzene (45 mL). The reaction mixture was heated under nitrogen at reflux temperature for 3 h. The solvent was then removed under reduced pressure, and the residual material was chromatographed (silica gel; *n*-hexane/dichloromethane, 1:1) to give *azido-2′-isocyanatobiphenyl* in 57% yield.

The isocyanate from 2-amino 2′-nitrostilbene was prepared with **triphosgene** and triethylamine in dichloromethane [194].



302 **303**

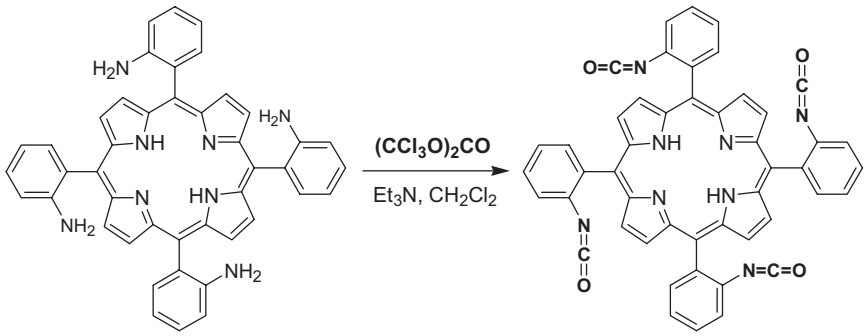
Porphyrin isocyanates prepared with triphosgene

Isocyanate and isothiocyanate precursors have been extensively used in the preparation of peptide analogues and other bioactive compounds. There are a few isolated examples of urea-functionalized porphyrins. No general method has been reported for the construction of urea-linked superstructured porphyrins.

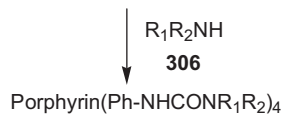
The critical discovery [195] was that, under mild conditions, **triphosgene** can be used to convert the four amino groups of 4.0-tetrakis(*o*-aminophenyl)porphyrin (4.0-TAPP) to isocyanato groups. This generates the useful new intermediate, α,α,α,α-tetrakis(*o*-isocyanatophenyl)porphyrin (4.0-TIPP), which can be derivatized with an almost unlimited range of functional groups, giving the freedom to prepare sophisticated superstructures that may more accurately mimic natural heme-protein structures.

Any aminoporphyrin may be used. For example, reaction of α,α,α,α-tetrakis(*o*-aminophenyl)porphyrin (4.0-TAPP, **304**) (1.0 mmol) with 4/3 equiv. of **triphosgene**

and 8 equiv. of triethylamine at 0 °C in dichloromethane (200 mL) gives α,α,α,α-*tetrakis(o-isocyanatophenyl)porphyrin* **305** (4.0-TIPP). The product shows a strong IR band at 2260 cm^{-1}, indicating the presence of the cumulative double bond of N=C=O rather than of a carbamoyl chloride.



4.0-TAPP, 304 **4.0-TIPP, 305**



307

Further reactions with nucleophiles are best carried out by a one-pot protocol, without isolating the isocyanate intermediate.

Typical procedure, as exemplified by the preparation of **307b** [195]: To a stirred solution of 4.0-TAPP (67 mg, 0.10 mmol) and triethylamine (89 mg, 0.88 mmol) in dichloromethane (50 mL) under N_2 was added **triphosgene** (39 mg, 0.13 mmol). The reaction mixture was stirred at room temperature for 1 h, and then piperidine (43 mg, 0.50 mmol) was added and stirring was continued for a further 1 h. The solvent was removed in a rotary evaporator, and the residue was chromatographed on silica gel (eluent: MeOH/CH_2Cl_2, 1:100) to give **307b** (94%).

As shown in Table 4.11, the reactions of various aliphatic amines with TIPP gave, in consistently high yields, superstructured porphyrins having a variety of interesting properties. Entries 4 and 5 show that amine addition reactions occur selectively in competition with other nucleophilic functional groups such as imidazole or carboxyl. The multifunctional amino compounds histamine and alanine undergo clean amine addition to afford the urea-functionalized porphyrins **307d** and **307e**, which feature cation- and anion-binding pocket superstructures, respectively. Alanine and its sodium salt gave poor yields under standard conditions due to their low solubilities in dichloromethane. Under optimized conditions, alanine sodium salt is reacted with TIPP in THF in the presence of a catalytic amount of tetrabutylammonium bromide. Other nucleophiles, such as phenolate and alcoholate, also react with isocyanate intermediates to give carbamate-functionalized

Tab. 4.11. Urea-functionalized porphyrins[A] [195].

Entry	*R_1 in 307*	*R_2 in 307*	*307*	*Yield[b] (%)*
1	$PhCH(CH_3)$	H	**307a**	96
2	R_1R_2NH = piperidine		**307b**	94
3	*i*Pr	H	**307c**	91
4	$ImCH_2CH_2$	H	**307d**	92
5[c]	$HO_2CCH(CH_3)$	H	**307e**	89
6[d]	Ph	H	**307f**	66

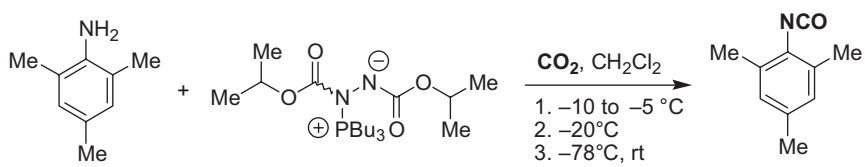
[a] Reaction conditions, see *the typical procedure* below, [b] isolated yield, [c] the reaction was carried out using alanine sodium salt (4 equiv.) and $(n\text{-Bu})_4NBr$ (0.3 equiv.) in THF, [d] 10 equiv. aniline was used, and the reaction time was 24 h.

porphyrins. In these cases, the carbamate groups serve not only as structural linkers but also as protective groups that may be removed subsequently.

Aryl isocyanates prepared with dialkyl azodicarboxylate, carbon dioxide, and phosphines

A very mild method for the preparation of isocyanates from primary amines (RNH_2) and **carbon dioxide** ($\mathbf{CO_2}$) involves the use of a *Mitsunobu zwitterion* generated from either **diisopropyl azodicarboxylate** (**DIAD**) or di-*tert*-butyl azodicarboxylate and triphenylphosphine or tri-*n*-butylphosphine.

2-Isocyanato-1,3,5-trimethylbenzene **310** was prepared from 1,3,5-trimethylaniline **308** and $\mathbf{CO_2}$ in the presence of **DIAD** and **triphenyl**- or **tributylphosphine** [196].



308 **309** **310**

High yields of several isocyanates from hindered aromatic amines can also be obtained, but only when the zwitterion generated from Bu_3P is used (Table 4.12) [196, 197].

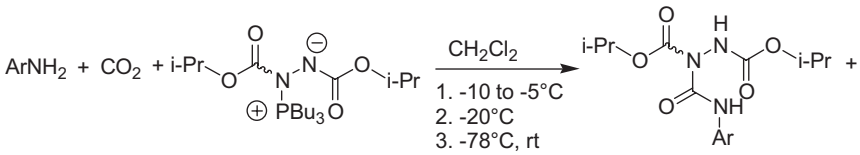
General procedure *for the synthesis of isocyanates* with dialkyl azodicarboxylate, carbon dioxide, and triphosphines [196]: At −10 to −5 °C, anaerobic grade $\mathbf{CO_2}$ was gently bubbled through a solution of the freshly distilled amine in dichloromethane. More $\mathbf{CO_2}$ was then vigorously bubbled through the solution for 30–60 min. In a separate flask, a stirred, cold (−20 °C) solution of $\mathbf{PPh_3}$ in dichloromethane was treated with **DIAD** or **di-*tert*-butyl azodicarboxylate**. The ratio of amine, phosphine,

Tab. 4.12. Hindered aryl isocyanates prepared by the *Mitsunobu method* [196].

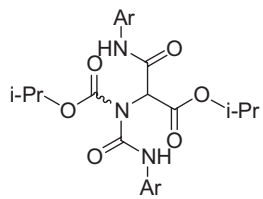
Amine R	*Isocyanate yield (%)*[a]	*Isocyanate isolated yield (%)*
2,4,6-$Me_3C_6H_2$	100	92
2,6-$Et_2C_6H_3$	80	75
2-Et-6-MeC_6H_3	77	72
2,6-*i*$Pr_2C_6H_3$	100	89
2,4,6-trimethylbenzene-1,3-diamine	68	65
4,4′-methylenebis(2,6-dimethylaniline)	84	81
2-*i*PrC_6H_4	<2	[b]
C_6H_5	<2	[c]

[a] Estimated by infrared spectroscopy; [b] A mixture of three products including carbamoylhydrazine (**311**; Ar = 2-*i*PrC_6H_4), dicarbamoylhydrazine (**312**; Ar = 2-*i*PrC_6H_4), and symmetrical urea was formed; [c] A mixture of the carbamoylhydrazine (**311**; Ar = Ph) and dicarbamoylhydrazine (**312**; Ar = Ph) was formed.

and dialkyl azodicarboxylate was 1:1.2:1.2. Both reaction vessels were cooled to −78 °C prior to cannulation of the zwitterion solution into the carbamate salt solution. The reaction mixture was allowed to slowly warm to room temperature over a period of 30–60 min while maintaining a steady stream of CO_2. The mixture was then stirred overnight under 1 atm of CO_2. IR analysis of the solution obtained, made up to a specific volume with dichloromethane, was used to determine the yield of in situ produced isocyanate. The isocyanates were isolated by either fractional distillation or column chromatography. In reactions employing PBu_3 in place of PPh_3, an equimolar ratio of amine, PBu_3, and DIAD was used, and the reaction mixture was worked-up as soon as it reached ambient temperature.



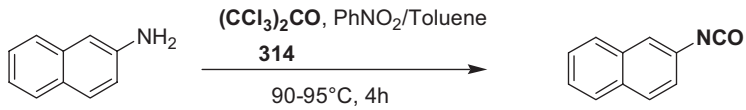
311



312

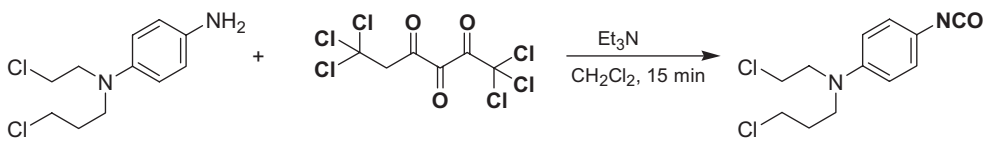
1,4-Diisocyanatobenzene was prepared by a multi-step reaction from the corresponding amine by first treating it with **CO_2** in the presence of triethylamine and *N*-cyclohexyl-*N*′,*N*″,*N*″,*N*″-tetraethylguanidine in acetonitrile at 80 psi, and then with $POCl_3$ in acetonitrile [198].

Aryl isocyanates prepared with hexachloroacetone and hexachloropentane-2,3,4-trione
2-Aminonaphthalene **313** reacts with **1,1,1,3,3,3-hexachloropropan-2-one** (**hexachloroacetone**) **314** in a mixture of nitrobenzene and toluene to form *2-isocyanatonaphthalene* **315** [199].



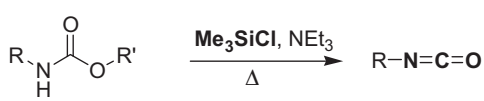
313 **315**

4-[*N*,*N*-Bis(2-chloroethyl)]-*p*-phenylenediamine **316** reacts with **1,1,1,5,5,5-hexachloropentane-2,3,4-trione 317** in dichloromethane to form the corresponding isocyanate **318** [200].



316 **317** **318**

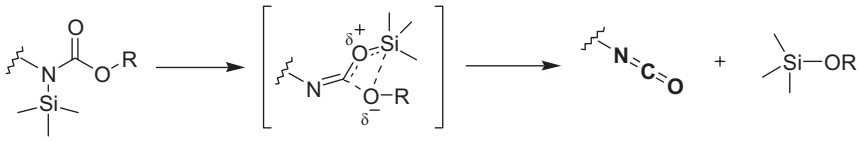
Halosilanes for conversion of carbamate to ureas via isocyanates
About 30 years ago, Greber and Kricheldorf [201] found that **trimethylchlorosilane** promotes the conversion of carbamates **319** into isocyanates **320**.



319 **320**

Subsequent work by Pirkle and co-workers demonstrated that **highly chlorinated silanes** are even more effective at inducing this transformation [202–204]. Recently, a systematic study of the reaction of carbamates with various chlorosilanes has been reported [205]. It was found that, in general, the silane reactivity increases in the order $Me_3SiCl < Me_2SiCl_2 < MeSiCl_3 < HSiCl_3$. Moreover, steric hindrance at the reaction center slows down the reaction, and, with *N*-Boc carbamates, isocyanate production is quite sluggish. In the cases involving *O*-alkyl carbamates, the reactions normally need to be conducted between room temperature and 70 °C.

It is believed that the transformation probably involves an initial *N*-silylated carbamate **321**, which presumably collapses via **322** to the *isocyanate* **323** and a stable alkoxysilane **324**, thereby preventing readdition of the alcohol to **323**.



321 **322** **323** **324**

Alternative reagents, which might allow isocyanate formation under milder reaction conditions, particularly when *N*-Boc systems are involved (when chlorosilane-induced reaction would lead to extensive decomposition), have been proposed [206].

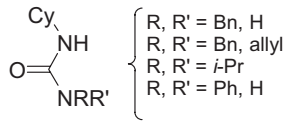
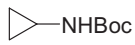
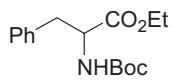
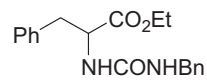
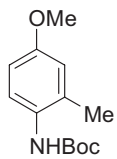
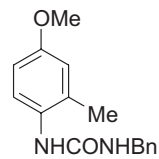
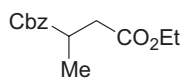
For example, it has been reported that commercially available **diiodosilane** is a particularly useful reagent for this transformation (for other synthetic uses of this silane, see [207]). *Isocyanates* are formed under very mild, low-temperature reaction conditions from a wide variety of carbamates, some bearing other functional groups that are potentially reactive toward electrophiles, by treatment with commercially available $\mathbf{SiI_2H_2}$ and $i\mathrm{Pr_2EtN}$ (*Hunig's base*) (Table 4.13). *In situ* trapping of the isocyanate with primary or secondary amines efficiently leads to ureas [206].

General procedure *for the conversion of carbamate to ureas via isocyanates with* $\boldsymbol{SiI_2H_2}$ [206]: Treatment of a carbamate with 1.2 equiv. of *Hunig's base* and 1.2 equiv. of **diiodosilane** for 30 min, from −30 to −5 °C in dichloromethane, led to complete disappearance of the starting material, as verified by TLC analysis. The formation of an *isocyanate* was established in the case of *N-tert*-butoxycarbonyl-4-methoxy-2-methylaniline (Table 4.13, entry 9) by the observation of the characteristic isocyanate IR absorption at 2289 cm^{-1} (KBr pellet) in the crude product before the addition of benzylamine. In general, however, the isocyanates were not isolated, but could be trapped *in situ* with amines to afford ureas in good to excellent yields, depending on the nature of the starting carbamate as well as the amine used (see also Section 4.3.2 and [208]).

From Table 4.13, it can be seen that the reaction proceeds with all types of carbamates, including *N*-Boc derivatives, while carbamates of secondary amines are not affected under the reaction conditions (entry 10). The ethyl ester functionality in the example in entry 7 proved compatible with the reagent. A tertiary alkylamine base is required to effect the desired transformation. When pyridine is used, the reaction simply affords the parent amine from the carbamate instead of the isocyanate.

Since in exploratory runs with the model carbamate *N*-Boc-cyclohexylamine slightly better yields of urea were produced with *Hunig's base* compared to triethylamine, which is the commonly used base in chlorosilane reactions, the former base was generally used for the above transformations.

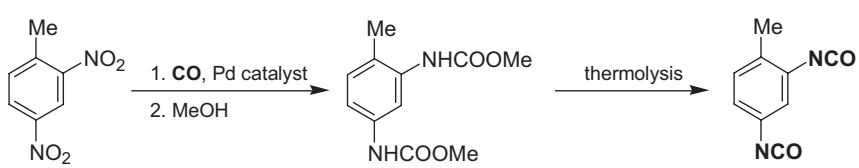
Tab. 4.13. Conversion of carbamates to ureas via isocyanates formed with SiI_2H_2 [206].

Entry	*Carbamate*[a]	*Urea*	*Isolated yield (%)*
1a–d	CyNHBoc		84 76 57 68
2	CyNHCbz	CyNHCONHBn	94
3	$CyNHCO_2Me$	CyNHCONHBn	87
4	$CyNHCO_2Ph$	CyNHCONHBn	89
5			78
6	$Ph(CH_2)_2NHBoc$	$Ph(CH_2)_2NHCONHBn$	91
7			74
8	PhNHBoc	PhNHCONHBn	83
9			78
10		recovered SM (91%)	

[a] Cy = cyclohexyl

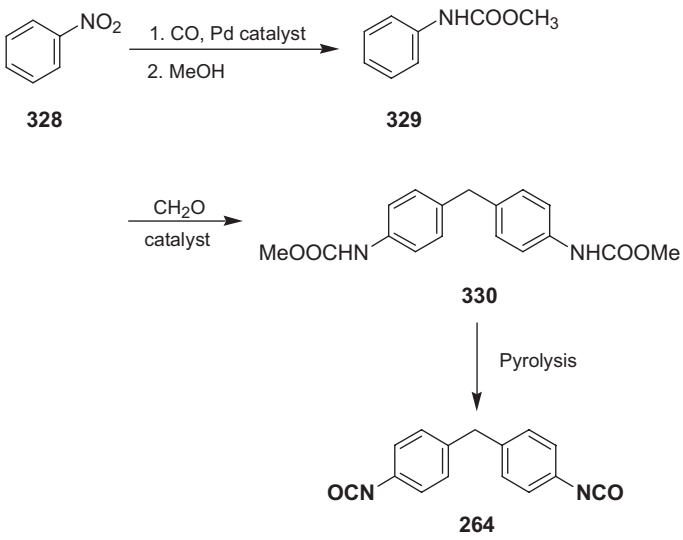
Carbon monoxide as a carbonylating reagent

Many examples of phosgene-free processes, mainly concerning the carbonylation of aryl nitro derivatives, have been claimed. Some of the most representative, cited in part in the *Kirk–Othmer Encyclopedia of Chemical Technology* (4th ed., vol. 19), are illustrated below. 2,4-Dinitrotoluene undergoes **reductive** *carbonylation* with **CO** to form *2,4-toluene diisocyanate (TDI)* in the presence of palladium catalysts [209–213]. A variation on this process involves capturing the *isocyanate* formed with methanol, followed by thermolysis of the bis(carbamate) **326** [212].



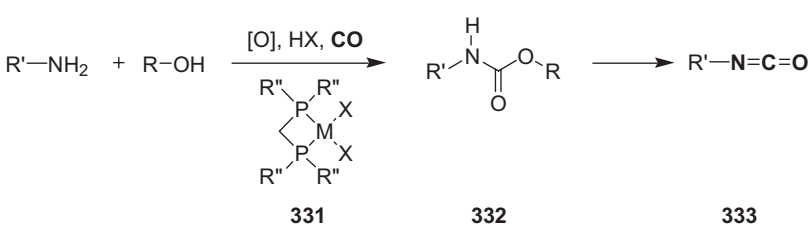
325 **326** **327**

Similarly, nitrobenzene, **CO**, and methanol can react sequentially in the presence of noble metal catalysts, to produce methyl *N*-phenylcarbamate **329**. The phenylcarbamate is subsequently coupled with formaldehyde to yield the methylene-bis(carbamate) **330**, which is pyrolyzed to yield *4,4′-diphenylmethylene diisocyanate (MDI)* **264** [209].



Polymeric blocked isocyanates were obtained by reductive carbonylation of nitropolystyrene with **CO** [214]. Nitrated polystyrene was reductively carbonylated using $Ru(CO)_{12}/Et_4NCl$ in MeOH at 170 °C and 400–450 psi **CO** to give a polymer containing amino, urea, and Me carbamate groups, with the latter being "deblockable" at 200 °C to give *NCO groups*. This would constitute a phosgene-free method for polymeric isocyanate production.

A new route to urethanes avoids *phosgene* and *isocyanates* by reacting amines and alcohols directly with **CO** over a catalyst in the presence of an acid. The urethanes **332** hitherto prepared in this way have been designed to be cracked to isocyanates **333**, and a new BASF patent application covers both the synthesis of urethanes and their thermolysis to isocyanates [215]. The catalyst consists of a cationic Group VIII metal (e.g. Pd) with weakly coordinating counterions and methylene-bisphosphine ligands.



A method of manufacture of *4,4′-diphenylmethane diisocyanate (MDI)* **264**, in which aniline, **CO**, EtOH, and oxygen are used, has been reviewed in the past [216]. The reaction to prepare $PhNHCO_2Et$ has been tested in the presence of Pd and an iodide; this was followed by treatment with aqueous formaldehyde to give a diurethane (akin to **330**, but with Et rather than Me) and decomposition of the latter to give *4,4′-diphenylmethane diisocyanate (MDI)* **264** and EtOH.

In the above described carbonylation processes, the formation of by-products, primarily isocyanate oligomers, allophanates, and carbodiimides, is difficult to control and is found to greatly reduce the yield of the desired isocyanate. Thus, a number of *non-phosgene processes* have been extensively evaluated in pilot-plant operations, but none have been scaled-up to commercial production of diisocyanates primarily due to process economics with respect to the existing *amine-phosgene route*. Key factors preventing large scale commercialization include the overall reaction rates and problems associated with catalyst recovery and recycling [144].

Dimethyl carbonate and diphenyl carbonate as amine carboxylating reagents

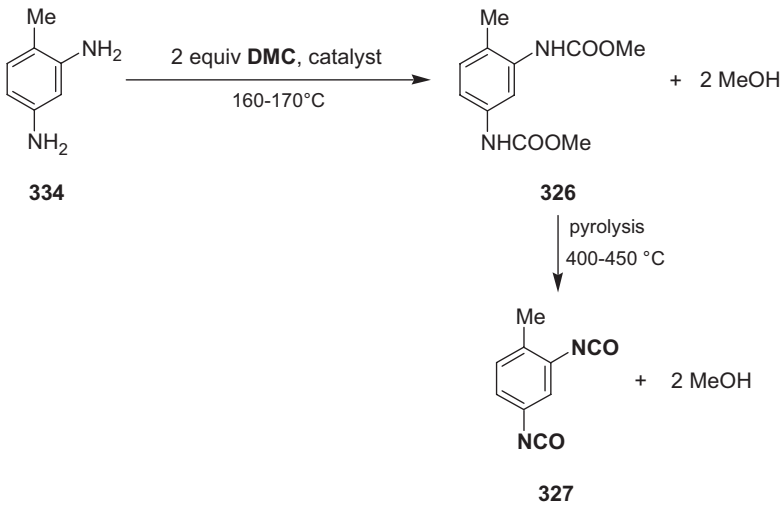
Dimethyl carbonate (**DMC**) and **diphenyl carbonate** (**DPhC**) have been used in place of carbon monoxide as reagents for the conversion of amines into *isocyanates* via the carbamate (urethane) route [217, 218]. Aniline, toluene diamines, and methylene dianilines (MDA) have also been used as starting materials in the carbonylations, providing a wide variety of isocyanate monomers [144].

A proprietary bench-scale phosgene-free process applicable to the synthesis of *2,4-toluene diisocyanate (2,4-TDI)*, starting from 2,4-toluene diamine **334** and using **DMC**, was developed by EniChem [219]. The process configuration is based on two-stage chemistry: in the first stage, 2,4-toluene diamine **334** is reacted with **DMC** at 160–170 °C in the presence of a catalyst to selectively (95%) furnish the corresponding diurethane compound **335**. In the second stage, the diurethane **326** is thermally cracked in the gas phase at 400–450 °C in a tubular reactor to give 2,4-toluene diisocyanate **327**. At such temperatures, the equilibrium is completely shifted toward isocyanate and consequently high urethane conversions are achieved. Moreover, very high reaction rates, and therefore short residence times, prevent the formation of by-products. The methanol formed is recycled in the process to produce **DMC**. An advantage of the above process is that it produces an acid-free *2,4-TDI*, suitable for use in high quality urethane polymers [220].

Activated carbonates: di-*tert*-butyl dicarbonate, di-*tert*-butyl tricarbonate

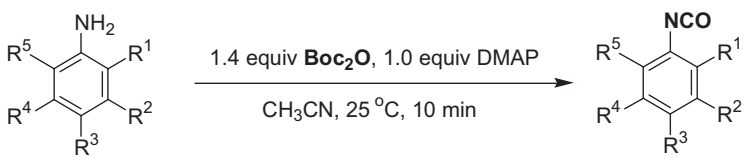
Di-*tert*-butyl dicarbonate, Boc_2O Unfortunately, most of the known methods for transforming amines into isocyanates are not mild enough and furnish undefined products as a result of uncontrolled side reactions. However, 4-dimethylaminopyridine (DMAP)-catalyzed reaction with activated carbonates as C_1 building blocks constitutes a convenient laboratory method for the phosgene-free isocyanation of amines. A procedure has been described whereby alkyl- and arylamines are converted into isocyanates in high yields by reaction with activated carbonates (for

example, **di-*tert*-butyl dicarbonate**, **Boc_2O**) in the presence of a catalytic amount of a nucleophilic nitrogen base at room temperature [221, 222].



Boc_2O is a widely used reagent for introducing protecting groups in peptide synthesis [223, 224]. The reaction of substituted anilines with **Boc_2O** in the presence of a stoichiometric amount of 4-dimethylaminopyridine (DMAP) in an inert solvent (acetonitrile, dichloromethane, ethyl acetate, tetrahydrofuran, toluene) at room temperature leads to *aryl isocyanates* in almost quantitative yields within 10 min (Table 4.14) [225].

With this strategy, 2,6-disubstituted arylamines **337** can be converted almost quantitatively into aryl isocyanates **338** (see for yields of **338a–d** in Table 4.14). The application of the method is particularly straightforward when it is performed in acetonitrile followed by an acidic work-up with sulfuric acid.



337 **338**

When starting with 2-mono-substituted, 2,4-di-substituted, or 2,3,4-tri-substituted arylamines, the yields of the aryl isocyanates range between 40 and 90% (**338e–k**). In order to obtain 2,6-unsubstituted aryl isocyanates, such as **338l**, even in moderate yields, the products have to be isolated by column chromatography on silica gel at −45 to −30 °C. The lower yields obtained with sterically less hindered aryl-

Tab. 4.14. Aryl isocyanates **338** prepared with **Boc_2O** [221].

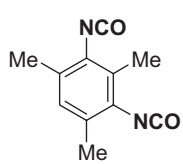
338	*R^1*	*R^2*	*R^3*	*R^4*	*R^5*	*Method[a]*	*Yield of 338 (%)*
a	Me	H	Me	H	Me	A (B)	96 (93)
b	Me	H	H	H	Me	A	94
c	*i*Pr	H	H	H	*i*Pr	A	99
d	OMe	H	OMe	H	OMe	A	97
e	Me	H	H	H	H	A	44
f	OMe	H	H	H	H	A	86
g	OMe	H	Me	H	H	A	88
h	Me	H	OMe	H	H	A	58
i	OMe	H	OMe	H	H	A	76
j	Me	Me	OMe	H	H	A	89
k	-(CH=CH)$_2$-		OMe	H	H	A	42
l	H	H	OMe	H	H	B	41

[a] *Method A*: work-up with sulfuric acid (reaction in CH_3CN at 25 °C, 10 min; work-up by addition of H_2SO_4 (7.0 equiv) in CH_3CN [40%] and subsequent extraction with hexane).

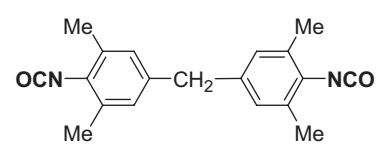
Method B: low-temperature chromatographic work-up (reaction in CH_2Cl_2 at 25 °C, 10 min; purification by column chromatography on silica gel at −45 °C to −30 °C).

amines can be attributed to reaction of the isocyanates with the simultaneously formed *tert*-butanol affording an *N*-Boc derivative (urethane) and to product loss during work-up.

When the arenediamines 2,4,6-trimethylbenzene-1,3-diamine and 2,2′,6,6′-tetramethyl-4,4′-methylenediphenylamine were treated under the same reaction conditions with 1.4 equivalents of **Boc_2O** and 1.0 equivalent of DMAP per amino group in acetonitrile at room temperature (*Method A*, work-up with sulfuric acid), *2,4,6-trimethylbenzene-1,3-diisocyanate* **339** and *2,2′,6,6′-tetramethyl-4,4′-methylenediphenyl isocyanate* **340** were obtained in yields of 84% and 93%, respectively. *Arenediyl diisocyanates* play a very important role as monomers for the industrial synthesis of polyurethanes and polyureas [226].

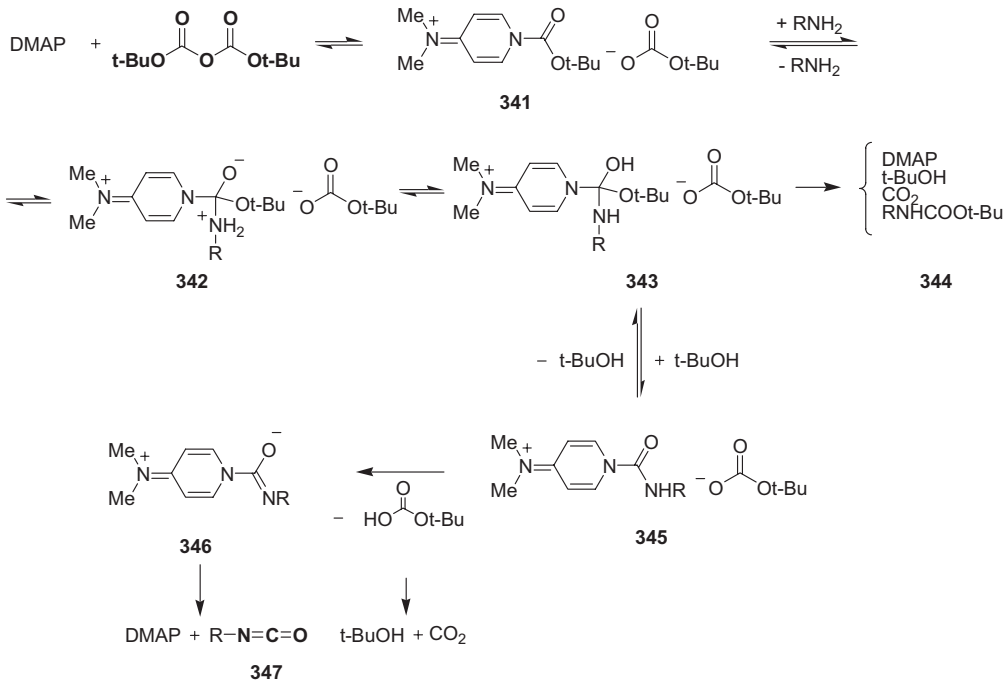


339



340

The high efficiency of 4-dimethylaminopyridine (DMAP) as a catalyst in acylation reactions has long been recognized. The reactive intermediates of these acylation reactions are *N*-acylpyridinium ions [225].



Scheme 4.2. Mechanism of the formation of *isocyanates* (**347**) by the reaction of amines with **Boc_2O**/DMAP [221].

Based on spectroscopic studies, the reaction mechanism depicted in Scheme 4.2 has been postulated for this novel isocyanate synthesis [221]. The reaction mixture initially forms an equilibrium between the two starting reagents (DMAP and **Boc_2O**) and 1-*tert*-butoxycarbonyl-4-dimethylaminopyridinium-*tert*-butyl carbonate **341**; **341** is the key reagent in this synthesis.

Mechanistic studies have also emphasized the key role of intermediates analogous to **341** in the DMAP-catalyzed reaction of dialkyl dicarbonates and carboxylic acids, as has recently been reported for the preparation of esters [227].

The reaction of an arylamine with **Boc_2O** in the absence of a nucleophilic nitrogen base leads exclusively to the *N*-Boc derivative (urethane), as is well-established in protecting group chemistry. The urethane is not an intermediate of the isocyanate synthesis described here, since it does not undergo a reaction with either **Boc_2O** or DMAP alone.

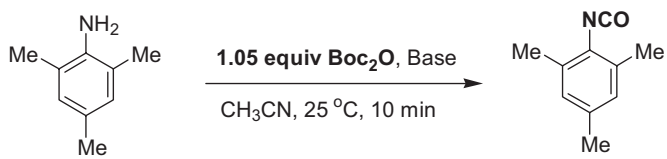
Reaction of the urethane with **Boc_2O** in the presence of DMAP, however, results in a nucleophilic reaction with **341** in which the *N*,*N*-bis-Boc derivative is formed [228]. The generation of *N*,*N*-bis-Boc derivatives can be explained in terms of the formation of the [Boc-DMAP]$^+$ cation, resulting from the activation of Boc_2O by DMAP (Scheme 4.2). The regeneration of DMAP, as postulated in the mechanism outlined in Scheme 4.2, suggests the possibility of using this component in catalytic amounts [221].

Tab. 4.15. Effect of the nature and concentration of the base on the generation of mesityl isocyanate **349** with **Boc_2O** (reaction conditions and work-up according to *Method A*, Table 4.14) [221].

Base[a]	*Equiv.*	*Yield of 349 (%)*	*Base*[a]	*Equiv.*	*Yield of 349 (%)*
DMAP	1.0	96	PPY	0.01	92[b]
DMAP	0.1	97[b]	PPY	0.001	14[b,c]
DMAP	0.01	92[b,c]	4-MeOPy	1.0	51[b,d]
DMAP	0.001	32[b,c]	Py	1.0	43[b,d]
PPY	1.0	94[b,c]	Et_3N	1.0	17[b,d]
PPY	0.1	91[b]			

[a] Abbreviations: DMAP = 4-dimethylaminopyridine, PPY = 4-pyrrolidinopyridine, 4-MeOPy = 4-methoxypyridine, Py = pyridine; [b] Formation of *N,N*-dimesitylurea as a by-product; [c] Incomplete reaction; [d] Formation of *tert*-butyl-*N*-mesityl carbamate (R = mesityl) as a by-product.

This possibility was extensively investigated in the synthesis of mesityl isocyanate **349** (Table 4.15).



348 **349**

When employing low concentrations of DMAP, increasing amounts of the by-product *N,N′*-dimesitylurea were isolated, arising from reaction of the isocyanate with mesitylamine [229]. Nevertheless, the isocyanate was obtained in 92% yield when using 1 mol% of DMAP as the catalyst. With 0.1 mol% of DMAP, the reaction was incomplete after 10 min as a result of the low catalyst concentration. The yields, however, increased with increasing reaction time.

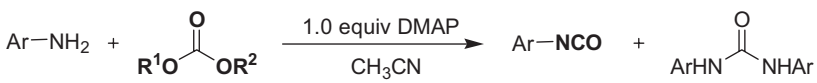
General procedure *for the synthesis of alkyl and aryl isocyanates with stoichiometric amounts of DMAP and* **Boc_2O** [221]: A solution of **Boc_2O** (1.4 equiv.) in acetonitrile was treated successively with a solution of 4-dimethylaminopyridine (1.0 equiv.) in acetonitrile and a solution of the arylamine (1.0 equiv.) in acetonitrile. The resulting mixture was stirred for 10 min at room temperature (dichloromethane was used as the solvent for work-up, according to *Method B*).

Work-up, *Method A*: The reaction mixture was treated with sulfuric acid (7 equiv.) as a 40% solution in acetonitrile ($\rho = 1.03$ g cm^{-3}) and the resulting mixture was stirred for 2 min. It was then extracted three times with hexane. The combined hexane layers were dried over magnesium sulfate and the solvent was removed in vacuo.

Work-up, Method B: The solvent (dichloromethane) was completely removed, and the residue was extracted several times with small amounts of eluent (for example, hexane/ethyl acetate, 4:1). The resulting suspension was subjected to silica gel chromatography at between −45 and −30 °C.

Typical procedure. *Mesityl isocyanate* **349** *using a catalytic amount of DMAP and* **Boc_2O** [221]: A solution of **Boc_2O** (619 mg, 2.84 mmol) in acetonitrile (2 mL) was treated successively with a solution of 4-dimethylaminopyridine (33 mg, 0.27 mmol) in acetonitrile (2 mL) and a solution of **348** (365 mg, 2.7 mmol) in acetonitrile (2 mL). The reaction mixture was stirred vigorously for 10 min. After the addition of concentrated sulfuric acid in acetonitrile (40% solution, $\rho = 1.03$ g cm^{-3}, 0.47 mL), the resulting mixture was stirred for 5 min. Water (0.47 mL) was then added, and the mixture was stirred for a further 5 min. The reaction mixture was then poured into an equal volume of water. The solution was extracted three times with hexane, and the combined hexane layers were dried over magnesium sulfate. Removal of the solvent in vacuo afforded *mesityl isocyanate* **349** (420 mg, 97%) as colorless crystals; mp 42 °C.

Other activated carbonates Efforts have been made to accomplish the isocyanation of amines with C_1 building blocks that, unlike **Boc_2O**, can be synthesized without the use of *phosgene*.



348 **350** **349** **351**

Ar = Mesityl

In fact, **other activated carbonates 350** can be used for the isocyanation of amines in the presence of DMAP (Table 4.16). However, due to its extreme reactivity, **Boc_2O** provides the highest yields in a very rapid reaction. As an alternative to **Boc_2O**, *tert*-butoxycarbonyl pivalate **350b** has been synthesized, which is readily

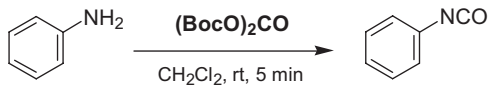
Tab. 4.16. DMAP-mediated synthesis of mesityl isocyanate (**349**) from mesitylamine **348** with the **activated carbonates 350** as C_1 building blocks (**350a** = Boc_2O) [221].

350	*R^1*	*R^2*	*T (°C)*	*t*	*349 yield (%)*	*351 yield (%)*
a	*t*BuOCO	*t*Bu	25	10 min	96	0
b	*t*BuCO	*t*Bu	25	4 h	17	64
c	C_6H_5	C_6H_5	82	15 d	0	29
d	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	25	18 h	19	64
e	4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	82	18 h	9	86

available by successive transformation of *tert*-butanol with potassium and carbon dioxide followed by an in situ acylation with pivaloyl chloride.

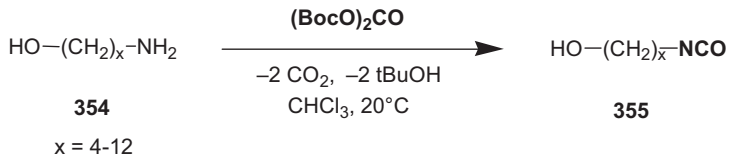
The reaction of **350b** with mesitylamine **348** in the presence of DMAP provided *isocyanate* **349** in 17% yield, along with 64% of urea **351**. It is important to note that the urea is formed exclusively from the isocyanate under these reaction conditions and not from the corresponding urethane. The isolation of larger amounts of the urea gives direct evidence for the intermediacy of the isocyanate, as shown in the pathway outlined above. While dimethyl carbonate, di-*tert*-butyl carbonate, and ethylene carbonate did not react, the reaction of **diphenyl carbonate 350c** with mesitylamine and DMAP in acetonitrile under reflux yielded urea **351** in a moderate 29% yield after 15 days. Under these reaction conditions, complete conversion of the isocyanate to the respective urea derivative is not unexpected. Because of the milder reaction conditions when **bis(4-nitrophenyl) carbonate 350d** is used, *isocyanate* **349** could be isolated along with the secondary product **351**. The combined yield of 95% at 82 °C indicates that the DMAP-catalyzed reaction pathway involving the isocyanate is virtually the exclusive route in this case [221].

Di-*tert*-butyl tricarbonate $(BocO)_2CO$ Recently, **di-*tert*-butyl tricarbonate** has been reported as a versatile and mild reagent for the synthesis of unusual *mono-* and *multi-isocyanates* (**232**) within minutes at room temperature [230, 231].



The synthesis of the reagent has been optimized and described in detail [232].

The facile synthesis of aliphatic [*n*]polyurethanes by using **di-*tert*-butyl tricarbonate** to prepare the appropriate monomers has yielded a general class of polymers. These structures are especially interesting in the context of biodegradable polymers, since the synthetic procedure is applicable to all amino alcohols with a spacer of at least four carbon atoms between the two functionalities. The reagent is the key element for the selective formation of the *α,ω-isocyanato alcohol* **355** intermediates for polymeric urethanes.



The reaction is accompanied by the formation of two equivalents of carbon dioxide and *tert*-butyl alcohol. The former escapes from the solution, while the latter stays in the reaction mixture. Under the conditions employed, *tert*-butyl alcohol is un-

reactive towards the isocyanate, and hence it is harmless. The amino alcohol solution was added by injecting it under the surface of the di-*tert*-butyl tricarbonate solution, in order to avoid turbidity of the reaction mixture due to the formation of carbamic acid by reaction of the escaping carbon dioxide with the amino alcohol. After decomposition of the unstable carbamic acid to the initial amino alcohol, the latter reacts with already formed isocyanate, resulting in urea derivatives. This side reaction distorts the perfect stoichiometry of the AB-type polymerization, and consequently, limits the molecular weight of the polymer.

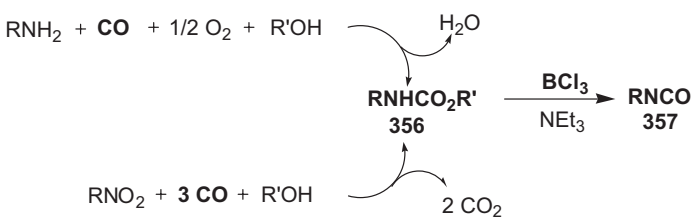
The formation of the *α,ω-isocyanato alcohols* has been confirmed by IR and ^{1}H NMR spectroscopy. In the IR spectrum of a solution of the product in chloroform, a strong absorption due to the N=C=O stretch is seen at 2274 cm^{-1}. ^{1}H NMR spectra show the absence of any side products and also prove the relative stability of *α,ω-isocyanato alcohols* in solution; however, concentration to dryness furnished undefined products.

Boron trihalides as mild reagents for the conversion of carbamate esters to isocyanates

Boron trihalides are known for their strong Lewis acid character, and for their ability to cleave a wide variety of ethers, acetals, and esters under relatively mild conditions [233].

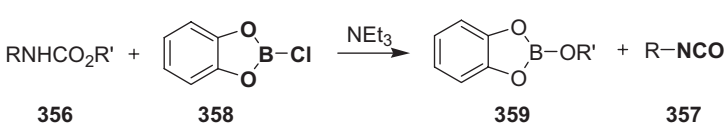
The conversion of carbamate esters to *isocyanates* and *diisocyanates* of industrial importance is possible using **BCl_3** in the presence of Et_3N [234]. The reaction is simple in its execution and work-up, proceeding under mild conditions and affording *isocyanates* **357** in excellent yields.

One such method (Scheme 4.3) involves the *oxidative carbonylation of amines* [235–238], or the catalytic production of carbamate esters by *reductive carbonylation of nitro compounds* [238–242], dealcoholysis of which gives *isocyanates*.



Scheme 4.3. Oxidative carbonylation of amines [235–238] and reductive carbonylation of nitro compounds [238–242].

It has recently been shown that elimination of alcohol from carbamate esters **356** to yield isocyanates **357** can be facilitated using **chlorocatecholborane 358** in toluene, in the presence of triethylamine [243].

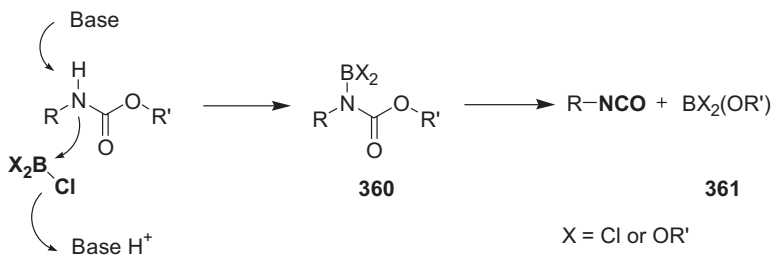


This work demonstrated that the way in which the alcohol product is irreversibly removed from the reaction solution, in the form of an alkyl catecholborate **359**, is pertinent to the significance of this method compared with those which employ the thermal decomposition of carbamate esters, in which recombination of the resulting isocyanate with alcohol is possible.

In pursuit of alternative methods of *isocyanate* production, the results of investigations with simple **boron halides**, $\mathbf{BX_3}$ (X = Cl, Br), in converting carbamate esters to isocyanates of industrial importance were reported. Additionally, it has previously been shown that $\mathbf{BX_3}$ can be generated in the production of benzyl esters by reaction of trialkyl borates with benzylic halides and **CO** in the presence of catalytic quantities of Pd^0 or Rh^1 [244–246]. This offers the rather attractive option of two concomitant processes achieving commercially valuable ends, together with constant recycling of boron.

General procedure *for the synthesis of isocyanates with* $\mathbf{BCl_3}$ *and* Et_3N [247]: Treatment of a carbamate ester with $\mathbf{BCl_3}$ (0.37 equiv.) and Et_3N (1.1 equiv.) for 30 min in refluxing benzene afforded the isocyanate in good yield. For a series of aryl, alkyl, alicyclic, and tosyl carbamate esters, quantitative or near-quantitative conversion to the product isocyanates was generally achieved under these relatively mild reaction conditions. The reactions were found to be highly selective, with only the product *isocyanates*, partially cleaved carbamate esters (when dicarbamate esters were employed as starting materials), or starting materials being observed in the final solutions. The product isocyanates are usually easily isolable by evaporation of the solvent and trialkyl borate under reduced pressure, followed by vacuum distillation at elevated temperatures.

For example, *toluene-2,4-diyl diisocyanate (TDI)*, *p-phenylene diisocyanate (PDI)*, *and 4,4′-methylenebis(phenyl isocyanate) (MDI)*, which are large-scale raw materials for the manufacture of polyurethane foams [248], can be isolated as spectroscopically pure materials from their corresponding methyl carbamate esters in yields of 70–79%. *Toluene-2,4-diyl diisocyanate* can also be isolated in good yield from its methyl carbamate ester when the reaction is performed in toluene (65% isolated yield) or hexanes (41% isolated yield). Chlorinated solvents, however, are not suitable media for this reaction. As expected, $\mathbf{BCl_3}$ is converted to trialkyl borate (identifiable by GC-MS after the reaction), consistent with Scheme 4.4.



Scheme 4.4. Reaction of carbamates with $\mathbf{BX_3}$ yielding *isocyanates*.

BBr_3, a stronger Lewis acid than **BCl_3**, was also effective in this reaction, with isocyanate yields being similar to those quoted for **BCl_3**. However, appreciable amounts of amine were also produced in some cases, bringing the selectivity of this reagent into question.

It has previously been shown that **PCl_3**, and other Lewis acids, can effect the removal of OH from carbamate anions to yield *isocyanates* by electrophilic, *oxophilic* dehydration [249]. However, it has been found that when **PCl_3** is used instead of **BCl_3**, the conversion of carbamate esters to *isocyanates* is less than ca. 5%. Similar yields were attained with **$AlCl_3$**, while **$TiCl_4$** was found to be totally inactive. It is conceivable that **PCl_3** can react as an electrophile at nitrogen in this case, and a possible reason for its overall inactivity might be its inability to promote cleavage of an alkoxy group from the resulting intermediate.

Isocyanates from carboxylic acids. Diphenylphosphoryl azide as a phosgene substitute

The classic Curtius route to isocyanates from carboxylic acids via the **acyl azides** involves three separate synthetic steps, two of which are potentially explosive.

Diphenylphosphoryl azide (**DPPA**) and triethylamine were formerly employed by Yamada and co-workers in a simple *one-pot* synthesis of urethanes from carboxylic acids [250]. This procedure involved treatment of a carboxylic acid with triethylamine to produce the triethylammonium carboxylate salt, followed by heating in the presence of **DPPA** to yield *the isocyanate* via a Curtius-type rearrangement of the acyl azide. An alcohol was then introduced, functionalizing the isocyanate *in situ* to yield the urethane.

The exact mechanistic details of this transfer step have not yet been determined [251]. Both concerted and bimolecular mechanisms have been proposed [145, 146].

Other groups have reported the application of Yamada's procedure, minus the *in situ* urethane formation, to prepare *1,3-diisocyanatoadamantane* [252], *n-heptadecyl isocyanate* [253], and *18-nordehydroabietyl isocyanate* [254].

A reinvestigation of Yamada's method resulted in low yields (10–20%) and isocyanate contaminated by triethylamine ($\geq$ 30%). These poor results were attributed to the composition of the reaction mixture at the end of the process, i.e. prior to work-up. Reaction of the triethylammonium carboxylate with **DPPA** yielded a crude mixture of the *isocyanate* and a triethylammonium phosphate salt **363**, which is believed to be in equilibrium with the free acid and base.

362 **363**

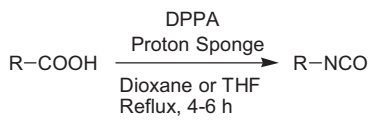
During purification by distillation, the volatile triethylamine distils continuously, thereby contaminating the isocyanate as it distils. A further complication is the reaction of the isocyanate with the diphenylphosphoric acid **362**, since heating iso-

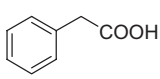
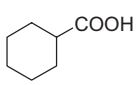
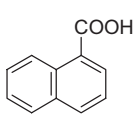
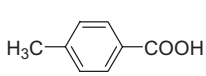
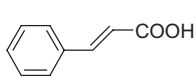
cyanates in the presence of even traces of an active-hydrogen compound can result in complete polymerization of the isocyanate [143]. Furthermore, triethylamine is known to catalyze the thermal isomerization of isocyanates to isocyanurates.

A variety of non-volatile tertiary amine bases, which would either completely favor the ammonium phosphate salt and/or form an ammonium phosphate salt that could be removed prior to distillation by precipitation and filtration, were evaluated. Only *1,8-bis(dimethylamino)naphthalene*, known for its bidentate nature [255], which most probably favors the formation of the ammonium phosphate salt, furnished *benzyl isocyanate* in good yield and with high purity [256]. About 75% of the ammonium phosphate salt was removed by precipitation and filtration prior to distillation. Consequently, a simple method for the synthesis of high purity isocyanates from carboxylic acids was developed using **DPPA** and *1,8-bis(dimethylamino)naphthalene*. Yields evaluated for the monoisocyanates ranged from 60% to 81.5% (Table 4.17) [256].

Typical procedure: *Preparation of isocyanates from carboxylic acids*, **DPPA**, *and 8-bis(dimethylamino)naphthalene* [256]: The carboxylic acid (40 mmol) was dissolved

Tab. 4.17. Isocyanates from carboxylic acids, **DPPA**, and 1,8-bis(dimethylamino)-naphthalene [256]:



RCOOH	*Yield, %*	
	in dioxane	in THF
	71.3	73.5
	40.7	60.5
	59.5	81.5
	36.1	60.0
	not isolable[a]	–
$HOOC(CH_2)_6COOH$	65.3	76.1

[a] isocyanate observable in IR at 2280 cm^{-1}

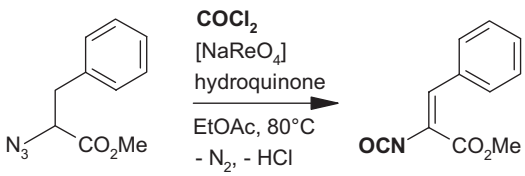
in dry dioxane or THF (freshly distilled from Na or Na/K benzophenone) (50 mL). 1,8-Bis(dimethylamino)naphthalene (*Proton Sponge*™; one equivalent per equivalent of carboxylic acid) was then added to the homogeneous acid solution and the resulting mixture was stirred for 15–30 min at room temperature. If necessary, the mixture was warmed to 50 °C to aid dissolution. **DPPA** (one equivalent per equivalent of *Proton Sponge*™) was then added by means of a syringe. The mixture was gradually heated to reflux temperature and kept under reflux for 6 h. It was then allowed to cool to room temperature, before storing at −2 °C overnight to precipitate the ammonium phosphate salt. The cold mixture was quickly frit-filtered, washing with anhydrous diethyl ether or diethyl ether/ethyl acetate (1:1, *v*/*v*). The filtrate was then partly concentrated and the residual liquid was vacuum distilled (short-path Vigreux column distillation apparatus, 0.20 mmHg) to yield the *isocyanate* product as a clear, colorless liquid, which was characterized by IR, ^{1}H NMR, and ^{13}C NMR.

This method allows the preparation of aromatic and aliphatic monoisocyanates in moderate yields and with very high purities. Of the di- and tricarboxylic acids evaluated, only *hexamethylene diisocyanate* was successfully synthesized.

4.3.1.3 Alkyl and Alkenyl Isocyanates

Phosgene *as carbonylation reagent*

Methyl 2-isocyanato-3-phenylpropenoate **365** is obtained in 68% yield by perrhenate-catalyzed decomposition of methyl 2-azido-3-phenylpropionate **364** in the presence of **phosgene** [257]. This reaction resulted in a higher yield compared to the same reaction employing **diphosgene** (instead of **phosgene**), which afforded the product in just 53% yield [257].



364 68 % **365**

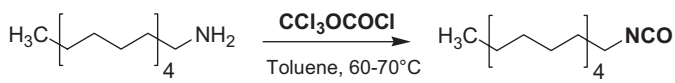
Typical procedure. *Methyl 2-isocyanato-3-phenylpropenoate* **365** [257]: At 80 °C, **phosgene** (for a *safe source*, see Chapter 7) was passed into a solution of ammonium perrhenate (1 mol%) in ethyl acetate (10 mL) saturated with HCl, until the solution was saturated. A solution of **364** (4.1 g, 20.0 mmol) and hydrochinone (50 mg) in ethyl acetate (10 mL) was then added dropwise, while the mixture was cooled to 65 °C. More **phosgene** was then passed in, until reaction was complete (monitored by IR spectroscopy). The mixture was filtered at room temperature, the filtrate was concentrated, and the residue was distilled in vacuo to afford 2.77 g (68%) of **365**. *Author's remark:* Note! Excess phosgene has to be passed into a vessel filled with ethanol to make it harmless, and thereby HCl gas is evolved (see Chapter 7).

Diphosgene and triphosgene as phosgene equivalents

L-Lysine diisocyanate (LDI) **367** was synthesized by refluxing L-lysine monohydrochloride with ethanol to form the ester, which was subsequently refluxed with 1,1,1,3,3,3-hexamethyldisilazane to yield a silazane-protected intermediate. *N*,*N*′-Bis(trimethylsilyl)-L-lysine ethyl ester **366** reacts with **triphosgene** to yield *ethyl 2,6-diisocyanatohexanoate* **367** [258, 259].

Typical procedure. *Ethyl 2,6-diisocyanatohexanoate* [258]: A dry 1000 mL three-necked, round-bottomed flask equipped with a mechanical stirrer was charged with purified *N*,*N*′-bis(trimethylsilyl)-L-lysine ethyl ester (50 mL), anhydrous diethyl ether (400 mL), and triethylamine (39 mL). The mixture was cooled to −20 °C, whereupon a solution of **triphosgene** (30 g) in anhydrous diethyl ether (200 mL) was added dropwise over a period of 30 min. The reaction mixture was kept at −20 °C for 4 h, and then the flask was removed from the cold bath and reaction was allowed to proceed at room temperature for an additional 36 h. Triethylamine hydrochloride was removed by vacuum filtration and the diethyl ether was evaporated in vacuo to yield the crude ethyl 2,6-diisocyanatohexanoate. The product was purified by vacuum distillation and approximately 15 mL of the fraction that distilled in the range 120–132 °C at 0.1 mmHg was collected.

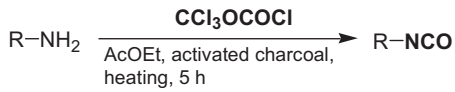
Octadecylamine was treated with **diphosgene** in toluene (starting from 60–70 °C and heating up to the bp) to yield 1-isocyanato-octadecane [260].



368 **369**

1-Isocyanato-dodecane has been prepared with **urea** in diethylene glycol monomethyl ether at 200 °C [261].

Diphosgene has been employed to synthesize several linear and branched *alkyl monoisocyanates* **371** [262–264].

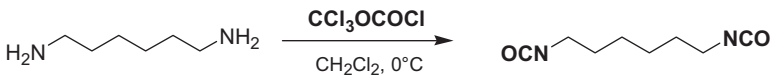


370 **371**

R = 1-propyl, 2-propyl, 1-butyl, 2-butyl, (*S*)-2-butyl, (*R*)-2-butyl, 1-pentyl, 1-methyl-butyl, (+/-)-2-methyl butyl, 3-methyl-butyl, (*S*)-2-methyl-1-butyl, 1-hexyl, 3,3-dimethyl-butyl, 3-methyl-pentyl, (−)-R-1-methyl-pentyl, 1-heptyl, 1-methyl-hexyl, (*S*)-2-heptyl, 1-octyl, 2-octyl, 1,5-dimethyl-1-hexyl, 2-ethyl-1-hexyl, 3-methylsulfanyl-1-propyl, 3-methoxy-1-propyl

Hexamethylene diisocyanate **373**, *benzyl isocyanate*, and *(R)-(+)-methylbenzyl isocyanate* were prepared in yields of 73%, 78%, and 81%, respectively, from their

corresponding amines using **diphosgene** in dichloromethane, in the presence of 1,8-bis(dimethylamino)naphthalene at 0 °C [265].

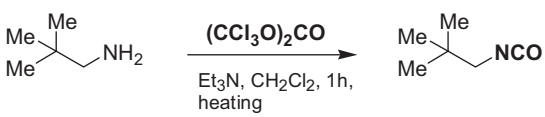


372 **373**

Typical procedure. *(R)-(+)-Methylbenzyl isocyanate* [265]: *Warning: Diphosgene and aliphatic isocyanates are toxic and should thus be handled wearing protective clothing in a well-ventilated area*. A solution of (*R*)-(+)-methylbenzylamine (0.470 g, 3.88 mmol) and 1,8-bis(dimethylamino)naphthalene (1.66 g, 7.75 mmol) in dichloromethane (10 mL) was added dropwise to a stirred solution of **diphosgene** (0.460 g, 2.33 mol) in dichloromethane (10 mL) at 0 °C over a period of 5 min. The ice bath was then removed and the solution was stirred for a further 10 min before evaporation of the volatiles in vacuo. The residue was partitioned between dichloromethane (20 mL) and 1 N aq. HCl (10 mL), and the organic phase was separated and washed successively with 1 N aq. HCl (3 × 10 mL) and 1 N aq. NaOH (10 mL). After drying the organic phase (Na_2SO_4), the solvent was removed in vacuo to yield *(R)-(+)-methylbenzyl isocyanate* as a pale-yellow oil (0.460 g, 81%), the optical purity of which was not determined.

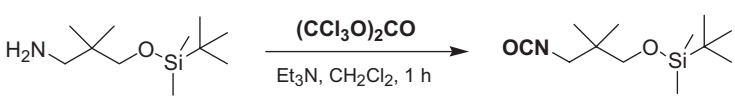
For the synthesis of *1,6-diisocyanatohexane*, the amounts of both **diphosgene** and 1,8-bis(dimethylamino)naphthalene were doubled. *Hexamethylene diisocyanate* was also successfully synthesized from 7-aminoheptanoic acid, **DPPA**, and 1,8-bis(dimethylamino)naphthalene [256].

Triphosgene was employed to prepare *2,2-dimethylpropyl isocyanate* **375** [266].



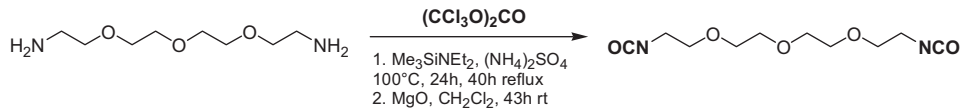
374 **375**

O-Dimethyl-*tert*-butylsilane protected 1,3-amino alcohols **376** react with **triphosgene** to give the corresponding *isocyanate* **377** [266].



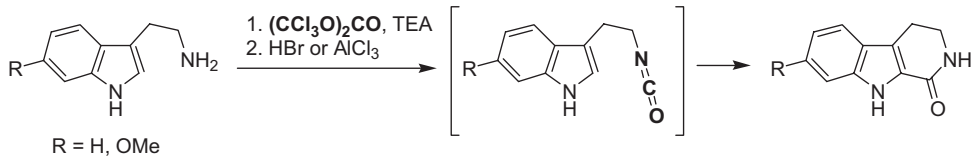
376 **377**

2,2′-(3-Oxa-pentane-1,5-diyldioxy)-bis(ethylamine) **378** was converted into the corresponding *diisocyanate* with **triphosgene** in a multi-step reaction [267].



378 **379**

To phosgenate tryptamine **380** in the presence of triethylamine, one-third of an equivalent of **triphosgene** was added. When HBr/AcOH was added and the reaction mixture was heated for a short time, the *intermediate isocyanate* cyclized spontaneously, affording the *lactam* in 74% yield in a one-pot reaction [268, 269].

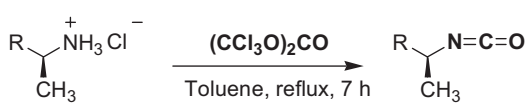


R = H, OMe

380 **381** **382**

Typical procedure. *2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indol-1-one* **382** [268]: Tryptamine **380** (9.0 g, 56.2 mmol) and triethylamine (13.8 g, 136.3 mmol) were dissolved in warm toluene (800 mL). Under vigorous stirring, a solution of **triphosgene** (6.7 g, 22.6 mmol) in toluene (35 mL) was added dropwise and the mixture was stirred for a further 20 min at room temperature. Then, HBr (30% in acetic acid; 13 mL) was added and the mixture was refluxed for 30 min. After cooling to room temperature, water (300 mL) and ethyl acetate (300 mL) were added and, after separation of the layers, the aqueous phase was extracted once more with ethyl acetate (300 mL). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was recrystallized from methanol/ethyl acetate (1:1) to afford 7.74 g (74%) of *2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-one* **382** as a white solid; mp 184 °C.

Chiral aliphatic isocyanates **384**, which are applied to aminopropyl columns to render them chiral for the resolution of racemic amines, alcohols, and acids as amide, urea, carbamate or hydrazide derivatives, have been prepared with **triphosgene**. The authors found that approximately 0.66 mol rather than 0.33 mol of **triphosgene** was required per mol of amine, presumably because of a loss of phosgene gas along with the HCl by-product [270].

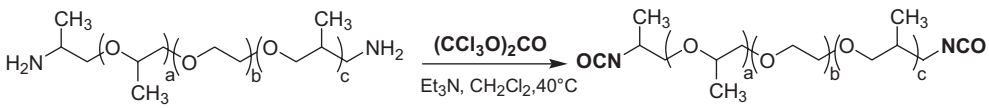


R = 4-NO_2-Phenyl, Benzyl

383 **384**

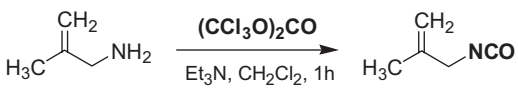
Polymer networks having glycerol ether cross-links joined by polyethylene oxide (PEO) chains, with a urethane group in the middle of each one, have been prepared [271].

Transformation of commercial PEO diamines into the corresponding *diisocyanates* **386** by reaction with stoichiometric amounts of **triphosgene** in refluxing dichloromethane, both in the presence and absence of triethylamine, and the subsequent condensation of these bifunctional oligomers with commercial PEO triols resulted in the aforementioned novel polymeric structures.



385 **386**

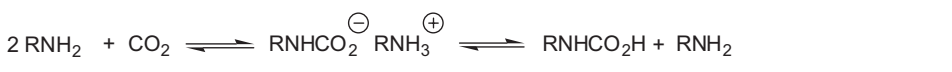
2-Methyl-allyl-isocyanate **388** was prepared from methallylamine **387** with **triphosgene** [266].



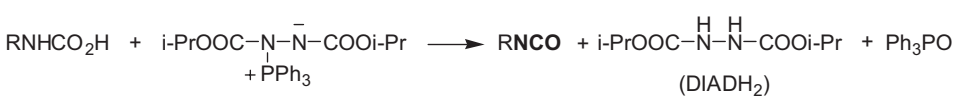
387 **388**

Carbon dioxide and dialkyl azodicarboxylate (Mitsunobu zwitterions) as phosgene substitutes

Primary alkylamines give high yields of *isocyanates* when reacted with **carbon dioxide** (CO_2) and the *Mitsunobu zwitterions* generated from **dialkyl azodicarboxylates** and Bu_3P or Ph_3P at −78 °C [196, 272]. The aliphatic isocyanates prepared in this way are listed in Table 4.18.



389 **390** **391**



391 **392** **393** **394** **395**

General procedure *for the synthesis of aliphatic isocyanates* [196]: At −10 to −5 °C, anaerobic grade CO_2 was gently bubbled through a solution of the freshly distilled amine in dichloromethane. More CO_2 was then vigorously bubbled through the solution for 30–60 min. In a separate flask, a stirred, cold (−20 °C) solution of PPh_3 in dichloromethane was treated with **diisopropyl azodicarboxylate** (**DIAD**) or

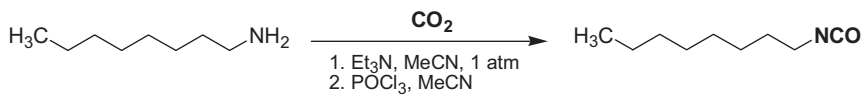
Tab. 4.18. Isocyanates from reactions of amines with **CO_2** and the *Mitsunobu zwitterion*[a] [196].

Amine R	*Yield of isocyanate (%) estimated by IR*	*Yield of isocyanate (%) isolated*
*i*Pr	94	86
*i*Pr	90[b]	–
*n*Bu	76	63
*t*Bu	95	84
cyclohexyl	90	80
n-octyl	69	65
tert-octyl[c]	93	87
3α-cholestanyl	89	86

[a] Reactions in dichloromethane from −78 °C to ambient temperature;
[b] reaction worked-up immediately on reaching ambient temperature, ca. 3 h, IR yield only;
[c] 2,4,4-trimethyl-2-pentylamine.

di-*tert*-butyl azodicarboxylate. The ratio of amine, phosphine, and azodicarboxylate was 1:1.2:1.2. Both reaction vessels were cooled to −78 °C prior to cannulation of the zwitterion solution into the carbamate salt solution. The reaction mixture was allowed to slowly warm to room temperature over a period of 30–60 min, while maintaining a steady stream of CO_2. The mixture was then stirred overnight under 1 atm of CO_2. IR analysis of the solution obtained, made up to a specific volume with dichloromethane, was used to determine the yield of the in situ produced isocyanate. The isocyanates were isolated by either fractional distillation or column chromatography. In reactions employing PBu_3 in place of PPh_3, an equimolar ratio of amine, PBu_3, and **DIAD** was used, and the reaction mixture was worked-up as soon as it reached ambient temperature.

1-Isocyanato-octane **397** has been prepared by a multistep reaction from the corresponding amine. Octylamine **396** was first treated with **CO_2** at 1 atm in acetonitrile in the presence of triethylamine as organic base. The carbamate anion derived from the primary amine was then dehydrated with $POCl_3$ in acetonitrile [198]. The method has been employed to prepare *hexamethylene diisocyanate* **373**, a commercial isocyanate [198].

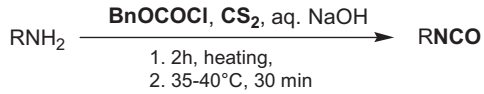


396 **397**

Chloroformates and carbon disulfide as carbonylating agents

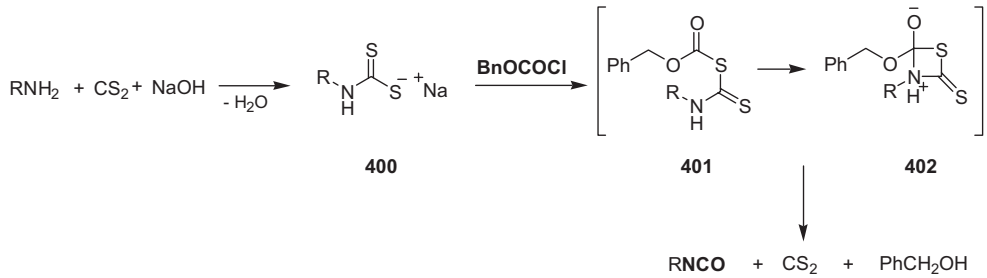
Benzyl chloroformate and **carbon disulfide** (**CS_2**) have been used to prepare *C_3–C_8 aliphatic isocyanates* **399**, e.g. *1-isocyanato-2-methyl-propane*, *4-isocyanato-octane*, *1-*

isocyanato-hexane, *1-isocyanato-propane*, *2-isocyanato-2-methyl-propane*, and *allyl isocyanate* [273].



R = c-Hex, *t*-Bu, Allyl, *i*-Pr, *i*-Bu, *4*-Octyl

The possible sequence of reactions leading to the formation of isocyanates is shown below.



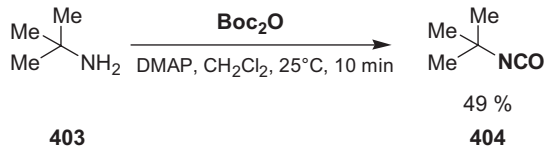
General procedure *for the synthesis of isocyanates by the reaction of certain amines with* **benzyl chloroformate** *and* **CS_2** [273]: **CS_2** (27.5 mL, 34.25 g, 0.45 mol) and a cold solution of NaOH (18 g, 0.45 mol) in water (40 mL) were placed in a 250 mL, three-necked flask fitted with a mechanical stirrer, a reflux condenser, a thermometer, and a 50 mL dropping funnel. The flask was cooled in an ice bath and a 35% aqueous solution of the amine (0.45 mol) was added dropwise over a period of 30 min. Stirring was continued for 2 h on a heated water bath. The colored solution was then cooled to 35–40 °C and benzyl carbonochloridate (76.72 g, 0.45 mol) was added over a period of 1 h with vigorous stirring. The solution was then stirred for 30 min at 35–40 °C and filtered. The filtrate was subjected to fractional distillation (under vacuum, if necessary) using a 20 cm, ring-filled Rashig column. The distillate consisted of the *isocyanate* contaminated with by-products such as isothiocyanates; it was redistilled through a spinning band column to give the product free of by-products. Yields were between 76 and 84%.

Di-*tert*-butyl dicarbonate and di-*tert*-butyl tricarbonate

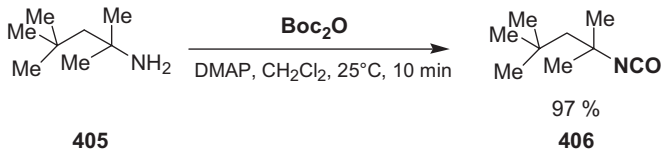
Di-*tert*-butyl dicarbonate (**Boc_2O**) [221, 225] and **di-*tert*-butyl tricarbonate** (**$(BocO)_2CO$**) [230] have been used as amine carbonylating reagents to obtain *linear or branched aliphatic isocyanates*.

The reaction of sterically hindered alkylamines, such as *tert*-butylamine **403** and 1,1,3,3-tetramethylbutylamine **405**, performed in dichloromethane under the same reaction conditions (*Method B*, low-temperature chromatography; see *Section*

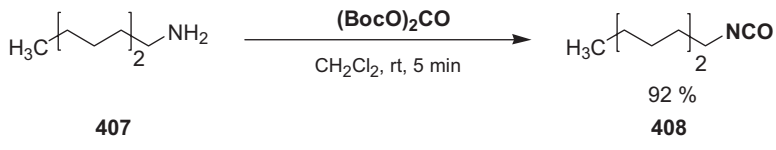
4.3.1.2 "Aryl Isocyanates Prepared with Boc_2O"), afforded the alkyl isocyanates *tert-butyl isocyanate* **404** and *1,1,3,3-tetramethylbutyl isocyanate* **406** in yields of 49% and 97%, respectively [221]. Isopropylamine can also be converted into the isocyanate by this method. As with *tert*-butyl isocyanate, isopropyl isocyanate has to be separated from the *tert*-butanol formed simultaneously. Consequently, its yield is reduced. In contrast, higher branched alkyl isocyanates, such as **406**, can be isolated in quantitative yield.



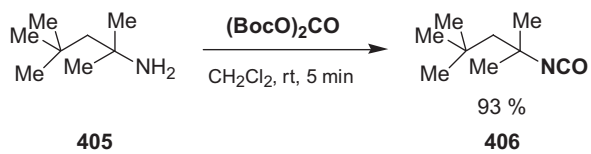
403 **404**



405 **406**



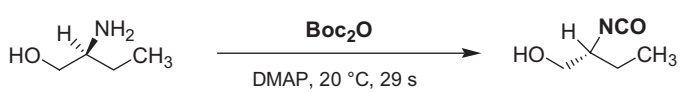
407 **408**



405 **406**

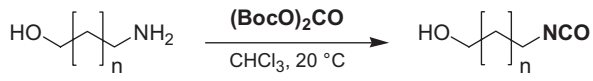
The same authors [230] reported the carbonylation of 2,2-dimethoxy-ethylamine by **$(BocO)_2CO$**.

(*R*)-2-Amino-butan-1-ol was rapidly and selectively converted to *2-isocyanato-butan-1-ol* **412** with **Boc_2O** [274].



411 **412**

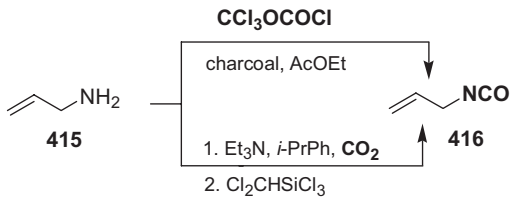
The series of C_4–C_{12} α,ω-amino alcohols **413** have been selectively carbonylated to give the corresponding isocyanates **414** using **$(BocO)_2CO$** [275].



n = 2 - 10

413 **414**

Alkenyl and *alkynyl isocyanates* have been prepared from amines and various carbonylating agents. *3-Isocyanato-propene* **416** was obtained either with **diphosgene** and activated charcoal by heating in ethyl acetate [264] or by using $\mathbf{CO_2}$ [276].



Aliphatic isocyanates from halosilyl or *O*-silyl carbamates of amines

Prop-2-ynyl isocyanate has been obtained by the latter method [118].

A method for the preparation of halosilyl carbamates and isocyanate involves direct synthesis from amines via halosilyl carbamate intermediates [277]. A primary amine is converted to its carbamic acid salt, which is then treated with a silane containing ≥ 2 halogen atoms bonded to Si. Gentle heating of the resulting halosilyl carbamate gives the isocyanate. In an alternative (exchange) procedure, the carbamic acid salt is treated with any halosilane to form a silyl carbamate, which is *trans*-silylated.

Typical procedure. *Methyl isocyanate and hexamethylenediisocyanate* [277]: Gaseous $MeNH_2$ (50 g) was treated with dry ice (50 g) to give methylammonium methylcarbamate. A mixture of methylammonium methylcarbamate (21 g) in PhCl or mixed xylenes (100 mL) was then treated with $SiCl_4$ (24 mL) to give 9 g of methyl isocyanate, which distilled off as soon as it was formed. In an example of the exchange procedure, 1,6-hexamethylenediamine was treated with $\mathbf{CO_2}$ and $\mathbf{Me_3SiCl}$ to give the silyl carbamate, which was *trans*-silylated with **trichloro(phenyl)silane** and heated under nitrogen to give *hexamethylene diisocyanate*.

A method for preparing alkyl isocyanates by the reaction of ammonium salts of *N*-alkylcarbamic acids with **chlorosilanes** has been reported [278].

Typical procedure: *Allyl isocyanate* [278]: $\mathbf{CO_2}$ was bubbled through a 1:1 allylamine/triethylamine mixture in diisobutyl ether at -25 to -10 °C to give a suspension of $CH_2{=}CHCH_2NCO_2^-\ {}^+HNEt_3$. To this was added 2 equiv. of $PhSiCl_3$ at ≤ 10 °C, and the mixture was distilled to decompose the intermediate $CH_2{=}CHCH_2NHCO_2SiCl_2Ph$. The fraction boiling at 81–95 °C was redistilled to give allyl isocyanate (62%).

A process for obtaining *organic isocyanates* via *O*-silylurethanes has been reported

[279]. Silyl urethanes $(RNHCO_2)_nSiR^1_{4-n}$ (R = Me, Bu, CH_2=$CHCH_2$; R^1 = Me, Et, Ph; $n = 1–3$) were prepared in yields of 66.1–99.0% by treating $(RNH)_nSiR^1_{4-n}$ with **CO_2** at approx. 20 °C. Thermal decomposition in the presence of H_3SiCl gave the isocyanate.

A method for obtaining isocyanates using a **silyl protective group** for amines has been reported [280]. $RNHSiMe_3$ was treated with **CO_2** at 20–50 °C to form $RNHCO_2SiMe_3$, which was treated with Me_3SiCl in the presence of Et_3N to give $RN(SiMe_3)CO_2SiMe_3$. The latter was pyrolyzed at 100–150 °C to give *RNCO* (R = Me, Bu, allyl). Passing a mixture of $(Me_3Si)_2NH$ and **CO_2** through a quartz tube at 500 °C gave the *isocyanate* in 20% yield via similar intermediates.

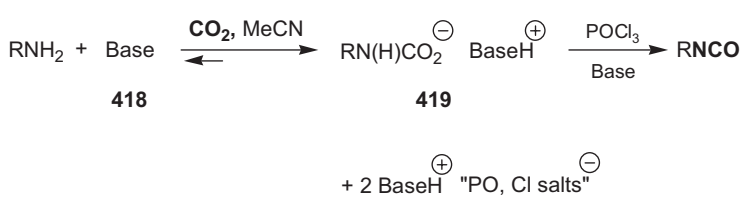
A versatile and efficient method for the synthesis of trimethylsiloxy-substituted isocyanates has been described [281]. The reaction of HO–Z–NH_2 [Z = $(CH_2)_n$, CH_2CMe_2, 4-C_6H_4, 3-C_6H_4, 4-C_6H_4CO, $n = 2–4$] with $(Me_3Si)_2NH$ containing 3 drops of **Me_3SiCl** at 130–150 °C gave Me_3SiO–Z–NH_2 in 75–94% yield, which on heating with 4,4′-diisocyanatodiphenylmethane at 120–200 °C gave Me_3SiO–Z–**NCO** in 76–96% yield. Similarly, Me_3SiO–**NCO** was prepared from Me_3SiO–NH_2 in 67% yield.

Carbon dioxide as a substitute for phosgene

A simpler non-phosgene process for the manufacture of isocyanates involves the reaction of amines with **carbon dioxide** (**CO_2**) in the presence of an aprotic organic solvent and a nitrogenous base. The corresponding ammonium carbamate is treated with an electrophilic "dehydrating agent" [198, 282, 283]. This concept has been applied to the synthesis of several aromatic and aliphatic isocyanates. The process relies on the facile formation of amine-carbon dioxide salts using acid halides such as phosphoryl chloride and thionyl chloride [284, 285].

Interesting studies on carbamate product formation, with a view to enhancing the nucleophilic nature of the oxygen center of the carbanion anion and to ascertain the factors that govern the reactivity of various carbamates in the S_N2 reactions, have been reported [286]. High yield conversion of carbamate anions into the corresponding isocyanates is observed under the extremely mild conditions employed (1 atm CO_2, 0–25 °C, <1 h). Symmetric urea formation can be readily inhibited through appropriate manipulation of the reaction conditions.

Carbamate anions **419** are readily generated by the addition of **CO_2** (1 atm) to a solution of the primary amine and 1–4 equiv. of an organic base **418** [*e.g.* NEt_3, *N*-cyclohexyl-*N*′,*N*′,*N*″,*N*″-tetraethylguanidine, *tert*-butyl-iminotris(dimethylamino)-phosphorane, quinuclidine]. Addition of one equivalent of $POCl_3$ or PCl_3/NH_2 to the reaction mixture leads to an exothermic reaction, after which the desired *isocyanate* can be isolated in excellent yield.



Tab. 4.19. Dehydration of carbamate anions with $POCl_3$ [286].

RNH_2[a]	Base[c]	CO_2	RNCO Isolated yield (%)
C_8H_{17}	NEt_3	80 psig	86
C_8H_{17}	NEt_3	1 atm	–
Cy	NEt_3	80 psig	82
HDA	NEt_3	1 atm	90
MeO-Leu-NH_3Cl[b]	CyTEG/NEt_3	1 atm	81
trans-1,4-CHDA	NEt_3	1 atm	72
PPDA[b]	CyTEG/NEt_3	80 psig	69
Jeffamine D-400[b]	CyTEG/NEt_3	1 atm	48
H_6-TDA	NEt_3	1 atm	81
TAN	NEt_3	1 atm	88

[a] HDA = 1,6-hexamethylenediamine; *trans*-1,4-CHDA = *trans*-1,4-cyclohexyldiamine; PPDA = 1,4-diaminobenzene; Jeffamine D-400® (Texaco) = polyoxoalkylenediamine $M_r \approx 400$; H_6-TDA = 20% 2,6-diaminomethylcyclohexane and 80% 2,4-diaminomethylcyclohexane (various mixtures of *cis* and *trans* isomers); TAN = 4-aminomethyl-1,8-diaminooctane. [b] 1 equiv. of CyTEG and 2 equiv. of NEt_3 per NH_2 moiety in cases where CyTEG was used (CyTEG = *N*-cyclohexyl-*N′*,*N′*,*N″*,*N″*-tetraethylguanidine). [d] CH_2Cl_2 was used as the solvent.

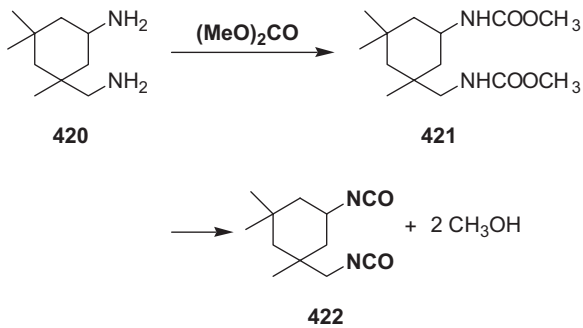
Typical procedure. *Dehydration of carbamate anions with* **$POCl_3$** [286]: The amine (5 mmol), base/NH_2 (15 mmol), and biphenyl (154 mg; internal standard) were dissolved in acetonitrile (25 mL) and **CO_2** (1 atm) was passed in for up to 1 h. **$POCl_3$** (1 equiv./NH_2) was diluted with acetonitrile (25 mL) and both solutions were cooled to 0 °C prior to addition of the carbamate solution to the $POCl_3$. The progress of the reaction was monitored by GC analysis until no more isocyanate was produced. Isolated yields, i.e. following an aqueous acid extraction to remove the phosphorus salts and purification by distillation, are reported in Table 4.19. Virtually identical yields were obtained by using 1 equiv. of PCl_3/NH_2 under the same conditions.

The preparation of polyisocyanates, as well as the conversion of functionalized primary amines with **CO_2** (e.g. isocyanates of amino acid esters and polyether amines), has also been demonstrated. For example, the conversion of 2,4-diaminomethylcyclohexane or hexamethylenediamine under 1 atm of **CO_2** in acetonitrile with **$POCl_3$** gives virtually quantitative yields of the corresponding *isocyanates*. This is particularly notable in that the corresponding conversion of 2,4-diaminomethylcyclohexane by **phosgenation** gives only low yields of the diisocyanate due to the intramolecular formation of cyclic ureas [287]. Similarly, the high yield preparation (>90%) of *4-isocyanatomethyl-1,8-diisocyanatooctane* at atmospheric **CO_2** pressure and 0 °C in <1 h is unique and demonstrates the synthetic utility of this technology.

Reviews on synthetic strategies that replace **phosgene** with **CO_2** and the use of the latter as a building block for *organic carbamates*, *carbonates*, and *isocyanates* have appeared [288, 289].

Dimethyl carbonate as a carboxylating agent

Huels is reportedly operating a commercial route to isophorone diisocyanate (IPDI) **422** based on the addition of isophorone diamine (IPDA) **420** to urea and an alcohol followed by decomposition of the intermediate carbamate to IPDI [290]. An alternative phosgene-free route to IPDI has been patented by Daicel [291]. In this method, **dimethyl carbonate** (**DMC**) is reacted with IPDA to afford isophorone dicarbamate (IPDC). The IPDC is decomposed in the liquid phase in a high-temperature boiling solvent under reduced pressure to give high yields of IPDI.



420 **421** **422**

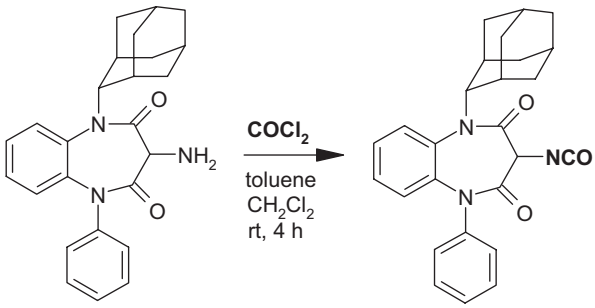
The first step of the process, the addition of IPDA **420** to **DMC**, is base-catalyzed, with alkali and alkaline earth metals being the preferred catalysts. In the patent, the yield quoted for the first step is >98%. The second step of the reaction, cracking the carbamate **421** to IPDI **422**, is facilitated by a manganese, molybdenum, tungsten or zinc catalyst. An interesting and economically important finding is that the yield of IPDI obtained from cracking the IPDC depends significantly on the time elapsed between synthesis of the IPDC and the cracking reaction. For example, a standing time of just 8 h from the time of synthesis of IPDC to the cracking step yields 74% IPDI, 19% monocarbamate (IPMI), and just 6% of high-temperature boiling materials. In contrast, allowing molten IPDC to stand for 48 h before cracking gives much reduced yields of 58% IPDI and 15% IPMC and increases the proportion of unwanted high-temperature boiling materials to 26%. The inventors suggest that the thermal energy needed to maintain IPDC in a molten state (130 °C) to facilitate handling leads to the formation of impurities, which can lead to increased amounts of involatile materials in the ensuing cracking stage.

4.3.1.4 Heterocyclic Isocyanates

In the synthesis of *Cholecystokinin-B receptor antagonists*, a benzodiazepin intermediate bearing an isocyanato group plays a key role. It is prepared from the corresponding amine **423** by carbonylation with **phosgene** in 98% yield [292].

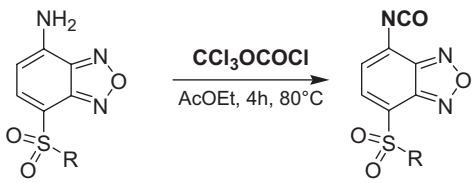
General procedure. *1-N-(Adamant-2-yl)-2,4-dioxo-3-isocyanato-5-N-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin* [292]: **Phosgene** (for a *safe source*, see Chapter 7) in tol-

uene (1.93 M solution, 10 mL) was added to a solution of the amine (0.285 g, 0.68 mmol) in dichloromethane (10 mL). The resulting solution was stirred at 23 °C for 4 h, and then concentrated in vacuo at 50 °C for 2.5 h to give the title compound as a white foam (0.29 g, 0.67 mmol, 98%); IR: $\nu_{max} = 2220\ cm^{-1}$ (N=C=O).



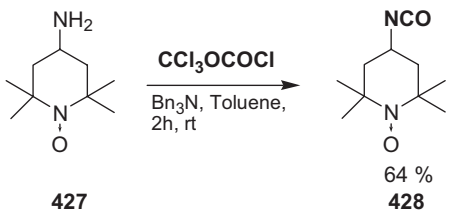
423 **424**

Diphosgene in ethyl acetate has been used as a carbonylating agent to prepare various *S-substituted 7-sulfonyl-benzo[1,2,5]oxadiazole isocyanates* **426** [293].



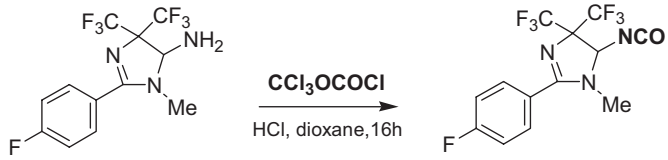
425 **426**

The *4-amino-TEMPO derived isocyanate* **428** was prepared with **diphosgene** at ambient temperature in 64% yield [294].



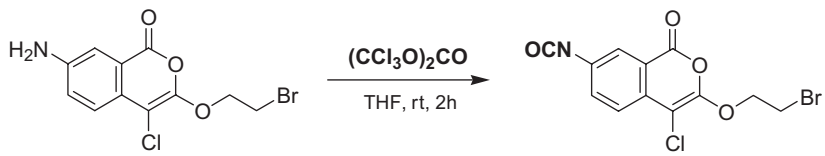
427 **428**

2-(4-Fluorophenyl)-5-isocyanato-1-methyl-4,4-bis(trifluoromethyl)-4,5-dihydro-1H-imidazole **430** was prepared with **diphosgene** in dioxane [295].



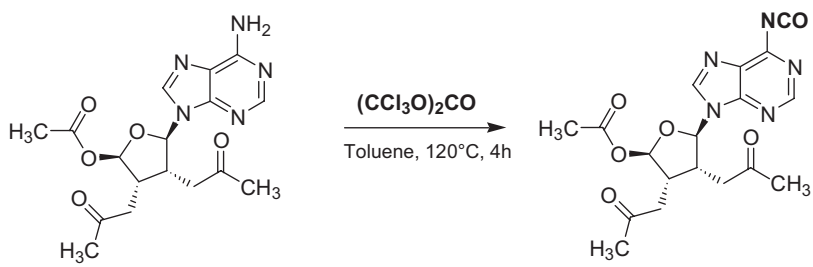
429 **430**

3-(2-Bromoethoxy)-4-chloro-7-isocyanato-isochromen-1-one **432** has been prepared with **triphosgene** in THF at ambient temperature [296], while *acetic acid 4-acetoxy-5-acetoxymethyl-2-(6-isocyanato-purin-9-yl)-tetrahydrofuran-3-yl ester* has been prepared by carbonylating the corresponding amine with **triphosgene** in toluene at 120 °C [297].

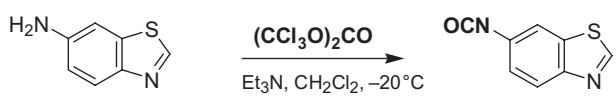


431 **432**

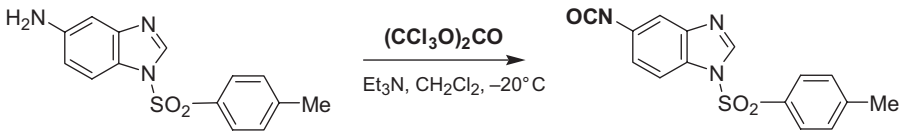
Triphosgene has been used to carbonylate several heterocyclic amines in the presence of triethylamine in dichloromethane at −20 °C [298]. Thus, 3-isocyanatopyrimidine (**434**), 6-benzothiazolyl isocyanate (**436**), 5-isocyanato-1-(toluene-4-sulfonyl)-1*H*-benzoimidazole (**438**), 5-*tert*-butyl-3-isocyanato-isoxazole (**440**), and 5-isocyanato-1*H*-benzotriazole (**442**), have been prepared.



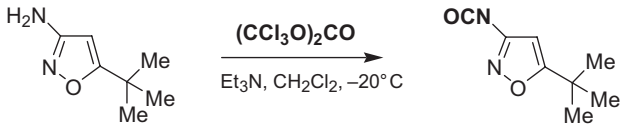
433 **434**



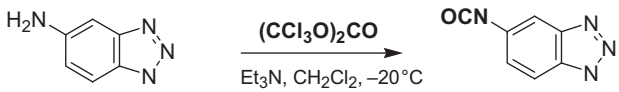
435 **436**



437 **438**

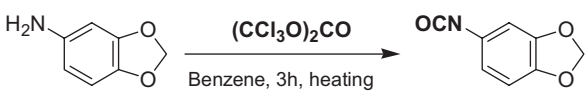


439 **440**



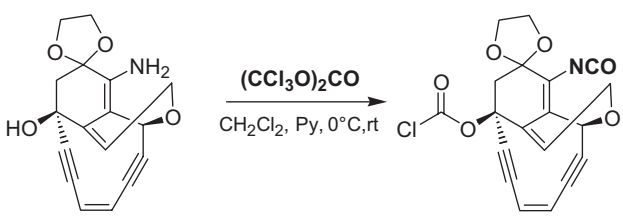
441 **442**

Triphosgene has also been used to carbonylate benzo[1,3]dioxol-5-yl amine **443** [299] and 8′-amino-5′,6′-dihydro-5′-hydroxyspiro(1,3-dioxolane-2,7′(3′*H*)-[1,5][3]hexene[1,5]diyno[1*H*-2]benzopyran)-3′-one **445** [60].



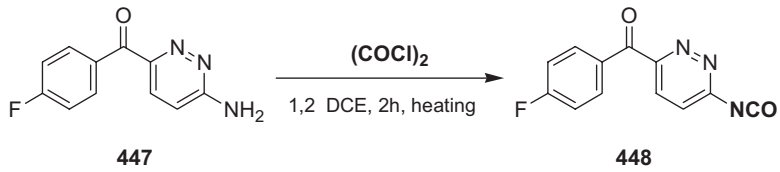
47 %

443 **444**

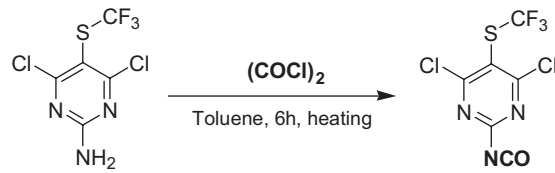


445 **446**

Oxalyl chloride has been used as a phosgene substitute to prepare *4-fluorophenyl-6-isocyanato-pyridazin-3-yl methanone* **448** [301] and *5-trifluoromethylmercapto-2,4-dichloro-6-isocyanato-pyrimidine* **450** [302].



447 448



76 %

449 450

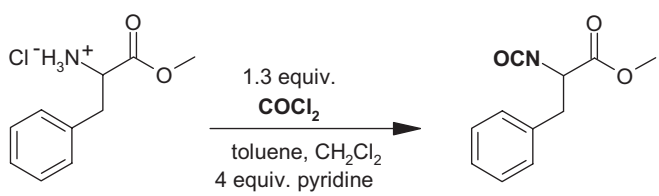
4.3.1.5 Isocyanates of Amino Acids

The reactions of amino acids or amino alcohols with **phosgene** are interesting since they provide in one step molecules with two different functional groups, namely isocyanato acid chlorides or isocyanato chloroformates.

Below are reported reactions of **phosgene**, **diphosgene**, and **triphosgene** with protected amino acids, namely with amino acid esters. Amino acid ester isocyanates are useful synthetic building blocks, precursors to peptides and azapeptides [303, 304], chiral derivatizing agents [305, 306], and reagents for the preparation of chiral chromatographic media [307, 308].

(*S*)-2-Isocyanato-3-phenylpropanoate (phenylalanine methyl ester isocyanate) has been used as a building block for 1,2,4-triazine azapeptides [304], which are inhibitors of thermolysin [309] and human leukocyte elastase (HlE) [310].

A series of various enantiomerically pure *amino acid ester isocyanates* (for example **452**) has been synthesized in yields of 72–95% by carbonylation of the appropriate amino acid ester hydrochlorides (for example **451**) with **phosgene** [311]. The products are based on the amino acids alanine, valine, leucine, isoleucine, phenylalanine, methionine, serine, and glutamic acid.



451 94 % 452

General procedure *for the preparation of amino acid ester isocyanates* [311]: A 250-mL, three-necked, round-bottomed flask, fitted with two rubber septa, a nitrogen inlet adapter, and a magnetic stirring bar, was charged with the amino acid ester hydro-

chloride **451** (0.030 mol), dichloromethane (100 mL), and pyridine (9.8 mL, 0.121 mol). The resulting suspension or solution was cooled in an ice bath for 15 min. A solution of **phosgene** (for a *safe source*, see Chapter 7) (1.93 M in toluene, 20 mL, 0.039 mol) [CAUTION: USE HOOD!] was added by means of a syringe over 20–30 s, and the resulting light-yellow solution was stirred at 0 °C for 2 h. The reaction mixture was extracted twice with cold 0.5 M aqueous HCl (300 mL) and crushed ice (ca. 300 mL). Each aqueous layer was re-extracted with dichloromethane (100 mL). The combined organic phases were extracted with a mixture of cold saturated aqueous NaCl solution (300 mL) and crushed ice (ca. 200 mL), dried over $MgSO_4$, filtered, and concentrated in a rotary evaporator to afford the crude *isocyanate* **452** as a light-brown oil. (During work-up, the isocyanate was only exposed to water for a total of 5–10 min). The product was purified by kugelrohr distillation under reduced pressure.

An earlier publication [312] described the synthesis of *d,l-amino acid ester isocyanates* (at that time called *d,l-carbonyl-amino acid esters*) from the corresponding amino acid ester hydrochlorides by carbonylation with **phosgene**. Ester hydrochlorides of alanine, leucine, phenylalanine **451**, aminobutyric acid, phenyl glycine, norvaline, norleucine, benzyl cysteine, methionine, aspartic acid, and glutamic acid were used; yields of *isocyanates* were 85–97%.

General procedure *for d,l-carbonyl alanine ethyl ester* [312]: In a three-necked, round-bottomed flask fitted with a mechanical stirrer, a gas inlet, and a reflux condenser were placed abs. toluene (50 mL) and d,l-alanine ethyl ester hydrochloride (dried over P_2O_5 at 50 °C in vacuo) (15 g). The mixture was warmed by an oil bath, which was heated to 130–160 °C, and, under vigorous stirring, **phosgene** (for a *safe source*, see Chapter 7) was passed in for 1.5 h. HCl was evolved and the hydrochloride was gradually dissolved. The toluene was then removed by fractional distillation in vacuo at 45 °C and the residue was purified by distillation; bp 69 °C (11 Torr), affording a colorless liquid; yield 13 g (91%). *Author's remark:* Excess phosgene has to be passed into a vessel filled with ethanol to make it harmless, and thereby HCl gas is evolved (see Chapter 7).

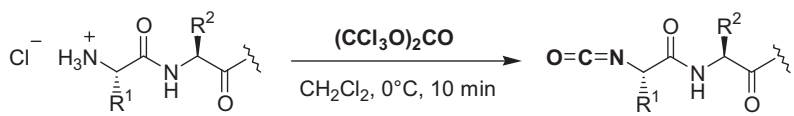
Procedures using **triphosgene** as an equivalent of a solution of **phosgene** in toluene and either pyridine or aqueous sodium hydrogen carbonate as a base have been reported [313]. These mild reaction conditions are superior to alternative methods for the preparation of *amino acid ester isocyanates*, as described in the present chapter, which involve either refluxing the amino acid ester hydrochloride in toluene for several hours while purging with **gaseous phosgene** [312] or treating the amino acid ester hydrochloride with **di-*tert*-butyl dicarbonate** and 4-dimethylaminopyridine (DMAP) [314].

Amino acid ester isocyanates are produced cleanly by this method and can often be used without purification. If desired, volatile amino acid ester isocyanates, such as the title compound, can be purified to analytical purity by kugelrohr distillation. The amino acid ester isocyanates generated by this method are formed without detectable racemization (>99.5% *ee*); the enantiomeric purity of the isocyanates can be checked by trapping with (*S*)-1-phenylethylamine followed by ^{1}H NMR

analysis of the resulting urea adducts. If this method is used to generate isocyanates of peptides, then efficient stirring is necessary to prevent epimerization of the peptide isocyanates [315].

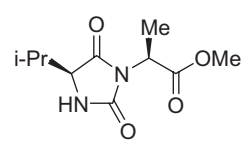
Typical procedure. *Methyl (S)-2-isocyanato-3-phenylpropanoate* (optical isomer of **452**) [315]: A 250-mL, three-necked, round-bottomed flask was equipped with a mechanical stirrer and charged with dichloromethane (100 mL), saturated aqueous sodium hydrogen carbonate solution (100 mL), and L-phenylalanine methyl ester hydrochloride (5.50 g, 25.5 mmol). The biphasic mixture was cooled in an ice bath and stirred mechanically while **triphosgene** (2.52 g, 8.42 mmol) was added in a single portion. The reaction mixture was stirred in the ice bath for 15 min and then poured into a 250-mL separatory funnel. The organic layer was collected, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), vacuum filtered, and concentrated at reduced pressure in a rotary evaporator to leave a colorless oil. This oil was purified by kugelrohr distillation (130 °C, 0.05 mmHg) to afford 5.15 g (98%) of *methyl (5)-2-isocyanato-3-phenylpropanoate* as a colorless oil. The optical purity of the product was determined to be >99.5% by trapping with (*S*)-1-phenylethylamine and ^1H NMR analysis of the resulting urea adduct, as described in reference [311].

Peptide isocyanates **454** have been prepared using **triphosgene** (0.7 mmol/mmol peptide hydrochloride) **453** under milder reaction conditions, so as to minimize the formation of hydantoins **455** and other side products [313].



453 **454**

R^1 = $PhCH_2$, R^2 = *i*-Bu Phenylalanylleucine methyl ester hydrochloride, Yield 91%
R^1 = *i*-Pr, R^2 = Me Valylalanine methyl ester hydrochloride, Yield 67 %

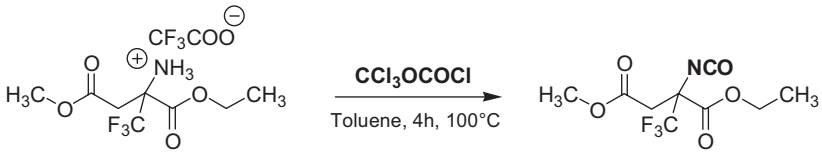


455

Typical procedure. *Valylalanine methyl ester isocyanate* [313]: Reaction of valylalanine methyl ester hydrochloride (123 mg, 0.515 mmol) with **triphosgene** (a solution of 112 mg in 1 mL of dichloromethane, 0.38 mmol) yielded 112 mg (95%) of the crude isocyanate **454** as a colorless oily solid. ^1H NMR analysis of the product revealed the presence of 8% of hydantoin **455** and 15% of an additional impurity.

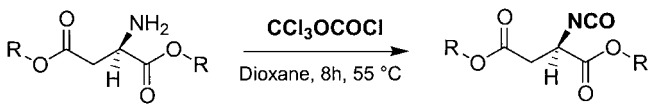
For the preparation of many other peptide isocyanates, **phosgene**, either neat or in toluene solution, rather than **triphosgene** was preferred.

The *isocyanate from 2-amino-2-trifluoromethyl succinic acid 1-ethyl ester 4-methyl ester* **457** was prepared in high yield using **diphosgene** in toluene [316].



456 **457**

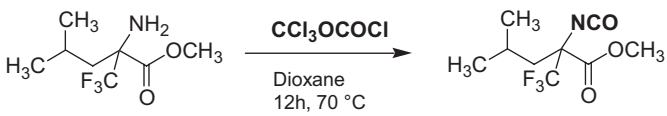
L-Aspartic acid esters **458** react with **diphosgene** in dioxane at 55 °C to give the corresponding isocyanate **459** in 62% yield [317].



458 **459**

R = *i*-Pr, yield 62 %
R = Me, yield 81 %

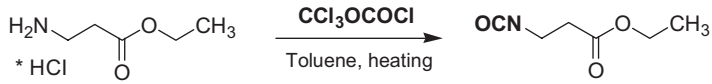
2-Isocyanato-4-methyl-2-(trifluoromethyl)pentanecarboxylic acid methyl ester **461** was prepared in 68% yield with **diphosgene** in dioxane [318].



racemate **460** 68 % **461**

Typical procedure. *m-(Trifluoromethyl)phenylalanine methyl ester isocyanate* [310]: **Diphosgene** (5.0 mL, 0.042 mol) was added to a suspension of *m*-(trifluoromethyl) phenylalanine methyl ester hydrochloride (8.51 g, 0.03 mol) in dry dioxane (75 mL) under nitrogen. The reaction mixture was refluxed overnight under an efficient hood, with the use of a gas trap (300 mL of 20% aqueous NaOH). Subsequent removal of the solvent in vacuo, followed by vacuum distillation of the oily residue, yielded 6.9 g (85%) of the pure isocyanate.

β-(Ethoxycarbonyl)ethyl isocyanate **463** was prepared by heating the *β*-alanine ethyl ester hydrochloride **462** with **diphosgene** in the presence of active charcoal in toluene (71.2% yield). Similarly, *α*-methoxycarbonyl-*β*-methylbutyl isocyanate was obtained by treating L-leucine methyl ester hydrochloride with **diphosgene** in toluene (69.7% yield) [319].

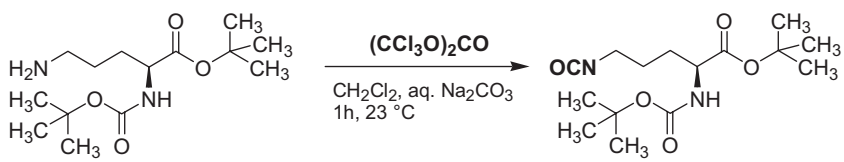


462 **463**

Typical procedure. *L-α-Ethoxycarbonyl-β-phenylethyl isocyanate* [319]: **Diphosgene** (16.0 g, 0.07 mol) was added dropwise to a mixture of L-phenylalanine ethyl ester hydrochloride (16.0 g, 0.07 mol) and active carbon (0.1 g) in toluene (200 mL). The reaction mixture was gradually heated to 80 °C over a period of 1 h, the addition of **diphosgene** being adjusted so as to finish at the time when the temperature reached 80 °C. The reaction was continued for an additional 2 h at 100–110 °C. Subsequent removal of the toluene and distillation of the reaction mixture gave *L-α-ethoxycarbonyl-β-phenylethyl isocyanate* (13.75 g, 89.6%), bp 141–142 °C.

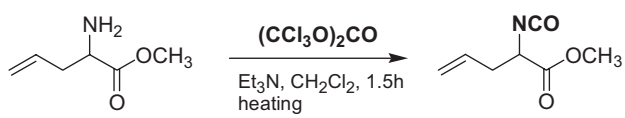
Typical procedure. *L-α-Ethoxycarbonyl-β-(methylthio)propyl isocyanate* [319]: To a mixture of methionine ethyl ester hydrochloride (14.96 g, 0.07 mol), active carbon (0.01 g), and toluene (200 mL), **diphosgene** (10.4 g, 0.0525 mol) was added dropwise with stirring. The reaction mixture was gradually heated to reflux, which was maintained for 2 h. Subsequent distillation of the reaction mixture gave 7.37 g (51.8%) of L-α-ethoxycarbonyl-β-(methylthio)propyl isocyanate as a colorless liquid; bp 133 °C (7 mmHg).

N^a-(Boc)-L-ornithine *tert*-butyl ester **464** was carbonylated with **triphosgene** to give the corresponding *isocyanate* **465** [320].



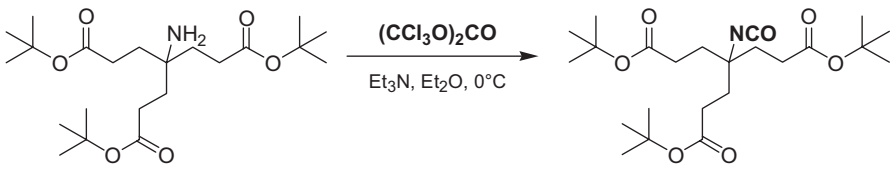
464 **465**

2-Isocyanato-pent-4-enoic acid methyl ester **467** was prepared by carbonylating allylglycine methyl ester **466** with **triphosgene** in dichloromethane [266].



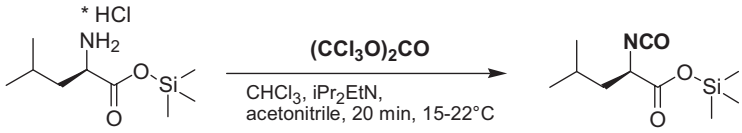
466 **467**

A high yield of *isocyanate* **469** was obtained by carbonylating 4-amino-4-(2-*tert*-butoxycarbonylethyl)-heptanedioic acid di-*tert*-butyl ester **468** with **triphosgene** in diethyl ether [321].



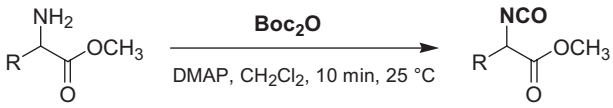
468 **469**

Trimethylsilyl esters of C5–C6 branched α-amino acids and their enantiomers **470** have been converted into the corresponding *isocyanates* **471** with **triphosgene** [322].



470 **471**

A convenient method for the synthesis and derivatization of *enantiopure α-isocyanato carboxylic acid esters* starting from α-amino acid esters has been devised [314]. The isocyanates are obtained in enantiomerically pure form (> 99% *ee*) by a DMAP-catalyzed isocyanation with **Boc_2O**, which proceeds in 10 min at room temperature (for typical procedures employing **Boc_2O**, see the *Boc_2O Section* of the present chapter). In situ derivatization of the isocyanates by reaction with amines and alcohols affords the corresponding enantiopure ureas and carbamates. Methyl esters of various amino acids **472** have been carbonylated by **Boc_2O** at ambient temperature [314].

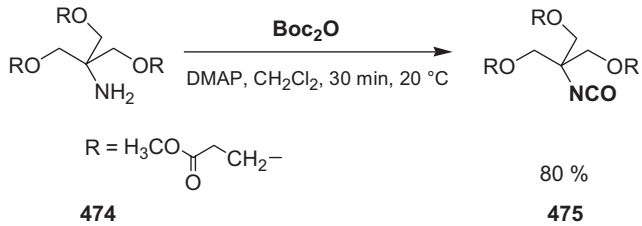


472 **473**

L-alanine Me ester yield 49 %
L-valine Me ester yield 91 %
L-isoleucine Me ester yield 90 %
L-leucine Me ester yield 82 %

3-[2-Amino-3-(2-methoxycarbonylethoxy)-2-(2-methoxycarbonylethoxymethyl)propoxy]-propionic acid methyl ester **474** was carbonylated with **Boc_2O** at ambient temperature [323].

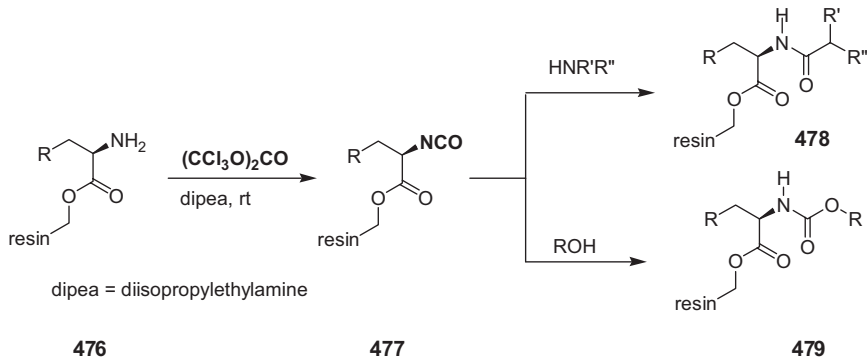
11-Isocyanato-undecanoic acid methyl ester was prepared in 80% yield by carbonylating *11-amino-undecanoic acid methyl ester* with **Boc_2O** [230].



Automated solid-phase synthesis with triphosgene

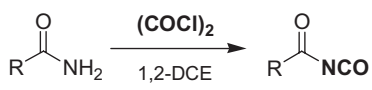
In investigations on automated solid-phase organic chemistry, transformations involving the use of the highly reactive reagent **triphosgene** have been conducted using the ACT Model 496 MOS [324]. In particular, applications to the parallel synthesis of a variety of urea and urethane derivatives, primarily derived from amino acid precursors, have been developed.

Since the urea moiety has been reported to be extremely effective in the design of certain active peptidomimetics, this automated methodology provides an excellent opportunity for further diversity studies in these as well as other systems.



4.3.1.6 Acyl Isocyanates

Oxalyl chloride has been used to prepare several acyl isocyanates starting from the corresponding amides (Table 4.20). All the reactions described below are amide carbonylations.

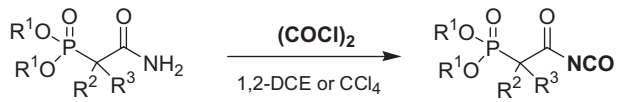


Typical procedure. *4-Toluoyl isocyanate* [325]: **Oxalyl chloride** (31.7 g, 0.25 mol) in 1,2-dichloroethane was added to 4-toluamide (24.3 g, 0.18 mol) in 1,2-dichloroethane at 0 °C. The solution was allowed to warm to room temperature, and then

refluxed with stirring for ca. 24 h. The solvent was subsequently evaporated in vacuo, and the residue was distilled under reduced pressure to give 4-toluoyl isocyanate (22.0 g, 0.14 mol, 79%), bp 61–67 °C (0.75 mmHg).

Typical procedure. *4-Fluorobenzoyl isocyanate and 4-methoxybenzoyl isocyanate* [333]: **Oxalyl dichloride** (1.25 molar equiv.) was quickly added to a suspension of 4-fluorobenzamide or 4-methoxybenzamide in dichloromethane (ca. 2.2 M) at 20 °C. The resulting clear solution was refluxed for 12–20 h, and then the solvent was evaporated. The crude acyl isocyanates were purified by distillation.

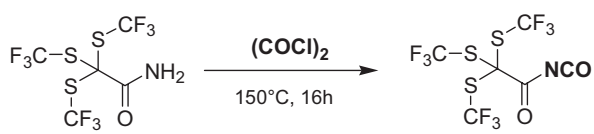
Similar transformations using **oxalyl dichloride** were applied to obtain *dialkoxyphosphono-acetylisocyanates* **483** [329, 337, 338].



482 **483**

R^1	R^2	R^3
Et	H	H
Et	H	Me
Et	Me	Me
Et	Cl	Cl
Pr	Cl	Cl
Pr	H	H
i-Pr	Cl	Cl
n-Bu	H	H
n-Bu	Cl	Cl

Tris(trifluoromethylsulfanyl)acetyl isocyanate **485** was prepared in 70% yield from the corresponding amide **484** and **oxalyl dichloride** at 150 °C [339].



484 70 % **485**

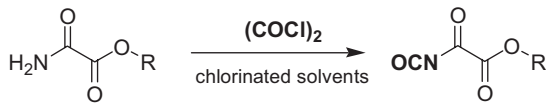
Methacryloyl isocyanate was prepared by the reaction of ethyl *N*-methacryloylcarbamate with thionyl chloride in the presence of hexabutylguanidinium chloride [340].

Tab. 4.20. Acyl isocyanates **481** prepared with **oxalyl dichloride**.

R (481)	*Reaction conditions*	*References*
Pivaloyl	Solv.: 1,2-DCE	325
Propionyl, Isovaleryl, Isobutyryl, Butyryl	Solv.: 1,2-DCE	326
Propionyl	Solv.: dichloromethane	325
Trifluoroacetyl	Solv.: 1,2-DCE	327, 328
Chloroacetyl	Solv.: 1,2-DCE, 5 h, heating, 71%	329, 330
	Solv.: benzene, 5 h, heating	331
	Solv.: 1,2-DCE, 64%	332
Dichloroacetyl	Solv.: 1,2-DCE, 68%	331
2,2-Dichloropropionyl	Solv.: 1,2-DCE	325
Trichloroacetyl	Solv.: 1,2-DCE, 60%	326, 331, 333
3-Bromo-2,2-dimethylpropanoyl	Solv.: 1,2-DCE, 24 h, heating, 81%	334
Phenyl-acetyl	Solv.: 1,2-DCE, 24 h, heating, 36%	331
Diphenyl-acetyl	Solv.: 1,2-DCE, 24 h, heating, 37%	331
3,4-Dichlorophenyl-acetyl	Solv.: 1,2-DCE, 24 h, heating, 97%	331
Benzoyl	Solv.: 1,2-DCE, 24 h, heating, 75%	331
	Solv.: dichloromethane, 80%	333
Bromoacetyl	Solv.: 1,2-DCE	335
4-Fluorobenzoyl	Solv.: dichloromethane, 95%	333
4-Methoxybenzoyl	Solv.: dichloromethane, 90%	333

The acylation of diethyl iminocarbonate, $(EtO)_2C{=}NH$, with **oxalyl chloride** or **phosgene**, gave $(EtO)_2C{=}NC(OEt){=}NCO_2Et$, EtO_2CNCO, $(EtO_2CNH)_2CO$, $[CON{=}C(OEt)_2]_2$, and $(CONHCO_2Et)_2$. The primary intermediates in the reactions were $(EtO)_2C{=}NCOCl$ and $(EtO)_2C{=}NCOCOCl$ [341].

Several oxoacetyl isocyanates (Table 4.21) have been prepared with **oxalyl dichloride** starting from the corresponding oxalamic acid esters.

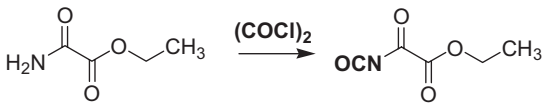


486 **487**

Tab. 4.21. Oxoacetyl isocyanates prepared with oxalyl dichloride.

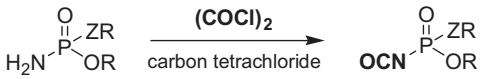
R (487)	*Reaction conditions*	*References*
Me	Dichloromethane, 15 h, heating	342
	Dichloromethane	325
	Chloroform, 55%	343
Et	Chloroform	344
	1,2-DCE, 5 h, 0 °C and then heating at reflux for 5 h, 82%	345, 346
Pr		342

Ethoxalyl isocyanate **489** was obtained from oxalamic acid ethyl ester **488** [347] with oxalyl chloride.



488 **489**

Phosphoramidic or thiophosphoramidic acid dialkyl esters (Et, *i*Pr) react with oxalyl dichloride to give the corresponding isocyanates [348, 349] under mild conditions, i.e. 1 h, 50 °C in tetrachloromethane; 64% yield [350].

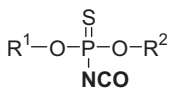


R = *i*-Pr, Et
Z = O, S

490 **491**

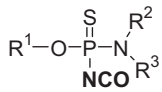
Typical procedure. *Diethoxyphosphinyl isocyanate* (*diethyl phosphorocyanatidate*) [350]: A solution of diethyl phosphoramidate (30.6 g, 0.2 mol) in tetrachloromethane (50 mL) was slowly added dropwise with stirring and efficient external cooling to a solution of **oxalyl chloride** (27.9 g, 0.22 mol) in the same solvent (150 mL). The reaction temperature was kept at −5 to 0 °C. After completion of the addition, the temperature of the mixture was slowly increased to 50 °C and this was maintained for 1 h. The mixture was then cooled to room temperature, filtered, and concentrated in vacuo. The residual liquid product was distilled in vacuo (bp 85–87 °C/10 Torr); yield 22.9 g (64%).

Similar transformations have been reported for the preparation of amidothiophosphoric acid *O*,*O*′-dialkyl ester isocyanates **492** [348, 349] and *O*-alkyl-*N*-dialkylphosphorothioate diamide **493** [351].



492

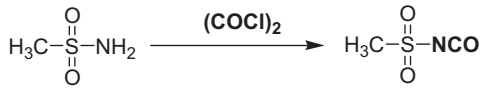
R^1 = Pr R^2 = Pr
R^1 = Et R^2 = Et
R^1 = Bu R^2 = Bu
R^1 = Me R^2 = Et



493

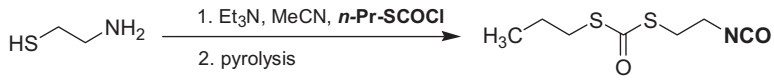
R^1 = Et R^2 = Bu R^3 = Bu
R^1 = Pr R^2 = Et R^3 = Et
R^1 = Et R^2 = Pr R^3 = Pr
R^1 = Et R^2 = Et R^3 = Et

Methanesulfonyl isocyanate **495** was prepared from methanesulfonamide **494** with **oxalyl dichloride** [352].



494 495

2-(Propylmercaptocarbonylmercaptoethyl)isocyanate **497** was obtained from 2-amino-ethanethiol **496** and the *S*-propyl ester of thiocarbonochloridic acid [353].

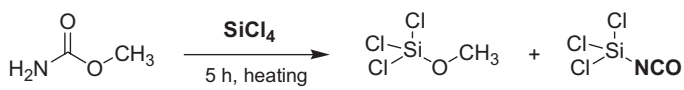


496 497

Typical procedure. *2-(Propylmercaptocarbonylmercapto)ethylisocyanate or 2-(n-propyldithiolcarbonato)ethyl isocyanate* **497** [353]: To a suspension of 2-mercaptoethylamine hydrochloride (11.4 g, 0.10 mol) in acetonitrile (50 mL) was added triethylamine (30.4 g, 0.30 mol). A new solid precipitated. The resulting suspension was added in portions, with stirring and cooling, to a solution of ***n*-propyl chlorothiolformate** (27.6 g, 0.20 mol) in acetonitrile (50 mL). When there was no further increase in temperature, the mixture was allowed to stand for 1 h, and was then poured into ice/water. An oil separated, which was extracted into diethyl ether (150 mL), and the solution was dried over magnesium sulfate. Evaporation of the ether left 24.2 g of liquid. Three distillations under reduced pressure with accompanying pyrolysis were carried out on a 10.0 g sample at a pot temperature of 188–197 °C and a pressure of 0.7 mmHg. A fourth distillation gave 2.5 g (30%) of pure *2-(n-propyldithiolcarbonato)ethyl isocyanate*; bp 108–110 °C (1 mmHg).

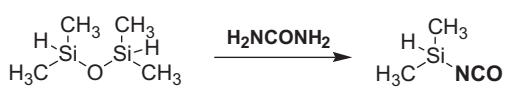
4.3.1.7 Silane Isocyanates

Methyl carbamate **498** reacts with **tetrachlorosilane** to give *trichloroisocyanatosilane* **500** and trichloromethoxysilane **499** [354].



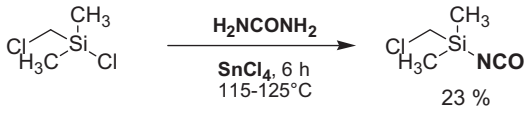
498 499 500

Dimethylisocyanatosilane **502** was prepared from urea and 1,1,3,3-tetramethyldisiloxane **501** [355].

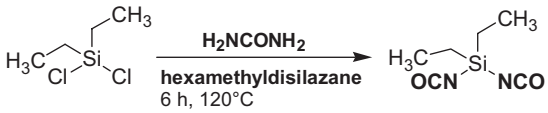


501 502

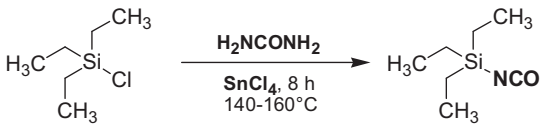
(Chloromethyl)isocyanatodimethylsilane **504**, *triethylisocyanatosilane* **508**, and various silane diisocyanates were prepared by heating chloro(chloromethyl)dimethylsilane or dichlorodialkyl silanes with **urea** in the presence of $SnCl_4$ or **hexamethyldisilazane** for 5–6 h at 115–125 °C [356].



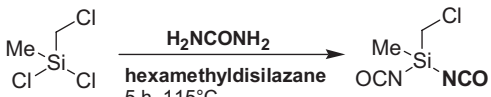
503 **504**



505 **506**

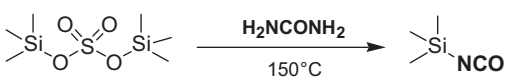


507 **508**



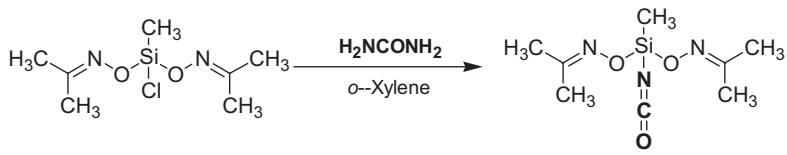
509 **510**

Isocyanato-trimethyl silane isocyanate **512** was obtained in high yield (80%) from bis(trimethylsilyl)sulfate **511** and dried **urea** at 150 °C, the product being distilled [357].



511 **512**

A low yield of *bis(acetoximino)isocyanatomethyl silane* **514** was obtained by reacting bis(acetoximato)methylchlorosilane **513** with **urea** in *o*-xylene [358].

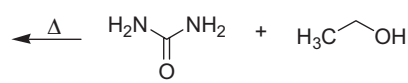


513 **514**

4.3.2 Carbamates

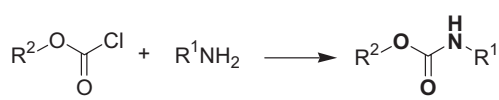
N-Substituted esters of carbamic acid (carbamic acid is the mono-amide of carbonic acid) are compounds containing the *-NHCOOR* group, and are named *carbamates* or *urethanes*. Urethane (or urethan) is also used as a name for ethyl carbamate **515**, NH_2COOEt (a compound which has been shown to act as a carcinogen in some animals), and sometimes even for the whole class of carbamate esters. It is formed by reaction of ethanol with isocyanic acid **516** or urea **517**. Since *"urethane"* nomenclature may be confusing there is little justification in its continued use.

516 **515**



517

As outlined in Scheme 4.2, carbamates are formed when *chloroformates* (R^2OCOCl) or *N,N*-disubstituted *carbamoyl chlorides* (R^1R^3NCOCl) are treated with primary amines or alcohols, respectively [359–362]. One equivalent of a base such as a tertiary amine is used to promote these reactions.



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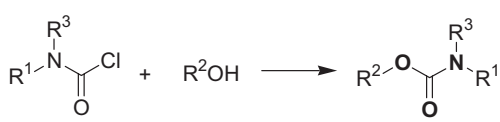

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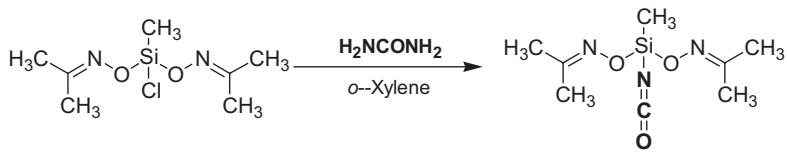

513 **514**

4.3.2 Carbamates

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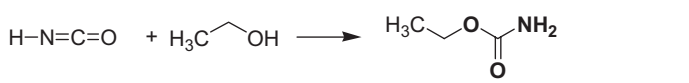
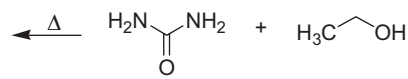
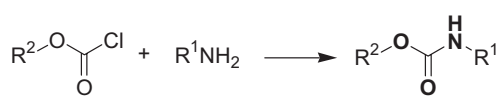


516 **515**



517

As outlined in Scheme 4.2, carbamates are formed when *chloroformates* (R^2OCOCl) or *N,N*-disubstituted *carbamoyl chlorides* (R^1R^3NCOCl) are treated with primary amines or alcohols, respectively [359–362]. One equivalent of a base such as a tertiary amine is used to promote these reactions.



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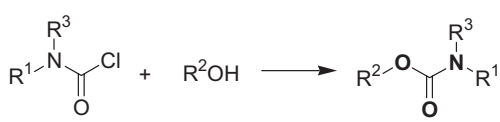


519

Phosgenations – A Handbook. L. Cotarca, H. Eckert

ISBN: 3-527-29823-1

Carbamates are generally prepared from *isocyanates* or *chloroformates* (see Scheme 4.2). Since isocyanates and chloroformates are usually prepared with **phosgene**, the corresponding synthetic routes are subject to the relevant safety considerations regarding the phosgene source (for a *safe phosgene source*, see Chapter 7). Moreover, the handling of several *lower alkyl isocyanates* is associated with a similar hazard level (toxicity), and therefore the search for a less hazardous procedure has been intense.

Several synthetic methods are available for the preparation of *cyclic carbamates* such as oxazolidin-2-ones or thiazolidin-2-ones. General reviews on the synthesis and chemistry of 2-oxazolidinones detailing the reactions of *N,O*- or *N,S*-binucleophilic substrates with various carbonylating agents have been published [363, 364].

4.3.2.1 Phosgene and Haloformates as Reagents

Many procedures for carbamate preparation have been developed in connection with the high demand for amine group protection of amino acids in peptide synthesis [155, 365]. Some examples of reported procedures employing **phosgene**, **alkyl-** or **alkylene chloroformates** are given below.

N-Alkyloxycarbonyl derivatives of amino acids [366, 367] are of increasing interest owing to the fact that they can be submitted to deprotection by mild acidolysis, aminolysis or hydrogenolysis (Table 4.22).

The choice of protecting group is usually determined by the compatibility of the cleavage reaction that is appropriate for each protected substrate. In the special

Tab. 4.22. Cleavage of alkyl carbamates (deprotection methods for the most common alkoxycarbonylamines).

N-Protecting group	*Short name*	*Cleavage method*
Methoxy- and ethoxycarbonyl		Alkaline hydrolysis under vigorous conditions, or with powerful nucleophiles such as thiolates
tert-Butoxycarbonyl	Boc	Acidolysis (CF_3COOH)
Benzyloxycarbonyl	Cbz, Z	Hydrogenolysis (H_2/Pd-C), or acidolysis (48% HBr/AcOH)
4-Nitro benzyloxycarbonyl	4-NO_2-Z	Hydrogenolysis (easier than Cbz, more resistant to acidic cleavage)
9-Fluorenylmethoxycarbonyl	Fmoc	Mild aminolysis (20% piperidine in DMF)
Allyloxycarbonyl	Aloc	Pd(0)-dimedone, or 2-Et-hexanoic acid/$Pd(Ph_3P)_4/Ph_3P$
2-(Trimethylsilyl)ethoxycarbonyl	Teoc	Tetra-*n*-butylammonium chloride and $KF{\cdot}2H_2O$ in MeCN
2,2,2-Trichloroethoxycarbonyl	Troc	Zn in AcOH at room temp. or in EtOH at reflux
2,2,2-Trichloro-*tert*-butoxycarbonyl	TCBoc	Zn in AcOH at room temp., or supernucleophiles such as $Li[Co^{I}Pc]$, Pc = phthalocyanine

case of amino acid analysis, the stability, reliability, and spectroscopic characteristics are important (thus, the 9-fluorenylmethoxycarbonyl group fluoresces), although a lack of appreciation of side reactions can undermine the credibility of results [368].

In the absence of any special factor, the *tert-butoxycarbonyl group* is used most widely because of its good handling characteristics; these derivatives are generally easy to purify by recrystallization. The *tert*-butoxycarbonyl group (abbreviated as *Boc* or *t-Boc*) remains one of the most frequently used amino protecting groups in organic synthesis. Being inert towards catalytic hydrogenolysis and extremely resistant towards basic and nucleophilic reagents, it is an ideal orthogonal partner to benzyl esters and carbamates used in peptide synthesis.

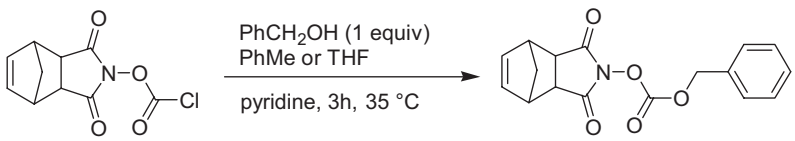
Introduction of the selectively removable *N-benzyloxycarbonyl*, *N-(9-fluorenylmethoxy)carbonyl*, and other *N-alkoxycarbonyl* groups is usually achieved by use of the corresponding *chloroformate* as reagent. *Methyl* and *ethyl carbamates* are typically formed by reaction of the amine with the corresponding chloroformate in the presence of a base such as K_2CO_3 or NEt_3.

Optimized procedures must be developed to avoid the side reactions that arise for the same reasons as those described for general acylation. The preparation of *N*-benzyloxycarbonyl *β*-benzyl-L-aspartate, for example, shows significant side-product formation [369–371]. The reasons for the different results – some acylations give substantial amounts of side-product while others do not – might be associated with the presence of functional groups nearby in the side-chain (as in the case of aspartic acid and threonine derivatives) that enhance the reactivity of the carboxyl group. Moreover, anions and other species in the reaction mixture may play a role in stabilizing a negative charge on the carboxyl group and thereby favoring the side reaction [368].

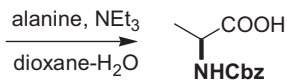
Benzyl chloroformate remains the most widely used reagent for *N*-benzyloxycarbonylation, although many alternative leaving groups are available. The protection is often abbreviated as *Cbz* or *Z*. **Benzyl chloroformate** (**Z-Cl**; see also Section 4.2.1), a cheap and commercially available reagent, reacts with an amine in the presence of triethylamine, aqueous $NaHCO_3$ or NaOH to give the *Z* derivative in good yield. The reagent deteriorates on storage and therefore should be freshly distilled under high vacuum immediately before use. Alternative reagents **BnOCOX** include those where **X** = ***O*-succinimidyl**, **benzotriazolyl**, **imidazolyl**, and **cyano**. A recent innovation, which offers a versatile method for preparing a wide range of carbamate-type protecting groups, including *Boc* and *Fmoc*, utilizes the crystalline reagent **5-norbornene-2,3-dicarboximido chloroformate 520** (mp 98–100 °C) [372].

Typical procedure. *N-Benzyloxycarbonyl-L-proline* [368]: Caution! *All procedures must be carried out in an efficient fume cupboard, wearing latex gloves and chemical-proof safety goggles*. L-Proline (10.0 g, 8.7 mmol) was dissolved in 2 M sodium hydroxide solution (40 mL), and the solution was cooled to ice-water temperature. **Z-Cl** (20.5 g, 12 mmol) was added portionwise, with vigorous stirring or occasional shaking, over a period of 30 min at 0–5 °C to the solution of L-proline. The ice bath was then removed and stirring or occasional shaking was continued for 30 min

while the reaction mixture warmed to room temperature. The mixture was then acidified to Congo red by the gradual addition of concentrated hydrochloric acid, and the oil was extracted into ethyl acetate. The extract was dried over magnesium sulfate, the mixture was filtered, and the filtrate was concentrated in vacuo. The residue was extracted/triturated with warm tetrachloromethane. The washings were decanted and the residue was further purified by recrystallization from ethyl acetate/petroleum ether. Product: 18.1 g, 89%, mp 76–77 °C; $[\alpha]_D{}^{21} = -61.7$ ($c = 5.3$, acetic acid); $[\alpha]^{21}{}_D = -60.6$ ($c = 2$, ethyl acetate).



520 **521**



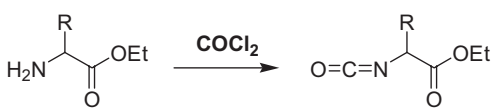
91 %

522

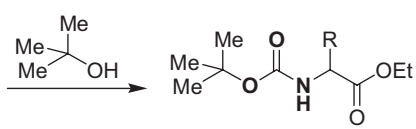
The *tert-butoxycarbonyl group* (*Boc*) is one of the most advantageous protecting groups in the preparation of complicated peptides. For peptides containing methionine, the *Boc* group offers some advantages over the carbobenzoxy group (*Z*, *Cbz*) [378]. The principal disadvantage to the use of the *Boc* group lies in the difficulty of preparing and storing *tert-butyl chloroformate*. The instability of *tert-butyl* chloroformate precludes its use for preparing *Boc* derivatives and hence a large number of a1ternative reagents and methods have been developed.

Although ***t*-butyl azidoformate** [373–375], ***t*-butyl *p*-nitrophenyl carbonate** [376], and ***t*-butyl cyanoformate** [375] have been recommended as *t*-butoxycarbonylating reagents, these cannot be synthesized as easily as **benzyloxycarbonyl chloride**.

Amino acid esters **523** are readily converted to *isocyanates* **524** with **phosgene** [377], and these will react with *tert*-butyl alcohol to form *Boc*-amino acids **525**.



523 **524**



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Typical procedure. *tert-Butoxycarbonyl- and p-methoxybenzyloxycarbonyl amino acids* [378]: Isocyanates were prepared from amino acid esters by passing **phosgene** (for a *safe source*, see Chapter 7) into a suspension of the appropriate ester hydrochloride in refluxing toluene until all the material had dissolved (3–7 h). Phosgene and toluene were then removed in vacuo and the crude *isocyanates* were allowed to react with the appropriate alcohol for 15 min at steam-bath temperature. After standing for 1 h at room temperature, the esters were saponified. It was necessary to extract *t*-butoxycarbonyl glycine from aqueous solutions with diethyl ether. Products were recrystallized from ethyl acetate (for *Boc* protection, yields of 56–80%).

The *t-amyloxycarbonyl* group (*AOC* group) and *3-methyl-3-pentyloxycarbonyl* group (MPC group) have proved to be much more convenient *N*-protecting groups than *Boc* in many cases, and have the advantage that they may be introduced quite readily into amino acid esters by using the corresponding *chloroformates* under the standard conditions of the Schotten–Baumann reaction [379, 380]. An improved procedure for *t*-amyl chloroformate preparation uses pyridine and excess phosgene at −60 °C.

Typical procedures. *AOC- and MPC-amino acids*. ***Method A*** [379]: ***t*-Amyl chloroformate**: Dried **phosgene** (105 g, 1.06 mol) (for a *phosgene* source, see Chapter 7) was introduced into a solution of *t*-amyl alcohol (46 g, 0.52 mol) in dry diethyl ether (500 mL), and then the mixture was cooled to −60 °C in an acetone/dry-ice bath. A solution of pyridine (41 g, 0.52 mol) in dry diethyl ether (500 mL) was added dropwise to the cooled mixture with vigorous stirring. Then the reaction mixture was stored overnight in a deep freezer at −20 °C. The formed pyridine hydrochloride was removed by filtration, and the mother liquor was concentrated to a small volume (about 120 mL) in an ice/water bath under reduced pressure. The product thus obtained was used without further purification in the following reactions. Its purity was determined by acylating a known amount of phenylalanine methyl ester as described below; it was found that about 4 mL of the product corresponded to 0.01 mol. The yield was about 60%.

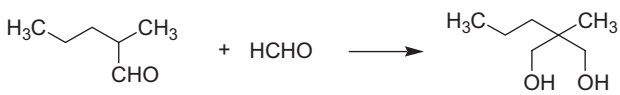
To a solution of an amino acid ester hydrochloride or tosylate (0.1 mol) in chloroform (200 mL), portions of ***t*-amyl chloroformate** or **3-methyl-3-pentyl chloroformate** and triethylamine (0.1 mol) were added alternately at −10 to −5 °C. The addition of chloroformate was continued until the ninhydrin-positive material had disappeared from the reaction mixture; this was checked by thin-layer chromatography. Then, the reaction mixture was washed successively with water, 0.5 N hydrochloric acid, and 5% sodium hydrogen carbonate solution. The organic phase was dried over anhydrous magnesium sulfate and then concentrated to an oil. The yield of the oil (**AOC** ester) was generally quantitative. The esters were subsequently subjected to saponification in acetone or, in the case of benzyl esters, to hydrogenation in a suitable organic solvent (such as methanol); the *AOC*- or *MPC*-amino acids were obtained after following the usual purification procedures.

General procedure *for the synthesis of AOC-amino acids*. *t-Amyloxycarbonyl-L-proline* [380]: ***t*-Amyl chloroformate**; ***Method B*** [380]: Liquid **phosgene** (for a *safe phosgene*

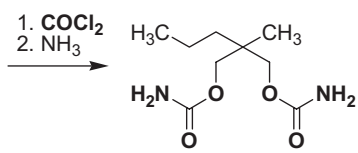
source, see Chapter 7) was collected and quantified (200 mL, ca. 2.8 mol) in a three-necked flask (capacity 5 L), and then a solution of *t*-amyl alcohol (176 g, 2 mol) in dry diethyl ether (3 L) was added. A solution of dry pyridine (150 g, 1.9 mol) in dry diethyl ether (3 L) was added slowly to the mixture at −30 to −20 °C over a period of 90 min, taking precautions to prevent the introduction of moisture. Efficient stirring was necessary in order to obtain a homogeneous reaction mixture. Stirring was continued for a further 30 min at the same temperature, and then the mixture was kept overnight in a deep freezer at −20 °C. The precipitate thus formed was filtered off, again taking care to prevent the introduction of moisture; the filtrate was then concentrated to a volume of about 400 mL under reduced pressure in an ice/water bath. This solution was used as a stock solution of ***t*-amyl chloroformate** without further purification. (It should be kept dry in a deep freezer and used within 10 days).

A stock solution of ***t*-amyl chloroformate** (1 mol, calculated on the basis of *t*-amyl alcohol) was slowly added to a solution of L-proline (69 g, 0.6 mol) in a mixture of methanol (150 mL) and 2 N aqueous sodium hydroxide (600 mL) at −5 to 0 °C. The mixture was agitated vigorously with a mechanical stirrer during the addition (over about 1 h). Stirring was continued for a further 2 h at 0 °C, and then for an additional 1 h at room temperature. (During the reaction, the solution should be kept at above pH 8 by the addition of 4 N aqueous sodium hydroxide. After the addition, the progress of the reaction should be monitored by TLC; if an appreciable amount of proline remains, more reagent should be added). The reaction mixture was subsequently adjusted to pH 2–3 with 1 N hydrochloric acid, and the product was extracted with ethyl acetate (1 × 300 mL; 3 × 100 mL). The combined extracts were dried over sodium sulfate. On concentration of the dried solution, crystals were obtained, which were subsequently recrystallized from ethyl acetate/petroleum ether; yield 137 g (88%).

2-Methyl-2-propyl-1,3-propanediol dicarbamate (*Meprobamate*) **528**, an active ingredient of pharmaceuticals (a general sedative), is synthesized with **phosgene** [381, 382].



526 **527**



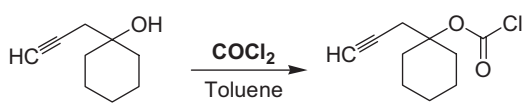
528

The method consists of low-temperature phosgenation of the substituted 1,3-propanediol in an inert medium in the presence of a tertiary amine, followed

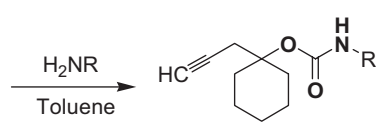
by conversion of the bis(chloroformate) derivative to the desired dicarbamate by ammoniation with gaseous NH_3. Antipyrine gave consistently higher yields than other tertiary amines [382].

Typical procedure. *2,2-Diethyl-1,3-propanediol dicarbamate* [382]: To a stirred solution of **phosgene** (20 g, 0.2 mol) (for a *safe source*, see Chapter 7) in toluene (200 mL) at −10 °C, a cooled solution of 2,2-diethyl-1,3-propanediol (13.2 g, 0.1 mol) and antipyrine (38 g, 0.2 mol) in chloroform (100 mL) was added at such a rate that the temperature of the reaction mixture was maintained at −5 to 0 °C. The mixture was then allowed to warm slowly to room temperature and was left at this temperature overnight. The antipyrine hydrochloride formed was removed by filtration and the bis(chloroformate) was converted directly to the carbamate by treating the filtrate with gaseous ammonia with moderate cooling. The carbamate was separated by filtration, freed from ammonium chloride by extracting with 250 mL of cold water, and recrystallized from hot water; 17.5 g (80%) of *2,2-diethyl-1,3-propanediol dicarbamate* was obtained.

Monocarbamate derivatives of 1,3-propanediol may be prepared in a similar manner, using an equimolar ratio of **phosgene** and diol, but this reaction yields, in addition to the desired monocarbamate derivative, a considerable amount of unreacted diol and appreciable quantities of the dicarbamate and cyclic carbonate derivatives. The difficulty of separating these products may be avoided by forming the monocarbamates through ammonolysis of the cyclic carbonate esters (yields of 53–75% are obtained) [382]. The latter compounds are prepared by the reaction of equimolar quantities of **phosgene** and propanediol in the presence of antipyrine at a temperature somewhat higher than that found most suitable for chloroformate formation.

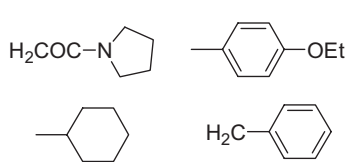


529 **530**

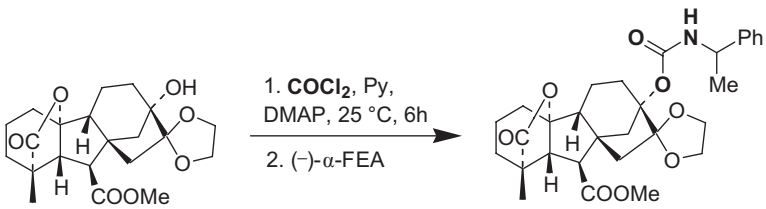


531

R = CH_2CH_2OH, CH_2COOEt, CH_2CONH_2,

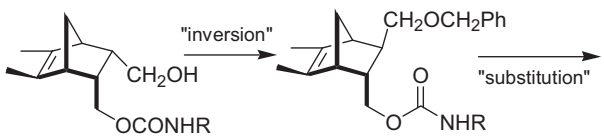


Carbamates **531** of propynyl carbinols were prepared using **phosgene** and various amines in toluene, in the presence of trimethylamine, without isolating the intermediate *chloroformate* **530** [384].

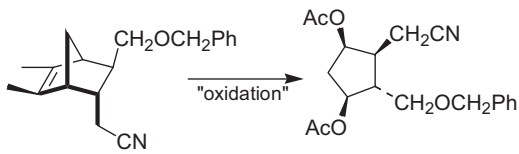


532 **533**

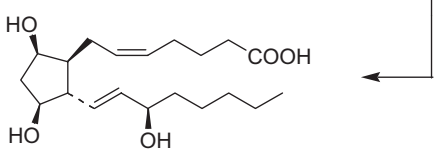
Optical resolution of alcohol **532**, an intermediate in the total synthesis of gibberellic acid, was effected through chromatographic separation of the derived diastereomeric carbamate **533**, prepared from the corresponding alcohol **532** with **phosgene** in the presence of pyridine, DMAP, and (−)-α-phenylethylamine at 25 °C [385].



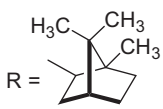
534 **535**



536 **537**

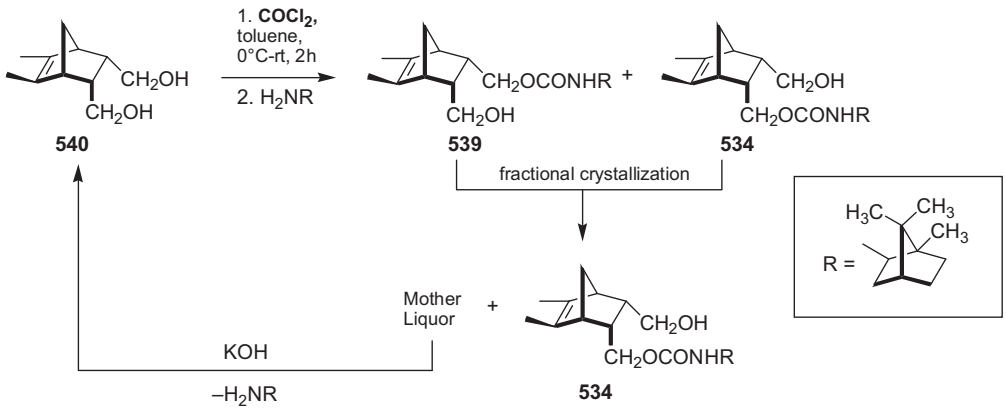


538

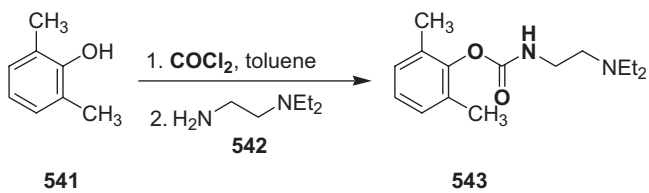


Using the carbamate *meso* compound **535**, which is asymmetrically substituted with a chiral moiety as an intermediate, prostaglandins **538** have been synthesized [386].

Since the undesired enantiomer is readily recycled, this approach should lead to a synthesis with high chiral efficiency. In addition, it is possible to prepare both enantiomeric configurations of prostaglandins by simply altering the sequence of reactions.



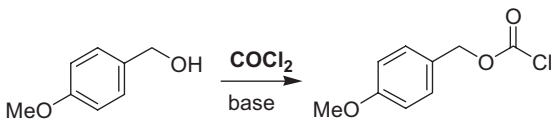
Carbamates of 2,6-disubstituted phenol **543** have been prepared with **phosgene** [387].



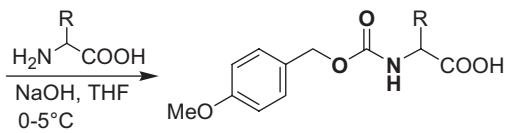
Typical procedure. *Carbamate* **543** [387]: 2,6-Dimethylphenol **541** (20.4 g) was added to a solution of **phosgene** in toluene (17%) (*for a safe phosgene source*, see Chapter 7). The mixture was kept at 2.5 °C for 1 h, then warmed to 30 °C, and then left to stand at rt for 20 h protected from moisture by a tube filled with $CaCl_2$. Dry air was blown through the solution for several hours to remove unreacted **phosgene**. Then, the solution was added dropwise to a stirred mixture of *β*-diethylaminoethylamine (17.4 g) in benzene (200 mL) and water (150 mL) at 20 °C. The resulting mixture was stirred for 1 h, then the required amount of 2 N NaOH was added, and the organic phase was separated. The latter was extracted with 2 N HCl to obtain the basic material, which was isolated in the usual way and distilled in a kugelrohr apparatus to afford the pure *carbamate* **543** as a free base; bp 150 °C (0.1 Torr); yield 20.8 g (50%).

The *p-methoxybenzyloxycarbonyl* group (*pMZ*) has been widely used as a blocking substituent of the amino moiety of amino acids in peptide synthesis. It was

found that *pMZ*-amino acids could be prepared directly from a number of amino acids and ***p*-methoxybenzyl chloroformate** under the conditions of the Schotten–Baumann reaction [388–390].



544 **545**

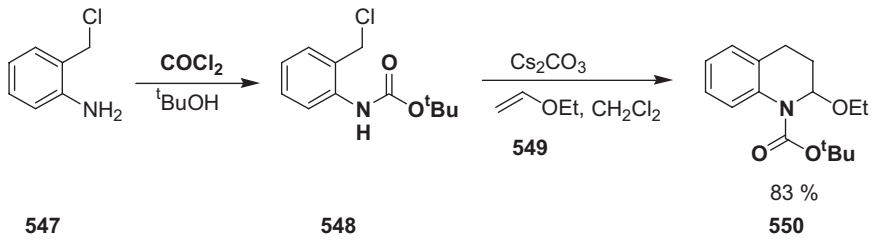


546

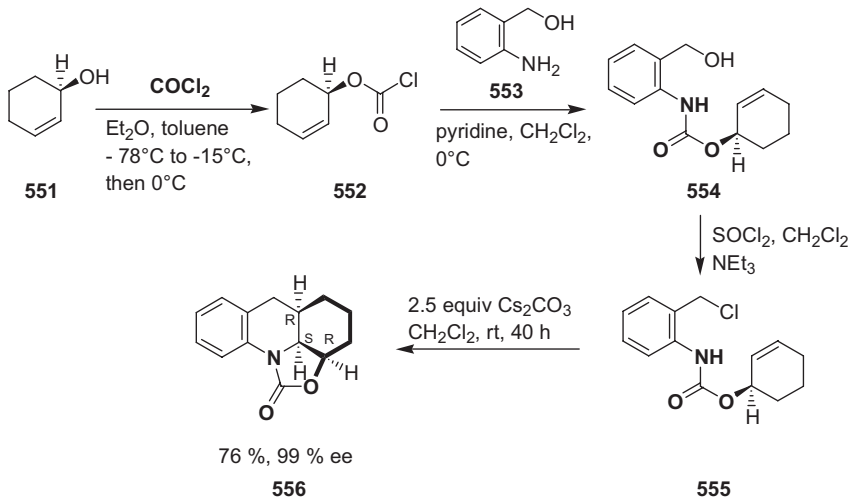
Typical procedure. *p-Methoxybenzyl carbamates of amino acids* **546** [388]: The reagent **545** was prepared as follows: a solution of anisyl alcohol (12.4 mL, 0.1 mol) in dry diethyl ether (100 mL) was added to a solution of **phosgene** (for a *safe source*, see Chapter 7) (21 mL, 0.3 mol) in dry diethyl ether (100 mL) over a period of 10 min. Then, a solution of dimethylaniline (12.7 mL, 0.1 mol) in dry diethyl ether (100 mL) was added dropwise over a period of 1 h and the resulting mixture was stirred for 2 h at −10 to −5 °C. After removal of the salt formed in the reaction by filtration, the filtrate was concentrated under reduced pressure below 0 °C to leave an oily residue. Twice more, dry diethyl ether (100 mL) was added and evaporation was repeated to remove excess phosgene. The residue was immediately dissolved in tetrahydrofuran (70 mL) to give a solution ready for use in the next reaction.

The solution of the *chloroformate* **545** was added in small portions over a period of 10 min to a solution of the amino acid (0.05 mol) in 1 N sodium hydroxide (200 mL) (L-glutamic acid: 1.5 N sodium hydroxide) containing tetrahydrofuran (40 mL) with vigorous stirring at 0–5 °C. Stirring was continued for 2 h; then, the reaction mixture was washed with diethyl ether (100 mL) and acidified by the addition of solid citric acid. The product was extracted with ethyl acetate (500 mL). This layer was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*; the residue, which was then crystallized from ethyl acetate/petroleum ether. If the product did not crystallize at this stage, the residue was neutralized with a calculated amount of dicyclohexylamine in diethyl ether and the *pMZ-amino acid* was crystallized as the dicyclohexylammonium salt.

A simple method for *o*-azaxylylene synthesis by base-induced elimination of hydrogen chloride from carbamate derivatives (for example, **548**), prepared with **phosgene**, has been reported. These intermediates are readily trapped by π-electron-rich alkenes, for example **549**, to form hydroquinoline derivatives, **550** [391].



This approach to hydroquinolines is especially powerful in the intramolecular version. As shown below, these intramolecular reactions proceed under mild conditions and provide hydroquinolines stereospecifically by a suprafacial (*cis*) cycloaddition [391].



Typical procedure. *Carbamate* **556** [391]: A solution of (*R*)-2-cyclohexen-1-ol **551** (147 mg, 1.5 mmol) in diethyl ether (1 mL) was added to a solution of **phosgene** (for a *safe source*, see Chapter 7) (3 mmol) in toluene (1.6 mL) at −78 °C. The mixture was stirred at −15 °C for 3 h and at 0 °C for a further 30 min. This solution of chloroformate **552** was then transferred by a cannula into a solution of *o*-aminobenzyl alcohol **553** (185 mg, 1.5 mmol) and pyridine (0.14 mL, 1.7 mmol) in dichloromethane (5 mL) over a period of 15 min at 0 °C. The reaction mixture was warmed to 23 °C and stirred for an additional 2 h. Aqueous work-up and chromatography on silica gel eluting with hexane/ethyl acetate (6:1) afforded the hydroxy carbamate coupling product **554** as a colorless crystalline solid (282 mg, 76%). A solution of thionyl chloride (102 μL, 1.40 mmol) in dichloromethane (4 mL) was then added over 15 min to a solution of the hydroxy carbamate **554** (240 mg, 0.97 mmol) and triethylamine (195 μL, 1.40 mmol) in dichloromethane (4 mL). The resulting mixture was stirred for 2 h and then the solvent was removed in

vacuo. Chromatography of the crude product on silica gel eluting with hexane/ethyl acetate (6:1) afforded *chloromethylarylcarbamate* **555** as a colorless crystalline solid (230 mg, 89%). A suspension of chloromethylarylcarbamate **555** (53 mg, 0.2 mmol) and cesium carbonate (163 mg, 0.5 mmol) in dichloromethane (5 mL) was stirred for 40 h at 23 °C. The reaction mixture was then filtered through a pad of Celite and the solvent was evaporated in vacuo. Chromatography of the crude product on silica gel eluting with hexane/ethyl acetate (6:1) gave **556** as a colorless, crystalline solid (35 mg, 76%); mp 149–150 °C.

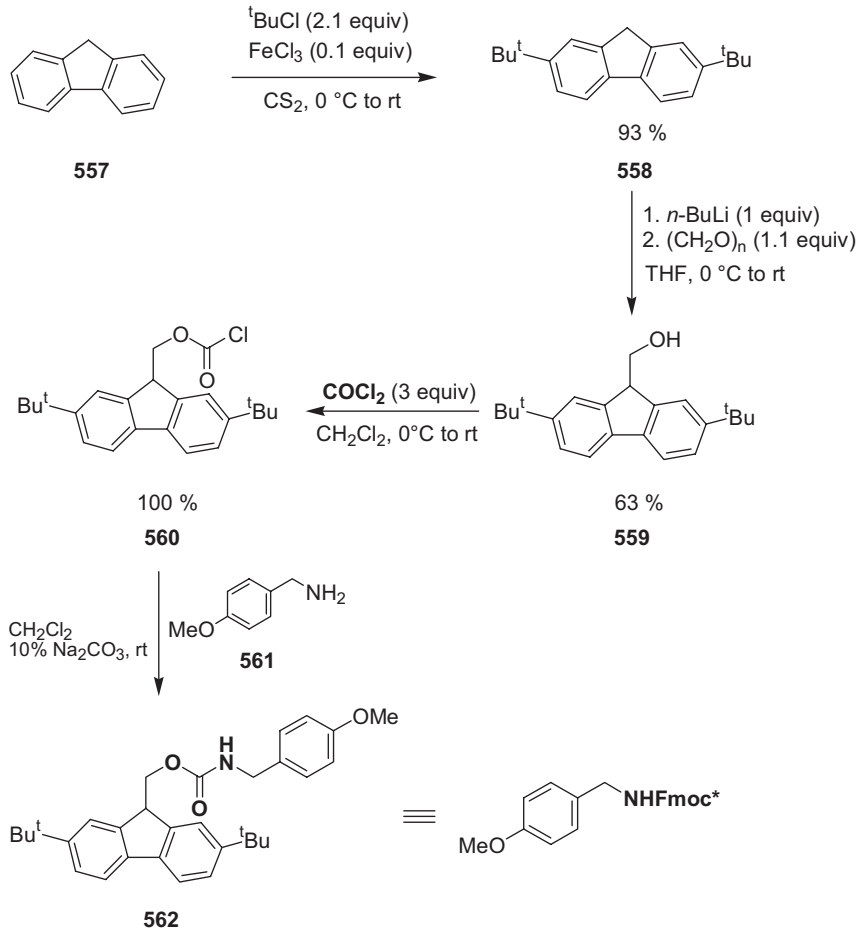
The *9-fluorenylmethoxycarbonyl* (*Fmoc*) group is exceptionally stable towards acid; thus, carboxylic acids can be converted to acid chlorides with thionyl chloride or *tert*-butyl esters using H_2SO_4 and isobutene. Furthermore, *Fmoc* groups are unaffected by HBr in HOAc or CF_3COOH, thereby enabling the selective deprotection of *Z* and *Boc* groups. On the debit side is the low solubility of many *Fmoc*-protected amino acids in common organic solvents and the need for chromatographic separation of the non-volatile by-products from the deprotection step. The use of the *Fmoc* group in peptide synthesis has been extensively reviewed [392–394].

The *2,7-di-tert-butyl-9-fluorenylmethoxycarbonyl* (*Fmoc**) group has been developed as a more soluble analogue of the 9-fluorenylmethoxycarbonyl (*Fmoc*) protecting group [395]. Like Fmoc, the *Fmoc** group is readily introduced as its chloroformate. The chloroformate (**Fmoc*-Cl**) **560** is prepared in three steps from fluorene **557**. The last of these is a slow chlorocarbonylation with **phosgene** [396].
Amines can be protected by treatment with **Fmoc*-Cl** in a biphasic mixture of dichloromethane and aqueous sodium carbonate [395, 397], and can be deprotected with a 20% solution of piperidine in DMF [395].

Typical procedure *for the Fmoc*-protection of an amine* [395]. An ice-cooled, 250-mL, three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a glass stopper, a rubber septum, and a magnetic stirring bar was charged with **559** (6.75 g, 21.9 mmol), dichloromethane (20 mL), and a solution of **phosgene** (for a *safe source*, see Chapter 7) in toluene (33.2 mL, 1.98 M, 65.7 mmol). The ice in the ice bath was allowed to melt, and the reaction mixture was stirred for 72 h. Concentration of the mixture yielded 8.13 g (100%) of **Fmoc*-Cl 560** as a light-brown oil of sufficient purity for its subsequent use. An analytical sample was obtained as a white solid by adding a minimal amount of pentane, chilling to −78 °C under nitrogen until crystals formed, decanting the mother liquor, and removing the residual pentane in vacuo; mp 63–65 °C.

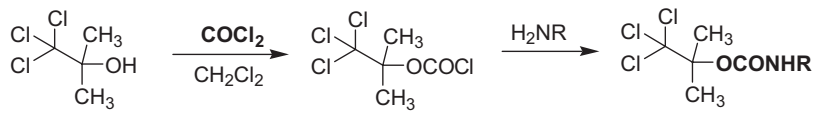
An ice-cooled, two-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen inlet adapter, and septum was charged with *p*-methoxybenzylamine **561** (0.422 g, 3.07 mmol), dichloromethane (1.0 mL), and 10% aqueous Na_2CO_3 (8.3 mL). After 5 min, a solution of **Fmoc*-Cl 560** (1.14 g, 3.07 mmol) in dichloromethane (3.2 mL) was added over a period of 2 min. The ice bath was removed, and the reaction mixture was stirred at room temperature for 2 h. It was then diluted with dichloromethane (60 mL) and washed with 1 M HCl (60 mL). The aqueous layer was extracted with dichloromethane (2 × 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield

1.38 g of a white foam. Purification by column chromatography on silica gel (EtOAc/hexanes, 1:3) yielded 1.28 g (88%) of **562** as a white solid.



β-Haloalkoxycarbonyl protecting groups [371, 398–402] are important because they can be removed selectively. The protecting groups *2-chloro-* [398], *2-bromo-* [399, 400], *2-iodo-* [400], *2,2,2-trichloroethoxycarbonyl* [401], as well as *2-bromo-tert-butyloxycarbonyl* [402] all show some degree of base lability, which limits their preparative scope. However, the *2,2,2-trichloro-tert-butyloxycarbonyl group* (*TCBoc*) is so stable towards acids and bases that conditions are fulfilled for its application in peptide synthesis [403].

The *TCBoc* group can be introduced by means of the stable and distillable chloroformate **564**, which is readily accessible from 2,2,2-trichloro-*tert*-butanol (chloretone) **563** and **phosgene** in dichloromethane or pyridine. Chloretone itself is an inexpensive commercially available reagent.



563 **564** **565**

H_2NR = amino acid or peptide ester **TCBoc-NHR**

Reaction of chloroformate **564** with amino acids or peptide esters can be accomplished under the usual Schotten–Baumann conditions. Thus, on treatment with **564**, valine affords the TCBoc-protected amino acid in good yield [403].

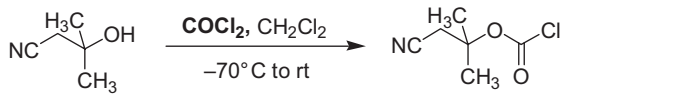
Typical procedure. *TCBoc-valine* [403]: At −20 °C, a solution of anhydrous chloretone **563** (178 g, 1.0 mol) in anhydrous dichloromethane (400 mL) was treated with **phosgene** (for a *safe source*, see Chapter 7) (140 mL, 2.0 mol). Pyridine (105 mL, 1.5 mol) in dichloromethane (70 mL) was then added dropwise at −20 °C and the mixture was stirred for 12 h at 20 °C. Subsequent washing of the dichloromethane solution with water at 0 °C (Caution: vigorous evolution of gas owing to liberation of excess phosgene!), 2 N sulfuric acid, and more water, followed by drying with sodium sulfate, evaporation of the solvent, and distillation of the residue, afforded 214 g (89%) of the *chloroformate* **TCBoc-Cl 564**; bp 77–81 °C/12 Torr. (For a preparation of **TCBoc-Cl** with **triphosgene**, see Section 4.2.1).

Valine (11.7 g, 0.1 mol), dissolved in water (200 mL) and 1 N sodium hydroxide solution (250 mL), was treated with diethyl ether (100 mL) and then emulsified at 0 °C with **TCBoc-Cl** (33.8 g, 0.14 mol) in dioxane (140 mL) for 1 h. The aqueous phase was washed with diethyl ether, acidified with 5 N hydrochloric acid, and extracted with ethyl acetate. After washing the combined extracts with water, *TCBoc-valine* (26 g, 82%) crystallized from the ethyl acetate extract; the product was recrystallized from hexane; mp 102 °C.

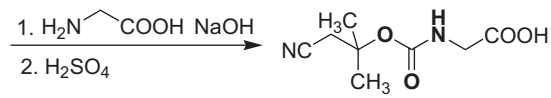
The *N-(cyano-tert-butoxycarbonyl)* (*CyOC*) residue has been proposed as an amino acid protective group that can be cleaved with weakly basic reagents through *β*-elimination. This N-masking moiety can be introduced by means of the appropriate *chloroformate* **567**, which is prepared with **phosgene**. The resulting (cyano-*tert*-butoxycarbonyl)amino acids (for example, **568**) can be coupled with amino acids and peptides using the active ester procedure [404].

Typical procedure. *Cyano-tert-butyloxycarbonyl-glycine (CyOC-Gly-OH)* **568** [404]: To a solution of cyano-*tert*-butanol **566** (10 g, 100 mmol) and pyridine (10 g, 125 mmol) in dichloromethane (150 mL) at −40 °C was added **phosgene** (40 mL, 600 mmol) (for a *safe source*, see Chapter 7), precooled to −70 °C. The mixture was stirred overnight at room temperature and then washed with ice-cooled 1 N HCl and twice with ice/water. The organic layer was successively dried by shaking it several times with fresh sodium sulfate (all aqueous phases and the sodium sulfate were extracted twice with dichloromethane). The solvent was evaporated in vacuo at 20 °C (bath temperature) to afford 17 g (quantitative) of crude **cyano-*tert*-butyl chloroformate 567**. Crude chloroformate **567** was dissolved in THF (100 mL) and the so-

lution was added dropwise under external cooling with ice/water over a period of 15 min to a solution of glycine (15 g, 200 mmol) in 1 N NaOH (200 mL). After stirring for a further 1 h at room temperature, the mixture had a pH of about 8; this was adjusted to 4–5 with 2 N H_2SO_4. The mixture was then concentrated in vacuo and the residue was taken up in ethyl acetate/water. The aqueous phase was separated, acidified to pH 1.5–2, and extracted twice with ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate, and concentrated in vacuo. The residue was crystallized from diethyl ether/petroleum ether. The crystals were dried in vacuo to afford 16.5 g (82%) of *CyOC-Gly-OH* **568**; mp 147–148.5 °C.



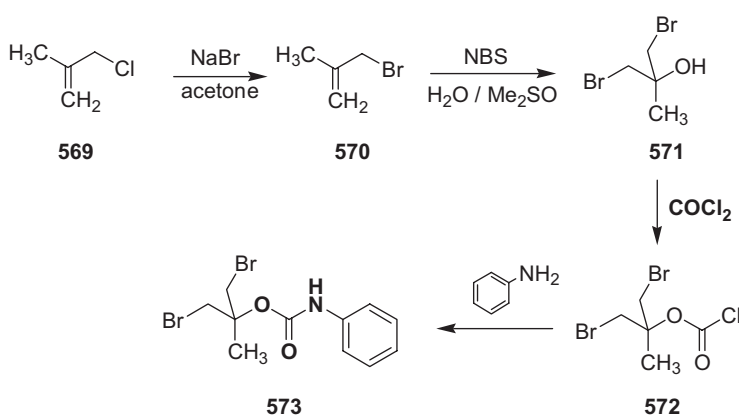
566 **567**



82 %

568

The effect of structure on the ease of solvolytic deblocking of an array of α-halo-*tert*-alkyl carbamates has been studied. The *1,3-dibromo-2-methyl-2-propyloxycarbonyl group* (*DB-t-Boc*) is easily deblocked by warming in ethanol or methanol and is therefore recommended as an acid-stable, solvolytically deblockable, amino protecting group. The key chloroformate **572** was readily synthesized from methallyl chloride **569** by conversion to methallyl bromide **570** followed by reaction with hypobromous acid to give the bromohydrin **571** and treatment of the latter with **phosgene**. Practical use of the *DB-t-Boc* group has been demonstrated by synthesis of the dipeptide phenylalanylleucine [405].



569 **570** **571**

573 **572**

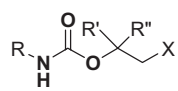
General procedure *for the preparation of bromoalkyl chloroformates and carbamates*. [405]: ***Bromoalkyl chloroformates*** *of type* **572**: A solution of **phosgene** (3.25 g, 0.032 mol) (for a *safe source*, see Chapter 7) in dichloromethane (15 mL) was cooled to −15 °C under a nitrogen atmosphere. A solution of the appropriate alcohol (0.016 mol) in dichloromethane (5 mL) was then added, followed by a solution of pyridine (1.44 g, 0.018 mol) in dichloromethane (15 mL). The reaction mixture was allowed to warm to room temperature and was stirred overnight. Nitrogen was then passed through the solution to remove excess phosgene, and the solution was washed successively with ice-cold water, ice-cold 5% $NaHCO_3$ solution, and ice-cold water. After drying over $MgSO_4$, the solvent was removed by distillation over a water bath with the aid of a water aspirator, and unless noted otherwise, the residue was distilled in vacuo to give the chloroformate. The product was examined spectroscopically (IR, NMR) and then used without further purification for conversion to the corresponding carbamate. Three chlorides were prepared: **1-bromo-2-methyl-2-butyl chloroformate** (55%, bp 53 °C/0.1 mmHg), **1-bromo-2,3-dimethyl-2-butyl chloroformate** (62%, bp 34 °C/0.15 mmHg), and **3-(bromomethyl)-3-pentyl chloroformate** (20%, bp 54 °C/0.19 mmHg (dec.)).

Carbamates of type **573**: A solution of the appropriate chloroformate (25 mmol) in benzene (100 mL) was stirred at room temperature. To this was added dropwise a solution of the amine (50 mmol) in benzene (50 mL) over a period of 30 min. After stirring for 1 h, the precipitated salt was filtered off and washed with a small amount of benzene. The solvent was removed in vacuo (20 mmHg) at 45 °C from the combined filtrate and washings, to leave the carbamate as an oily residue, which was recrystallized from *Skelly B*. Results are collected in Table 4.23.

For a detailed presentation of other haloalkyl chloroformate syntheses using *phosgene equivalents*, see Section 4.2.1 ''Chloroformylation''.

N-Carbobenzoxy-DL-serine benzyl ester **575** was converted to several *O*-(substituted carbamyl)-*N*-carbobenzoxyserine benzyl esters, either by condensation with

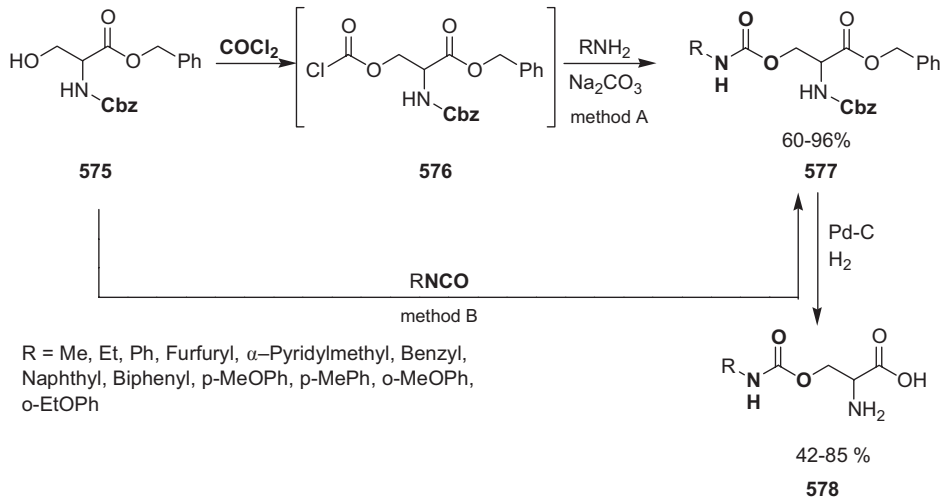
Tab. 4.23. Carbamates **574** prepared with ***α*-halo-*tert*-alkyl chloroformates** [405].



574

R	*R′*	*R″*	*X*	*Yield, %*	*mp, °C*
C_6H_5	Me	Et	Br	46	65
p-ClC_6H_4	Me	Et	Br	53	77
cyclo-C_6H_{11}	Me	Et	Br	64	80–80.5
C_6H_5	Me	*i*Pr	Br	65	66–66.5
p-ClC_6H_4	Me	*i*Pr	Br	67	86–87
cyclo-C_6H_{11}	Me	*i*Pr	Br	34	95
C_6H_5	Et	Et	Br	47	61–62
cyclo-C_6H_{11}	Et	Et	Br	70	98
C_6H_5	Me	Et	OTs	55	77

phosgene followed by aminolysis of the chloroformyl intermediate **576**, or by direct interaction with an appropriately substituted isocyanate derivative. The resulting carbamyl derivatives **577** were then hydrogenolyzed to yield the corresponding *O*-(substituted carbamyl)-DL-serine **578** [406].

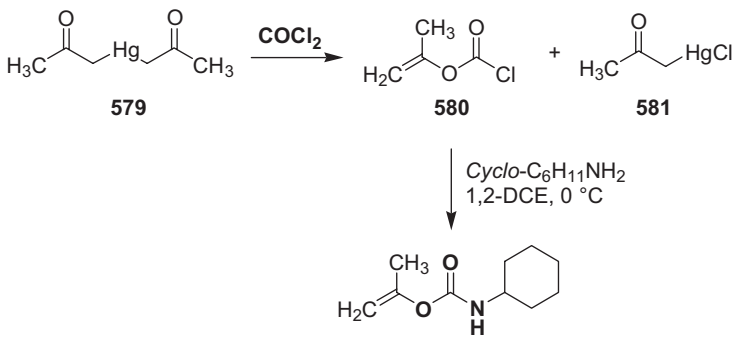


Typical procedure. *O-(Substituted carbamyl)-N-carbobenzoxy-DL-serine benzyl esters*, **577**. ***Method A***. [406]. *N*-Carbobenzoxy-DL-serine benzyl ester (5.5 g) was suspended in toluene (60 mL) containing a large molar excess of **phosgene** (for a *safe source*, see Chapter 7). The reaction mixture was kept in a tightly closed system at room temperature for about 16 h to effect complete dissolution. After removal of the solvent, a pale-yellow oil was obtained, which was freed of residual phosgene by the repeated addition and evaporation *in vacuo* of benzene. A solution of this oil in dioxane (25 mL) was slowly added to a well-stirred mixture containing 40% methylamine (2 mL) and anhydrous sodium carbonate (1.0 g) in ethanol/water (1:1; 50 mL) maintained at 5 to 10 °C. After stirring for a further 3 h at room temperature, the reaction mixture was concentrated to dryness *in vacuo*, thereby removing the solvents and excess amine. The residue was extracted with hot benzene, and the inorganic salts were removed by filtration. The resulting benzene solution was treated with *Skellysolve C* and placed in a deep freeze. As a first crop, 3.1 g of the product, *O-(methylcarbamyl)-N-carbobenzoxy-DL-serine benzyl esters* **577**; mp 72–75 °C, was obtained, and an additional 1.8 g of material was recovered from the mother liquor and washings. A sample was recrystallized from benzene/Skellysolve C and dried *in vacuo* over paraffin for analysis, mp 92–93 °C. With two amines, phenylethylamine and furfurylamine, the condensation product precipitated directly from the reaction mixture and could be recovered without evaporation of the solvent.

O-(Substituted carbamyl)-DL-serine. ***Method B***. [406]. Using the same general procedure for all of the *O*-(substituted carbamyl) serine benzyl ester derivatives, as

prepared by *Method A*, a mixture of *N*-carbobenzoxy-DL-serine benzyl ester (1.65 g, 0.05 mol) and two molar equivalents of the corresponding **isocyanate** in toluene (25 mL) was heated under reflux for 8–10 h. The reaction mixture was then cooled; in several instances a precipitate formed at this stage, which was collected by filtration, washed with *Skellysolve G*, and dried *in vacuo*. When an oil formed, the reaction mixture was concentrated to dryness under reduced pressure with warming. The residue was crystallized from benzene/*Skellysolve G* to yield the desired product. All of the *O*-(substituted carbamyl)-*N*-carbobenzoxyserine benzyl esters were recrystallized from benzene/hexane and dried over paraffin *in vacuo* for elemental analysis; however, the initially isolated material was sufficiently pure for direct hydrogenolysis to the corresponding *O-(substituted carbamyl)serine* **578** without further purification.

A series of **enol chloroformates** (vinyl, isopropenyl, and 1-cyclohexenyl) has been proposed as a valuable protecting tool in the development of much improved preparative routes to the important narcotic antagonists *Naloxone* and *Naltrexone*, as well as to the potent mixed agonist/antagonist analgesics *N*-cyclobutylmethylmoroxymorphone and *Nalbuphine* [407]. **Isopropenyl chloroformate 580**, prepared by adding diacetonylmercury **579** to excess **phosgene** in dichloromethane (86% yield after distillation; see Section 4.2.1 "Chloroformylation") was employed to obtain the corresponding enol carbamate derivative **582**.



579 **580** **581** **582**

Typical procedure. *Isopropenyl N-cyclohexylcarbamate* **582** [407]: At 0 °C, a solution of **isopropenyl chloroformate 580** (3.5 g, 0.029 mol) in anhydrous 1,2-dichloroethane was added to a stirred solution of cyclohexylamine (5.75 g, 0.058 mol) in the same solvent. The next day, the precipitated amine hydrochloride was filtered off and the filtrate was concentrated. *Isopropenyl N-cyclohexylcarbamate* **582** was isolated from the residue by vacuum sublimation at 57 °C (0.1 mmHg); yield 5.21 g (98%); mp 95.5–96.5 °C.

The following enol carbamates were similarly prepared from the appropriate *chloroformates* and amines [407]: *vinyl N-cyclohexylcarbamate*; sublimed at 50 °C (1 mmHg), mp 83–84 °C; *1-cyclohexenyl N-phenylcarbamate*; mp 119.5–120 °C; *1-*

phenylvinyl N-cyclohexylcarbamate; mp 104–105 °C; *1-cyclopropylvinyl N-phenylcarbamate*; mp 104–105 °C; *1-tert-butylvinyl N-cyclohexylcarbamate*; sublimed at 85 °C (0.1 mmHg); mp 79–80 °C.

A number of *allyl carbamates* have been synthesized from the corresponding *chloroformates* with amino compounds [408].

Typical procedures. *Allyl carbamate*. [408]: Ammonia was passed into a solution of **allyl chloroformate** (368 g, 3 mol) in benzene (1000 mL) at 25–35 °C until the reaction was complete. The ammonium chloride produced was filtered off and the salt was washed with small quantities of benzene. Distillation of the benzene solution through a short column gave 255 g (85% yield) of *allyl carbamate* (*allyl urethane*), bp 73–75 °C at 2 mmHg.

N-Carballyldioxyethyl allyl carbamate. [408]: **Allyl chloroformate** (964 g, 8 mol) was added at a rate of two grams per minute to a solution of monoethanolamine (245 g, 4 mol) in pyridine (712 g, 9 mol) at −15 to −10 °C. The resulting mixture was subsequently poured into cold, dilute hydrochloric acid solution. The oil layer was separated, washed with sodium hydrogen carbonate solution, and dried. Distillation of the neutral oil in small quantities through a short column gave 600 g (65% yield) of colorless (*N*-carballyldioxyethyl) allyl carbamate; bp 151–152 °C at 3 mmHg.

Bis(carbamate)s of dimethylol-1,1-cyclopentane have been prepared via the **bis(chloroformate)** using **phosgene** (for a *safe source*, see Chapter 7) in toluene and various amines at −5 °C, in the presence of antipyrine, or by reacting the starting diol with **phenyl isocyanate** [409].

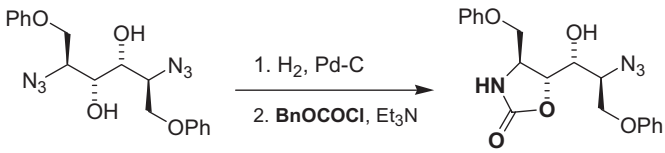
The *cyclocarbamation* of (2*S*,3*S*)-3-amino-2-hydroxy-5-methyl-1-phenylhexane (**583**) and of its (2*R*,3*R*) isomer has been studied as part of a synthetic strategy aimed at developing a method for synthesizing all the stereoisomers of statine with high enantiomeric purity. Carbonylation of **583** with **benzyl chloroformate** in dichloromethane in the presence of triethylamine at room temperature afforded the corresponding (4*S*,5*S*)-oxazolidin-2-one **584** in high yield [410].

583 **584**

Typical procedure. *(4S,5S)-5-Benzyl-4-isobutyloxazolidin-2-one* **584** [410]: To a stirred mixture of (2*S*,3*S*)-3-amino-2-hydroxy-5-methyl-1-phenylhexane **583** (1.3 g, 6.28 mmol), triethylamine (1.9 g, 18.84 mmol), and dichloromethane (12 mL), a 30% solution of **benzyl chloroformate** in toluene (4.46 mL) was added with ice cooling. After stirring at room temperature for 18 h, the mixture was diluted with chloroform (50 mL) and washed with 5% HCl and H_2O. The solvent was then evaporated, and the residue was chromatographed on silica gel (15 g). Elution with

hexane/EtOAc (5:1) afforded **584** (1.29 g, 88% yield) as an oil. Under the same conditions, the (4*R*,5*R*)-isomer of **584** was obtained in 86% yield (1.12 g) from the (2*R*,3*R*) isomer of **583** (1.30 g, 6.28 mmol).

Oxazolidin-2-one **586** formation with **benzyl chloroformate** in the presence of excess Et_3N at room temperature was reported as a key step in the synthesis of potent *HIV-1 protease inhibitors* by employing carbohydrate alditols as templates [411].

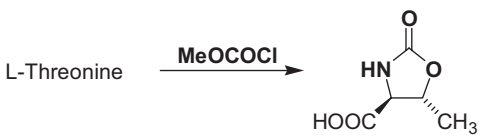


28 %

585 **586**

Benzyl chloroformate has also been employed as a cyclocarbamation agent in the presence of aqueous alkali (1 M NaOH, 5 °C) for the preparation of the corresponding *oxazolidin-2-ones* of *3-amino-2-hydroxy-4-methyl-hexadecanoic* and *3-amino-2-hydroxy-4-methyl-14-oxo-octadecanoic acids*, respectively [412], *(2RS,3SR)-2-amino-3-hydroxy-3-phenylpropionic acid* [413], and DL-*threonine* [414].

(4S,5R)-5-Methyl-2-oxazolidinone-4-carboxylic acid **587** was prepared from L-threonine with **methyl chloroformate** [415, 416].



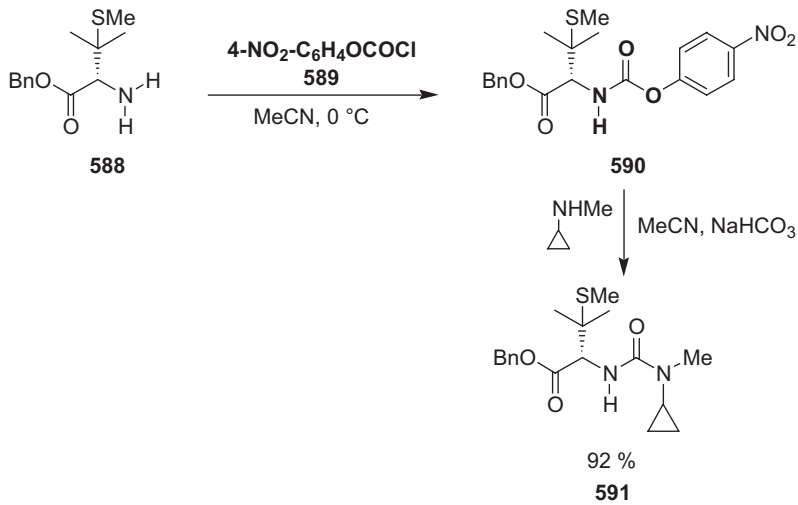
587

Typical procedure. *(4S,5R)-5-Methyl-2-oxazolidinone-4-carboxylic acid* **587** [415]: To a solution of L-threonine (2.38 g, 20 mmol) and a trace of thymolphthalein as indicator in 2 N NaOH (30 mL) at 0 °C, **methyl chloroformate** (2.4 mL, 30 mmol) was added dropwise. To maintain pH 10, it was necessary to add further portions of NaOH at intervals. The solution was allowed to slowly warm to room temperature and was stirred overnight. The reaction mixture was then neutralized with dilute HCl. After evaporation of the volatiles, a white precipitate was obtained. The product was extracted with ethyl acetate (250 mL), which was acidified with HCl. The solvent was again evaporated and the white product was recrystallized from ethyl acetate/petroleum ether (40/60) to afford 2.18 g (75%) of *oxazolidinone* **587**.

Ureas incorporating structurally complex frameworks, including amino acid derivatives, are efficiently prepared from **4-nitrophenylchloroformate 589**. To give an example, *S*-methyl-*O*-benzyl-L-penicillamine **588** reacts with **589** in acetonitrile at

0 °C within 30 min to give carbamate **590**. Subsequent addition of cyclopropylmethylamine in the same solvent and in the presence of $NaHCO_3$ gives the amino acid urea derivative **591** in 92% yield.

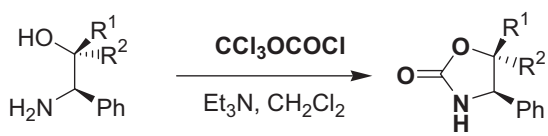
The reaction proceeds under very mild conditions owing to the good leaving group ability of the *p*-nitrophenyl moiety and hence is not applicable to the tetrasubstituted urea [417].



588 **590** **591**

Diphosgene

2-Oxazolidinones **593**, which represent potential chiral auxiliaries, have been prepared with **diphosgene** (**trichloromethyl chloroformate**) [418, 419].



592 **593**

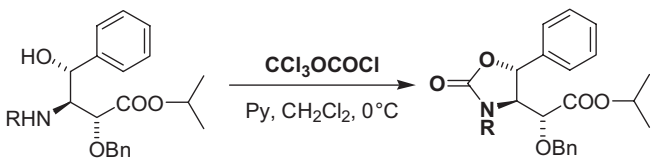
a : R^1 = Ph, R^2 = H
b : R^1 = R^2 = H
c : R^1 = R^2 = Ph

Typical procedures. *(4R,5S)-4,5-Diphenyl-2-oxazolidinone* **593a**. [418]: To a stirred suspension of commercially available **592a** (10.0 g, 47 mmol) and triethylamine (14.4 mL, 0.10 mol) in dichloromethane (100 mL), **diphosgene** (3.0 mL, 25 mmol) was added dropwise at 0 °C and the mixture was stirred for 1 h at the same temperature. After concentration *in vacuo*, the residue was poured into water to precipitate crystals. The crystals were collected by filtration, successively washed with

10% HCl and H_2O, and dried *in vacuo* at 50–60 °C for 3 h to afford **593a** as colorless crystals (10.9 g, 97%).

(4R)-4-Phenyl-2-oxazolidinone (**593b**) [418]: To a stirred solution of commercially available amino alcohol **592b** (2.0 g, 15 mmol) and triethylamine (4.0 mL, 29 mol) in dichloromethane (15 mL), **diphosgene** (0.9 mL, 7.3 mmol) was added dropwise at 0 °C. After stirring for 1 h, the mixture was diluted with dichloromethane, successively washed with a saturated solution of citric acid and with brine, and dried (Na_2SO_4). After filtration, the filtrate was concentrated *in vacuo* to afford **593b** as colorless crystals (1.80 g, 76%).

Isopropyl benzyloxy-(2-oxo-5-phenyl-oxazolidin-4-yl)acetate **595** has been prepared in high yield with **diphosgene** and pyridine in dichloromethane at 0 °C [420, 421].

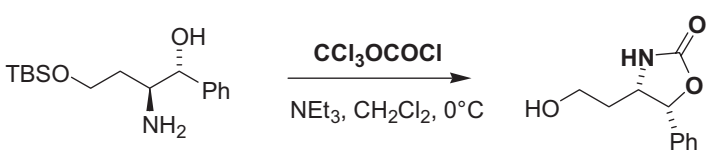


594 **595**

R = H (90%), Bn(64%)

Typical procedure. *(4R,5R)-5-[(R)-(1-Benzyloxy-1-isopropoxycarbonyl)methyl]-4-phenyl-2-oxazolidone*, **595**, and its enantiomer [421]: At 0 °C, pyridine (200 μL, 2.5 mmol) and **diphosgene** (72 μL, 0.60 mmol) were successively added to a solution of **594** (207 mg, 0.60 mmol) in dichloromethane (2 mL). After stirring at the same temperature for 10 min, the mixture was diluted with water and ethyl acetate. The upper ethyl acetate layer was separated, washed successively with saturated $NaHCO_3$ solution and saturated brine, dried over anhydrous $MgSO_4$, and then concentrated *in vacuo*. The residue was purified by column chromatography (hexanes/EtOAc, 4:1 → 3:1) to afford *(4R,5R)-5-[(R)-(1-benzyloxy-1-isopropoxycarbonyl)methyl]-4-phenyl-2-oxazolidone* **595** as a colorless oil (199 mg, 90%).

Stereoselective syntheses of various 2-oxazolidines have been reported using **diphosgene** and triethylamine in dichloromethane at −20 to 0 °C [422–424], or **diphosgene** and $K_2CO_3/H_2O/CH_2Cl_2$ at ambient temperature [425, 426].



76 %

596 **597**

Typical procedure. *(4S,5R)-4-Hydroxyethyl-5-phenyloxazolidin-2-one* **597** [424]: To a solution of the amino alcohol **596** (1 mmol) and triethylamine (0.306 mL, 2 mmol) in dichloromethane (2 mL) at 0 °C was added **diphosgene** (198 mg, 1 mmol), and the mixture was stirred at this temperature for 1 h. It was then washed with water, dried over anhydrous magnesium sulfate, and concentrated. The residue was redissolved in methanol (2 mL) and treated with 6 N hydrogen chloride in 1,4-dioxane (0.1 mL) at 25 °C. The resulting mixture was concentrated, and the residue was crystallized by adding *n*-hexane to afford **597** (157 mg, 76%).

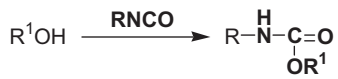
Typical procedure. *2-Propynyl p-methoxybenzylcarbamate* ($R^4 = p\text{-}MeOC_6H_4CH_2$), **605**. [427]: A 200-mL two-necked, round-bottomed flask, fitted with a dropping funnel and a reflux condenser, at the top of which was attached a nitrogen balloon, was purged with nitrogen. The flask was then charged with dry dioxane (30 mL) and **diphosgene** (2.5 mL, 20 mmol). A solution of *p*-methoxybenzylamine (2.74 g, 20 mmol) in dry dioxane (20 mL) was added over a period of 30 min by means of the dropping funnel at room temperature, and the reaction mixture was stirred at 50 °C for 2 h and then refluxed for 4 h. The solvent was subsequently distilled off at atmospheric pressure under nitrogen. To the residue, a mixture of 2-propyn-1-ol (1.12 g, 20 mmol) and triethylamine (4.05 g, 40 mmol) was added via the dropping funnel at 0 °C. After stirring for 2 h at ambient temperature, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (2 × 50 mL). The combined extracts were dried ($MgSO_4$), filtered, concentrated, and subjected to column chromatography on silica gel (eluent: benzene/ethyl acetate) to give *2-propynyl p-methoxybenzylcarbamate* in 42% yield.

Since fluoroformates exhibit much higher thermal stabilities than the corresponding chloroformates, they are of particular interest for the industrial production of protected amino acids. Thus, ***t*-butyl fluoroformate** (**Boc-F**) has proved to be an extremely clean and efficient reagent for the *Boc*-protection of amino acids. Unfortunately, **Boc-F** is not sufficiently stable to be safely transported because it can decompose into isobutene, carbon dioxide, and HF, thus developing autogenous pressure in containers. This has led SNPE and its subsidiary ISOCHEM to manufacture and use **Boc-F** on site, thus offering low-cost *N-Boc*-protected amino compounds [155].

Recently, **9-fluorenylmethyl fluoroformate** (**Fmoc-F**) was introduced as a cheap and efficient reagent that is now available in large quantities for the synthesis of *Fmoc*-amino acids [428, 429]. It is interesting to note that the good solubility of **Fmoc-F** permits the use of high concentration two-phase reaction conditions. As in the case of the **Boc-F** reaction, the addition of sodium borate after the addition of **Fmoc-F** prevents fluorine corrosion of the glassware.

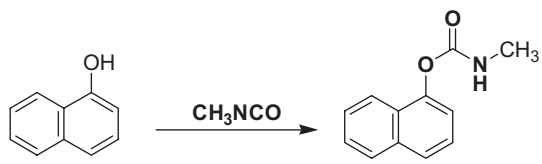
4.3.2.2 Carbamates Prepared with Isocyanates or Carbamoyl Chlorides

Carbamates are usually prepared by the addition of an alcohol to an isocyanate. The reaction of isocyanates with alcohols is fast and quantitative (indeed, it is used to characterize alcohols). The reaction with phenols is slower, but can be catalyzed by tertiary amines.



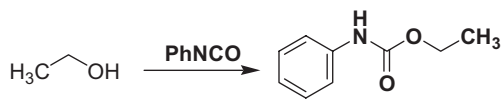
598 599

The *N-methyl-1-naphthyl carbamate* **601**, used as a pesticide (*Carbaryl*, *Sevin*), is prepared by the addition of 1-naphthol **600** to **methyl isocyanate**.



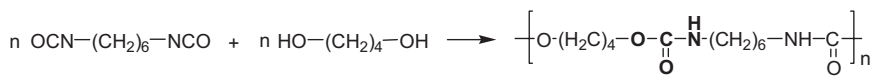
600 601

Aryl isocyanates also give crystalline adducts with anhydrous alcohols. **Phenyl**, **4-nitrophenyl**, **and 1-naphthyl isocyanates** are often used to prepare crystalline carbamates to assist in the identification of alcohols.



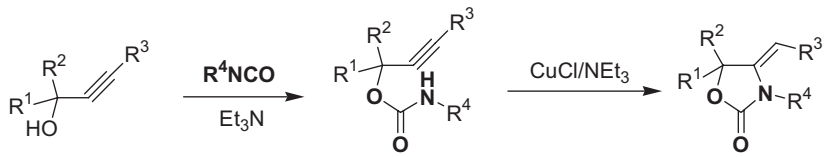
602 603

The reaction has attained great technological importance, since the addition of polyhydroxylic compounds to polyisocyanates discovered by O. Bayer [430] gives *polyurethanes*, an important class of polymers.



The mechanisms of uncatalyzed [431], tertiary amine catalyzed [432], metal-catalyzed [433, 434], and light-catalyzed additions of alcohols to isocyanates have been extensively investigated [142, 435–437].

2-Propynyl tosylcarbamates **605** undergo smooth cyclization under the catalysis of $CuCl/Et_3N$ or $AgNCO/Et_3N$ to furnish 4-methylene-2-oxazolidinones **606** in good yields. Similar cyclizations of *N*-acyl derivatives of **605** (PhCO, MeCO, EtOCO, etc.) are effectively catalyzed by AgNCO/*t*-BuOK. These reactions tolerate a variety of substituents at C_1 and C_3 of 2-propyn-1-ol **604** and provide (*Z*)-**606** as single stereoisomers. The scope of the cyclization of 3-butynyl carbamates is rather limited, and in general only *N*-tosyl derivatives of terminally unsubstituted 3-butyn-1-ols undergo cyclization to give 4-methylenetetrahydro-1,3-oxazin-2-ones in synthetically useful yields under the catalysis of $AgNCO/Et_3N$ or AgNCO/*t*-BuOK [438].



604 **605** **606**

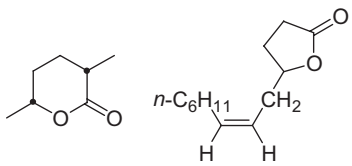
R^4 = Ph, Ts

General procedure. *2-Propynyl and 3-butynyl tosylcarbamates and phenylcarbamates* **605** [438]: To a solution of an acetylenic alcohol (20 mmol) and triethylamine (2.8 mL, 20 mmol) in diethyl ether (20 mL) at 0 °C under nitrogen, ***p*-toluenesulfonyl isocyanate** or **phenyl isocyanate** (3.0 mL, 20 mmol) was added by means of a syringe, and the mixture was stirred at room temperature for 2 h. To isolate *N*-tosylcarbamates, the mixture was washed with water (2 × 20 mL). The combined aqueous extracts were acidified with 2 M HCl (15 mL) and extracted with ethyl acetate (3 × 30 mL). To isolate *N*-phenylcarbamates, the mixture was washed with 2 M HCl (15 mL) and then extracted with ethyl acetate (2 × 20 mL). The organic extracts were dried ($MgSO_4$), filtered, concentrated, and subjected to column chromatography on silica gel (eluent: hexane/ethyl acetate, ca. 4:1) to give **605** (R^4 = Ts or phenyl) in 80–90% yield. **605** ($R^1 = CH_2{=}CH_2$, R^2 = H, R^3 = H, R^4 = Ts) was found to be unstable and was isolated as the triethylamine salt by evaporation of the water from an aqueous extract.

General procedure. *2-Propynyl and 3-butynyl allylcarbamates*. [438]: To a solution of an alkynyl alcohol (30 mmol) and **allyl isocyanate** (2.65 mL, 30 mmol) in diethyl ether (20 mL), boron trifluoride-diethyl ether etherate (3.7 mL, 30 mmol) was added by means of a syringe at room temperature over a period of 20 min. After stirring for 3 h at the same temperature and diluting with diethyl ether (100 mL), the mixture was washed with satd. aq. $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by kugelrohr distillation (ca. 110 °C/1 mmHg) to give *2-propynyl* and *3-butynyl allylcarbamates* in quantitative yields.

General procedure. *Cyclic carbamates* **606** *by intramolecular aminocyclization of alkynyl carbamates* **605** [438]: A 25-mL two-necked, round-bottomed flask, containing a magnetic stirring bar, **605** (R^4 = Ts) (253.3 mg, 1 mmol), and CuCl (10 mg, 0.1 mmol), was fitted with a serum cap and a reflux condenser equipped at the top with a three-way stopcock connected to a nitrogen balloon. The apparatus was purged with nitrogen by pumping and filling several times by means of the three-way stopcock. Dry THF (5 mL) and triethylamine (14 μL, 0.1 mmol) were added from syringes, and the resulting mixture was stirred at room temperature for 24 h. After the addition of satd. $NaHCO_3$ (20 mL), the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered,

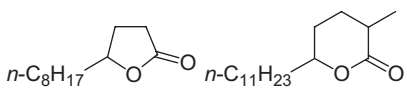
and concentrated. The residue was purified by means of column chromatography on silica gel (eluent: benzene) to give the *cyclic carbamate* **606** ($R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 = Ts$) in 94% yield; mp 145.0–145.5 °C.



607 LP of carpenter bee

608 LP of black-tailed deer

609 LP of Japanese beetle



610 LP of rove beetle

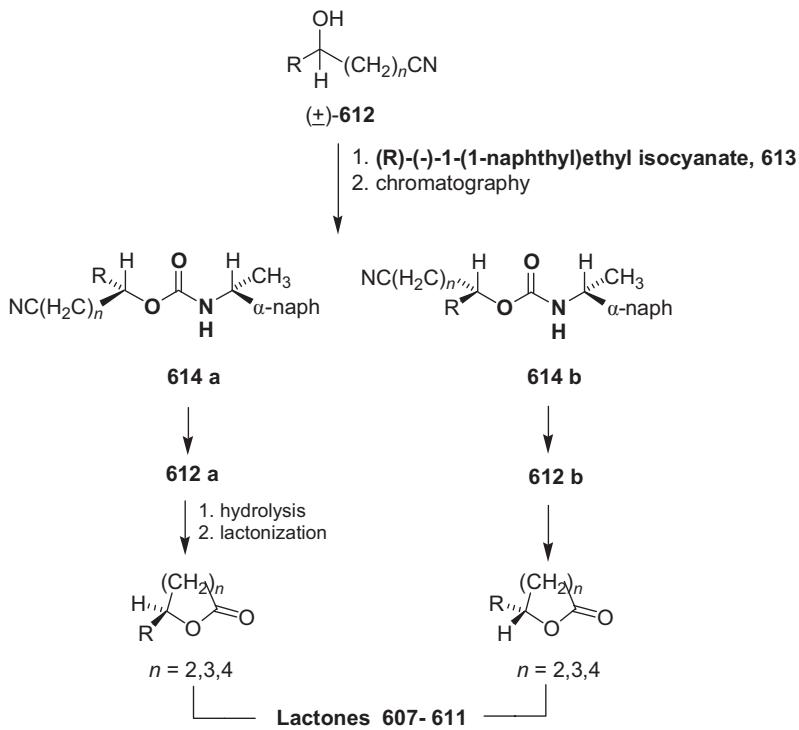
611 LP of Oriental hornet

Enantiomerically pure lactonic pheromones **607**–**611**, of the carpenter bee, black-tailed deer, Japanese beetle, rove beetle, and Oriental hornet, respectively, have been synthesized from racemic cyano alcohols of type **612**. The key to the success of the overall approach is the facile separation of diastereomeric carbamates derived from cyano alcohols of type **612** by automated multigram LC. The chosen approach also facilitates the assignment of absolute configurations to the lactone enantiomers and their precursors. In the case of **607**, direct determination of enantiomeric purity and absolute configuration is also possible using the chiral solvating agent 2,2,2-trifluoro-1-(9-anthryl)ethanol [439].

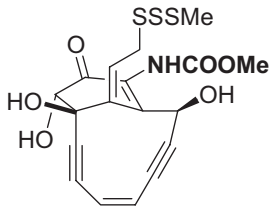
Typical procedure. *1-Methyl-4-cyanobutyl N-[1-(1-naphthyl)ethyl]carbamates* **614** (R = Me, $n = 4$) [439]. ***Procedure A***: A stirred solution of 5-cyanopentan-2-ol (8.0 g, 70.8 mmol), **(*R*)-(−)-1-(1-naphthyl)ethyl isocyanate** (13.9 g, 70.8 mmol), dry benzene (150 mL), and two drops of dimethylethanolamine catalyst was heated at reflux under N_2 for 24 h. The solvent was then removed in vacuo, and the crude diastereomeric carbamates were completely separated by chromatography (on acidic alumina, eluting with $CHCl_3$/hexane, 2:1) using an automated preparative LC system. A total of 8.9 g (81%) of the high R_f (*R*,*R*) diastereomer was collected as a yellow viscous oil.

(Z)-1-(2-Cyanoethyl)-3-nonene N-[1-(1-naphthyl)ethyl]carbamates **614** (R = 3-nonene, $n = 4$) [439]. ***Procedure B***: To a stirred solution of **phosgene** (5.8 g, 58.6 mmol) (for a *safe source*, see Chapter 7) in dry toluene (75 mL) at −5 °C under N_2,

a solution of (*Z*)-4-hydroxy-6-dodecenenitrile (2.8 g, 14.3 mmol) and dry pyridine (1.26 g, 15.9 mmol) in toluene (75 mL) was added over a period of 2 h. The mixture was allowed to slowly warm to 25 °C, and the solvent and excess phosgene were removed in vacuo at below 40 °C. The residue was immediately redissolved in dichloromethane (75 mL) and blanketed with N_2, and, with stirring, a solution of (*R*)-(−)-1-(1-naphthyl)ethylamine (2.45 g, 14.3 mmol) and pyridine (1.26 g) in dichloromethane (30 mL) was added in one portion (exothermic by 5–10 °C). The mixture was stirred at 25 °C for 10 h and was then washed with 1 M hydrochloric acid (2 × 75 mL) and H_2O (75 mL). Drying ($MgSO_4$) and removal of the solvent afforded the crude *(Z)-1-(2-cyanoethyl)-3-nonene N-[1-(1-naphthyl)ethyl]carbamates* **614**, which were separated chromatographically (on silica gel, eluting with hexane/EtOAc, 3:1). A total of 1.71 g (61.2%) of the high R_f (*S*,*R*)-diastereomer was collected as a light-yellow oil.



Highly functionalized carbamate intermediates suitable for potential elaboration to esperamicinone **615**, the aglycone of esperamicin A_1 (a member of the enediyne family of antitumor antibiotics exhibiting activity against murine tumor models), have been prepared employing either **phenyl isocyanate** or **phosgene** and following two different synthetic strategies for the installation of the vinylogous carbamate group [440]. The starting material is the readily available aromatic system **616**.



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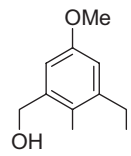

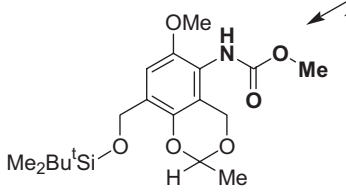

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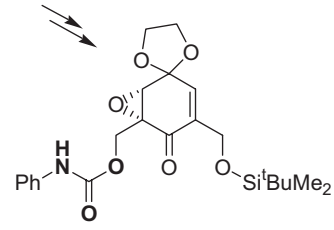
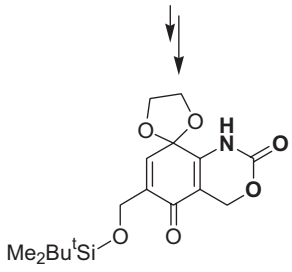


621



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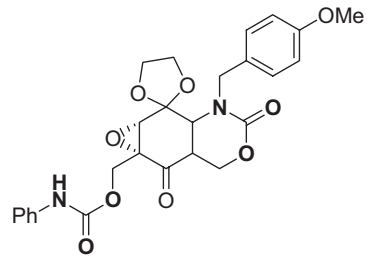

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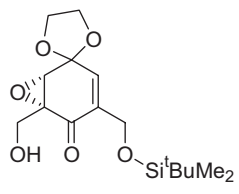
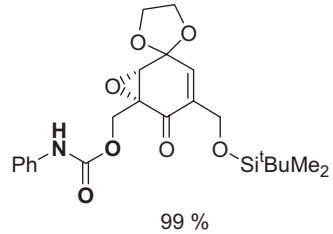


620

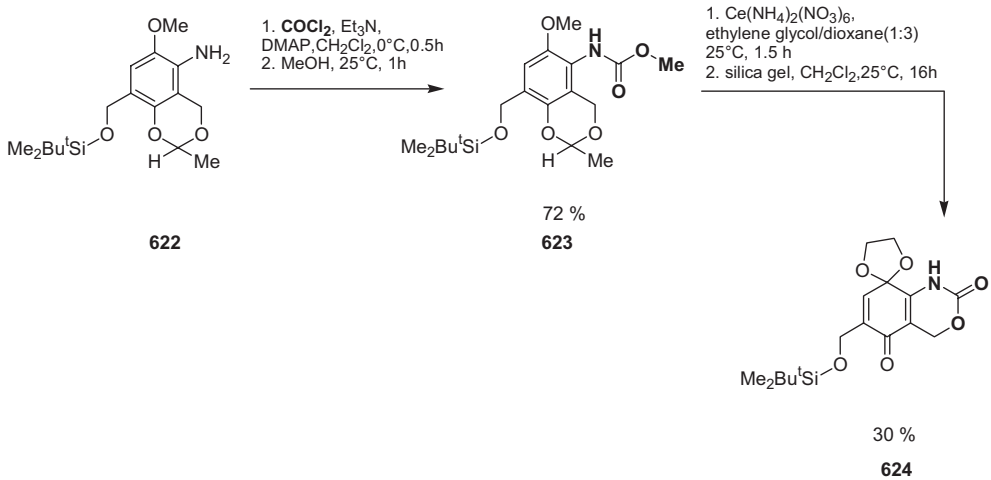
PhNCO, Et_3N,
CH_2Cl_2, 25°C, 1h



99 %

621

Typical procedure. *Carbamate* **621** [440]: To a solution of epoxide **620** (5.46 g, 16.0 mmol) in dichloromethane (53 mL) were added triethylamine (2.7 mL, 19.4 mmol) and **phenyl isocyanate** (1.9 mL, 17.5 mmol). After 1 h, the reaction mixture was diluted with diethyl ether (200 mL) and washed with 1 N HCl (2 × 50 mL) and $NaHCO_3$ (2 × 50 mL), and dried ($MgSO_4$). Concentration under reduced pressure and purification of the residue by flash chromatography (silica gel; 30 → 40% diethyl ether in petroleum ether) yielded *carbamate* **621** as a white foam (7.26 g, 99%).



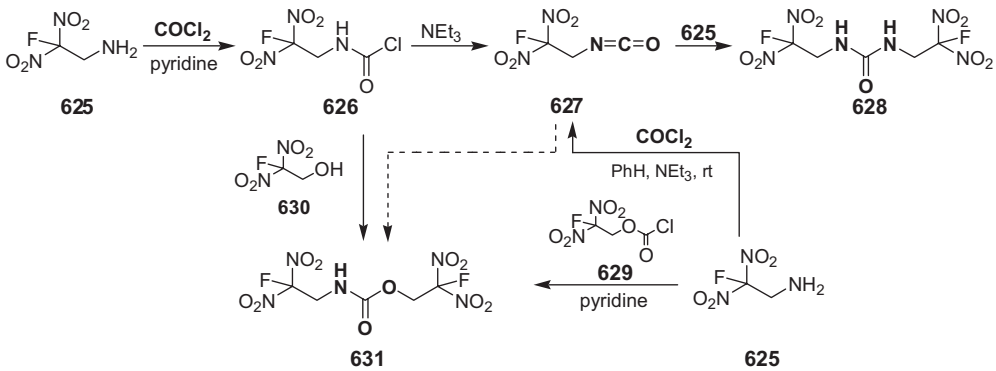
622 **623** **624**

Typical procedures. *Carbamate* **623** *and quinone monoketal* **624** [440]. *Carbamate* **623**: To a solution of crude amine **622** (37.0 g, 104 mmol) in dichloromethane (350 mL) was added triethylamine (57.9 mL, 416 mmol) and DMAP (635 mg, 5.2 mmol), and the mixture was cooled to 0 °C. **Phosgene** (for a *safe source*, see Chapter 7) (65 mL, 1.93 M in toluene, 125 mmol) was cautiously added and the reaction mixture was allowed to warm to ambient temperature. After 1 h, methanol (50 mL) was added and the reaction mixture was left to stand for 0.5 h. It was then diluted with diethyl ether (1 L), washed with 1 N HCl (2 × 300 mL), aq. $NaHCO_3$ solution (300 mL), and brine (300 mL), and dried ($MgSO_4$). The organic phase was concentrated under reduced pressure and placed under high vacuum (0.03 Torr) until the residue solidified. The solid was redissolved in the minimum volume of dichloromethane (ca. 30 mL), and petroleum ether (100 mL) was added. After cooling to −20 °C for 24 h, the product was collected by filtration (27.42 g) and the mother liquor was concentrated under reduced pressure and purified by flash chromatography (silica gel; 30% diethyl ether in petroleum ether) to yield a further 2.11 g of *carbamate* **623** (72% for two steps) as colorless, rhombohedral crystals (diethyl ether/petroleum ether); mp 85.5–86.0 °C.

Quinone monoketal **624**: To a solution of carbamate **623** (27.4 g, 69.0 mmol) in 1,4-dioxane (260 mL) and ethylene glycol (86 mL) at 0 °C was added ammonium cerium(IV) nitrate (75.7 g, 138 mmol). After 0.2 h, the cooling bath was removed

and stirring was continued for a further 0.25 h. The mixture was then left to stand for a further 1.5 h before being diluted with diethyl ether (1200 mL) and washed with H_2O (300 mL). The aqueous phase was extracted with diethyl ether (300 mL) and the combined organic phases were washed with aq. $NaHCO_3$ solution (3 × 300 mL) and brine (300 mL), and dried ($MgSO_4$). After concentration under reduced pressure, the residue was redissolved in dichloromethane (200 mL) and silica gel (60 g) was added. The slurry was stirred for 14 h, and then filtered and concentrated under reduced pressure. Crystallization of the residue from benzene (50 mL) yielded compound **624** (5.44 g). Purification of the mother liquor by flash chromatography (silica gel, 40 → 60 → 70% diethyl ether in petroleum ether) yielded a further 2.16 g of **624** (30%) as white crystals (benzene; mp 178–179 °C (dec.)).

The reaction of 2-fluoro-2,2-dinitroethylamine **625** with acid chlorides has been used to prepare a variety of fluorodinitroethyl-substituted amides, *carbamates*, and ureas [441]. Carbamates have also been prepared by the addition of alcohols to **2-fluoro-2,2-dinitroethyl isocyanate**.

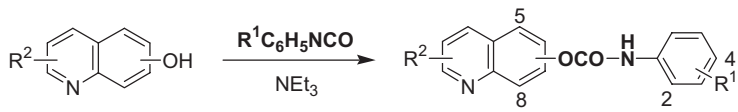


Typical procedure. *N,O-Bis(2-fluoro-2,2-dinitroethyl)carbamate* **631** [441]: *N-(2-Fluoro-2,2-dinitroethyl) carbamoyl chloride* **626**: To a solution of **phosgene** (11.5 g) (for a *safe source*, see Chapter 7) in benzene (50 mL), a solution of 2-fluoro-2,2-dinitroethylamine (17.7 g) and pyridine (9.5 g) in benzene (30 mL) was added dropwise at 5–10 °C. After completion of the addition, the mixture was heated to 50 °C for 1 h and the solvents were removed *in vacuo*. The residual oil was diluted to a volume of 100 mL with dichloromethane and reacted further as described below.

To 40 mL of the above solution of crude *fluorodinitroethylcarbamoyl chloride* **626**, 2-fluoro-2,2-dinitroethanol **630** (5.6 g) was added, followed, dropwise and with cooling in an ice bath, by pyridine (3.1 g). The mixture was stirred at room temperature for 2 h, diluted with dichloromethane (100 mL), washed with dilute sulfuric acid, dried, and concentrated. Repeated chilling, filtration, and concentration of the mother liquor gave several fractions of *N,O-bis(2-fluoro-2,2-dinitroethyl)-carbamate* **631** containing diminishing amounts of *N,N′*-bis(2-fluoro-2,2-dinitroethyl)urea as an impurity. The yield of crude product amounted to 3 g. The product was purified by recrystallization from dichloromethane/hexane; mp 63–64 °C.

Typical procedure: *N,O-Bis(2-fluoro-2,2-dinitroethyl)carbamate* **631** by reaction of 2-fluoro-2,2-dinitroethylamine **628** with **2-fluoro-2,2-dinitroethyl chloroformate 629** [441]: First, **629** was prepared *in situ* as follows. Pyridine (9.0 g) was added dropwise to an ice-cooled solution of 2-fluoro-2,2-dinitroethanol (15.4 g) and **phosgene** (ca. 12 g) (for a *safe source*, see Chapter 7) in dichloromethane (100 mL). The mixture was stirred at ambient temperature for 3–4 h, then rapidly washed with ice-cold dilute sulfuric acid, dried, and the solvent and excess phosgene were removed *in vacuo*. The remaining oil was taken up in dichloromethane (25 mL) and added dropwise and with stirring and cooling to an ice-cold solution of 2-fluoro-2,2-dinitroethylamine **628** and pyridine (6.3 g) in dichloromethane (100 mL). The mixture was stirred overnight at room temperature; the solvent was then removed and the residue was digested with dilute sulfuric acid. The crude product was recrystallized from dichloromethane/hexane to give 21 g (88.6% based on 2-fluoro-2,2-dinitroethylamine) of *N,O-bis(2-fluoro-2,2-dinitroethyl)carbamate* **631**.

A series of 5- to 8-quinolyl carbamates **653** was prepared by reacting the appropriate hydroxyquinolines with various substituted **phenyl isocyanates** (yields 27–92%). The procedure that gave the best results involved mixing the two reactants in diethyl ether with a catalytic amount of triethylamine and stirring at room temperature for several days [442].

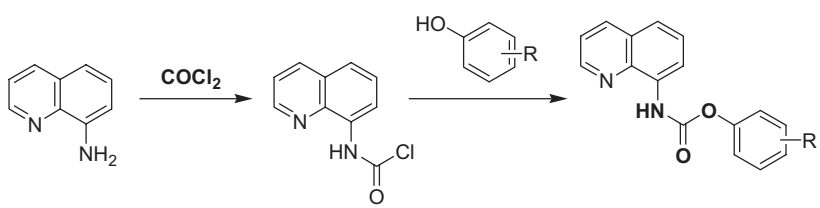


652 **653**

R^1 = 2-OCH_3, 4-OCH_3, 3-OCH_3, 4-Br,
2-CF_3, 3-CF_3, 2-CH_3, 3-CH_3, 4-CH_3
R^2 = H, 2-CH_3, 5-Cl, 5-SO_3H

Typical procedure. *8-Quinolyl 4-methoxyphenyl carbamate* **653** (R^1 = 4-OCH_3, R^2 = H) [442]: A suspension of 8-hydroxyquinoline **652** (1.45 g, 10 mmol) and **4-methoxyphenyl isocyanate** (1.49 g, 10 mmol) in diethyl ether (100 mL) was stirred for 2 days at room temperature. The precipitate obtained was collected by filtration and crystallized from diethyl ether/acetone to give 1.9 g (65% yield) of product **653**; mp 129–130 °C.

As a variation, phenyl 8-quinoline carbamates **656** were prepared as shown in the scheme below [442].



654 **655** **656**

R = 2-OCH_3, 4-OCH_3

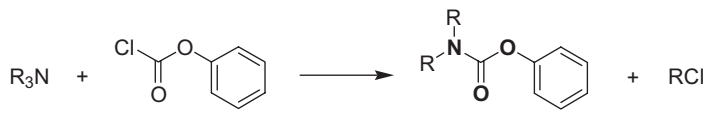
Typical procedure. *4-Methoxyphenyl 8-quinolylcarbamate* **656** [442]: At 0 °C, a solution of 8-aminoquinoline **654** (2.0 g, 13.9 mmol) in dichloromethane (10 mL) was added dropwise to a solution of **phosgene** (for a *safe source*, see Chapter 7) in dichloromethane (7 mL, 2.2 M, 15.4 mmol). The precipitate obtained was collected by filtration and dried, giving 3.1 g (92% yield) of the carbamoyl product **655**. The dark solid thus obtained proved to be unstable, and in practice it had to be used immediately for the next reaction.

A suspension of the above intermediate **655** (5.7 g, 23.4 mmol) in dry THF (100 mL) was treated with triethylamine (7 mL, 50 mmol). 4-Methoxyphenol (3.5 g, 23.4 mmol) was then added, and the reaction mixture was stirred overnight at room temperature. The solvent was then removed in vacuo. The residue was dissolved in chloroform/1.0 N sodium hydroxide and washed with 1.0 N sodium hydroxide (2×) and water; the organic phase was dried ($MgSO_4$) and concentrated to a solid. This solid was redissolved in ethyl acetate/acetone (1:1), treated with charcoal, and the mixture was filtered through Celite and silica gel. A crystalline solid formed, which was collected by filtration and dried to give 3.5 g (43% yield) of the product; mp 128–129 °C.

Carbamates are also formed by one-stage, two-step processes involving **isocyanates** as intermediates and precursors. Thus, carbamates are prepared under modified *Hofmann rearrangement* conditions, using NBS/NaOMe as the reagent [443], by *Curtius rearrangement* of the acyl azide if the reaction is carried out in alcohol, by the reaction of amides with lead tetraacetate [444], or by the *Lossen rearrangement*, if the carbamates are not sensitive to the presence of base.

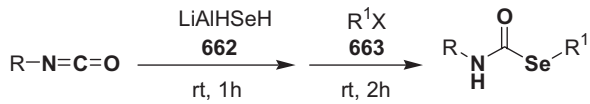
N-Unsubstituted carbamates can also be prepared by this route using cyanic acid, although reaction of the carbamate with a second molecule of cyanic acid may then occur. Alkylation [445] of these carbamates with alkenes in the presence of boron trifluoride yields *N*-alkyl carbamates.

Tertiary amines **657** are cleaved by reaction with chloroformate (for example, α-chloroethyl chloroformate, or phenyl chloroformate, **658**), resulting in carbamates **659** (for an extended discussion, see Section 4.7).



657 **658** **659** **660**

Several *N*-alkyl-*Se*-alkylselenocarbamates **663** with potential antiviral properties have been prepared using **isocyanates 661** (yields of 29–73%) [446].

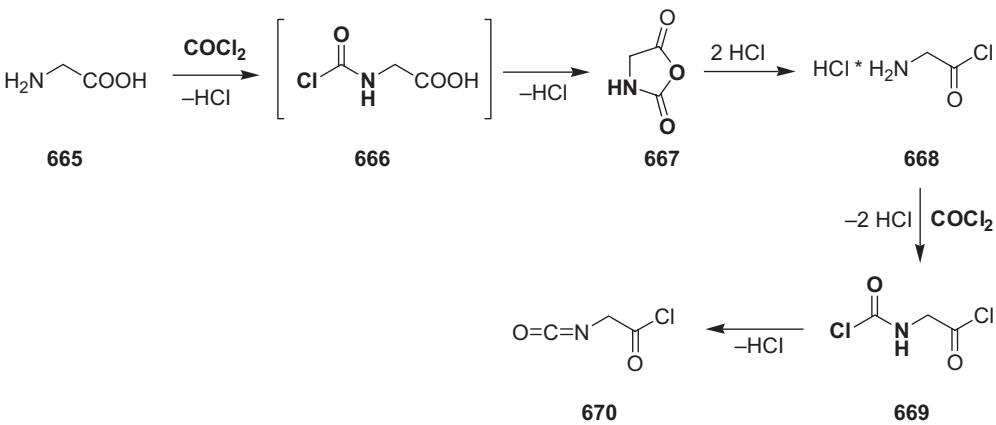


661 **664**

R = Ph, 4-ClPh, 4-MePh, *Cyclo*-C_6H_{11}
R^1X = MeI, EtI, n-BuI, BnBr, $Ph(CH_2)_2Br$

Typical procedure. *Se-Methyl-N-phenylselenocarbamate* **664** [446]: **Phenyl isocyanate 661** (R = Ph) (0.11 mL, 1.0 mmol) was added to a solution of LiAlHSeH **662** (1.0 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 1 h. Methyl iodide **663** (0.06 mL, 1.0 mmol) was then added, and the reaction mixture was stirred at room temperature for 2 h. It was then extracted with diethyl ether and the combined extracts were washed with water. The organic phase was dried over sodium sulfate and concentrated to dryness. The residue was purified by flash chromatography on silica gel eluting with dichloromethane/*n*-hexane (4:1) to give *Se-methyl-N-phenylselenocarbamate* **664** (0.15 g, 70%) as yellow crystals; mp 90.8–93.0 °C.

A series of *2-isocyanatoacyl chlorides* of type **670** was prepared by treating *glycine*, *DL-alanine*, *L-valine*, *L-leucine*, *and L-phenylalanine* with **phosgene** in an inert solvent such as dioxane [447].



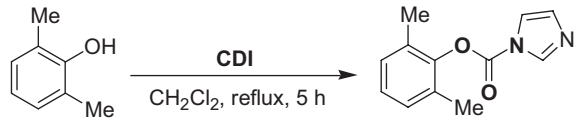
The acid chloride group of the 2-isocyanatoacyl chloride **670** is more reactive as an electrophile than the isocyanate group (see Section 4.3.5. ''Reactions with Binucleophiles''). For example, in reactions with equimolecular amounts of ethanol and water, **2-isocyanatoacetyl chloride 670** gave ethyl *2-isocyanatoacetate* and *2,5-oxazolidinedione*, respectively. With a molar excess of *p*-phenetidine, it gave *3-(p-phenethyl)hydantoin*, and with a 2 molar or greater excess of amine it gave the corresponding *ureidoamide*. Treatment with molar quantities of *N*-methylaniline in the presence of molar quantities of pyridine furnished *N-methyl-2-isocyanatoacetanilide* [447].

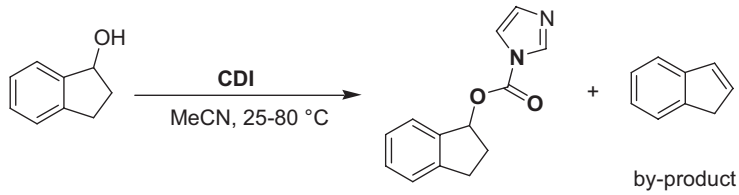
Typical procedure. *2,5-Oxazolidinedione* **667** [447]: Into a suspension of finely ground glycine (15 g) in dry dioxane (750 mL), **phosgene** (for a *safe source*, see Chapter 7) was introduced in a fine stream at 45–50 °C with efficient agitation. A clear solution was obtained after 5 h. This solution was filtered to remove unreacted glycine (1.7 g), and the dioxane was then removed under reduced pressure at a temperature below 40 °C with protection from moisture. The residue was

treated with dry diethyl ether (100 mL), and the crystals of *2,5-oxazolidinedione* **667** were collected by filtration and dried over P_2O_5 in a vacuum desiccator. The crude product so obtained, 16 g (89%), was recrystallized from ethyl acetate/petroleum ether to yield 14.3 g (77.2%) of pure material, which showed no melting point because of polymerization.

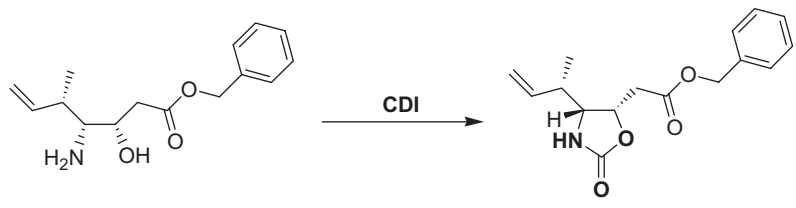
4.3.2.3 Carbamates Prepared with *N,N′*-Carbonyldiimidazole (CDI)

(*N*-Alkoxycarbonyl)- and (*N*-aryloxycarbonyl)imidazoles (carbamates) were unambiguously proven to be the products of the reaction of ***N,N′*-carbonyldiimidazole** (**CDI**) with alcohols [448]. Reaction of **CDI** with 2,6-dimethylphenol or 1-indanol gave (on the basis of IR and ^{1}H NMR evidence) the corresponding carbamate in yields of 91% and 42%, respectively.

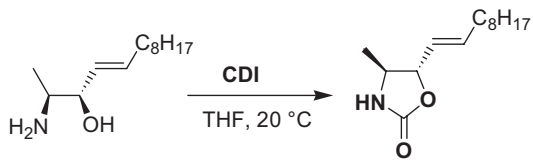




4-Amino-3-hydroxy-5-methylhept-6-enoic benzyl ester **676** reacts with **CDI** to give [4-(1-methylallyl)-2-oxo-oxazolidin-5-yl]acetic acid benzyl ester **677** [449].



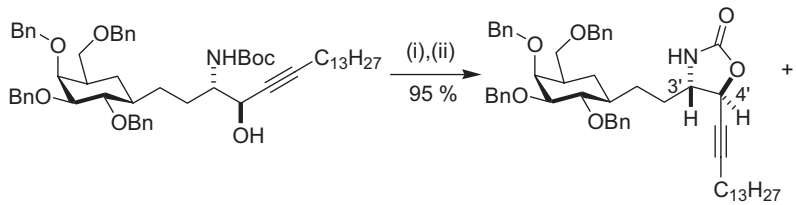
CDI has been employed to prepare (4*S*,5*R*)-5-[(*E*)-dec-1-en-1-yl]-4-methyl-2-oxazolidinone **679** [450, 451].



678 **679**

Typical procedure. *(4S,5R)-5-[(E)-Dec-1-en-1-yl]-4-methyl-2-oxazolidinone* [451]: In a flame-dried reaction flask were placed the amino alcohol (119 mg, 0.56 mmol), **CDI** (118 mg, 0.73 mmol), and freshly distilled THF (2 mL). The resulting solution was stirred for 2 h at room temperature. The THF was then evaporated, the residue was redissolved in Et_2O, and this solution was washed with 1 N HCl (3×) and with saturated $NaHCO_3$ (1×), and dried (K_2CO_3). Removal of the solvent under reduced pressure provided the crude material. Chromatography (EtOAc/hexane, 1:1) furnished 93 mg (70%) of pure product.

The stereochemistry of the amino alcohol *anti*-**680** was unequivocally assigned through its oxazolidone derivatives **681** and **682** prepared with **CDI** [452].



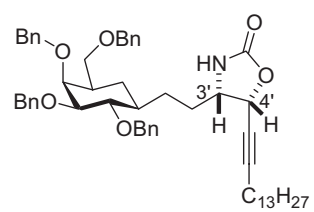
anti (syn/anti 5:95)

680

$J_{3',4'}$ = 6.0 Hz

681

(i) HCl/dioxane (4.8 M);
(ii) **CDI**, THF



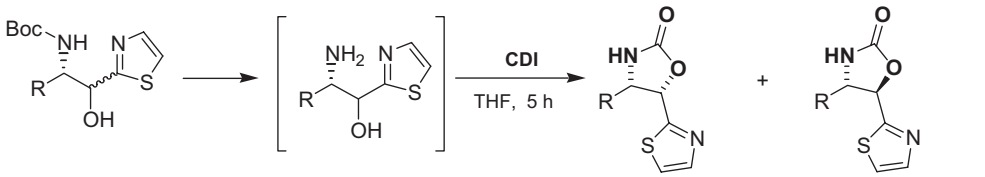
$J_{3',4'}$ = 8.0 Hz

682

Typical procedure. *Oxazolidinones* **681** and **682** [452]: A mixture of epimers **680** (0.13 g, 0.14 mmol) was dissolved in a solution of HCl in dioxane (4.8 M, 3.0 mL) containing water (0.50 mL). The solution was stirred at room temperature for 14 h and then concentrated. The residue was redissolved in anhydrous THF (2.0 mL), treated with **CDI** (0.03 g, 0.21 mmol) at 0 °C, and the resulting mixture was stirred for 45 min at room temperature and then concentrated. The ^1H NMR spectrum of the crude residue showed it to be a mixture of **681** and **682** in a ratio of ca. 70:30. Chromatography of this mixture on silica gel eluting with cyclohexane/AcOEt (2:1)

afforded first **681** (0.07 g, 63%) as a syrup and then **682** (0.03 g, 27%) contaminated by a small amount of **681**.

4-Benzyloxymethyl- and 4-benzyl-5-thiazol-2-yl-oxazolidin-2-one (**685** and **686**) have been prepared with 1,1-carbonyldiimidazole from deprotected amino alcohols **684** [453].



683

R = -CH_2OBn
R = Bn

684

R = -CH_2OBn
R = Bn

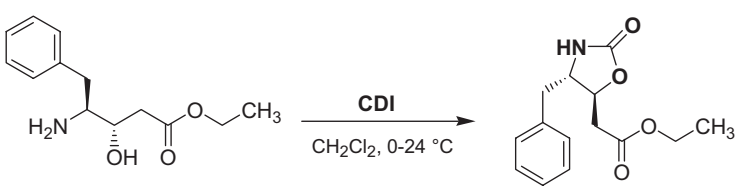
685a, $J_{4,5}$ = 8.5 Hz
686a, $J_{4,5}$ = 8.05 Hz

685b, $J_{4,5}$ = 4.9 Hz
686 b, $J_{4,5}$ = 4.9 Hz

General procedure. *Oxazolidinones* **685** and **686** [453]: To a stirred mixture of the amino alcohols **683** in dichloromethane (0.52 mmol) was added trifluoroacetic acid/water (95:5; 2 mL). After stirring for 1 h, the trifluoroacetic acid was evaporated in vacuo. The residue was dissolved in ethyl acetate (10 mL), and saturated aq. $NaHCO_3$ solution (5 mL) was added. After extraction with ethyl acetate (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated in vacuo. The deprotected amino alcohol **684** thus obtained was redissolved in THF (5 mL) and treated with a solution of **CDI** (1.06 g, 0.66 mmol) in the same solvent (3 mL). After stirring for 4–5 h, the reaction mixture was concentrated in vacuo, and saturated aq. $NaHCO_3$ solution was added. After extraction with ethyl acetate (3 × 15 mL), the combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. ^{1}H NMR analysis of the residue revealed the *syn*/*anti* diastereomeric ratio of the amino alcohols obtained.

Chromatography (silica gel; diethyl ether/petroleum ether, 95:5) of the oxazolidinone mixture derived from **684** (R = CH_2OBn) (ds_{syn} 80% in CH_2Cl_2) gave the *threo* isomer **685b** (0.113 g, 75%) and the *erythro* isomer **685a** (0.031 g, 20%).

Chromatography (silica gel; petroleum ether/ethyl acetate, 8:2) of the mixture derived from **684** (R = Bn) (ds_{syn} 80% in CH_2Cl_2) gave a mixture of the oxazolidinones **686a** and **686b** (96%).

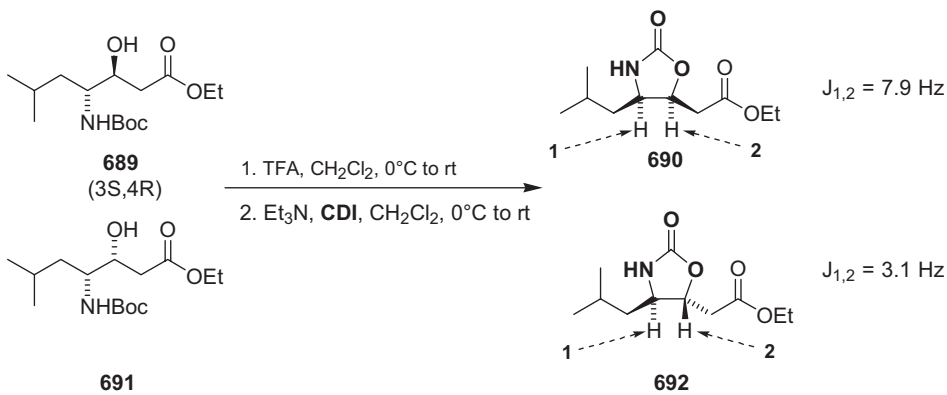


687
(4S,5S)

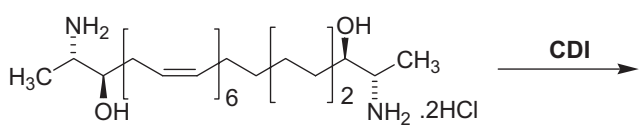
688

CDI has been employed for the preparation of ethyl (4*S*,5*R*)- or (4*S*,5*S*)-4-benzyl-2-oxo-oxazolidin-5-yl)acetate **688** [454].

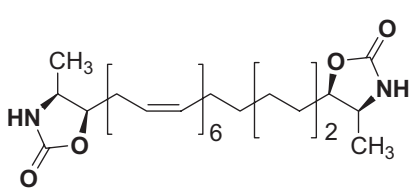
Vicinal amino alcohols have been transformed into 2-oxazolidinones with **CDI**, and their relative stereochemistries at C_2 and C_3 were determined by measuring the coupling constants (J_{H4}-J_{H5}) and observing the NOE cross-peak between the protons H-4 and H-5 [455, 456]. The respective large ($J = 8$–10 Hz) and small ($J = 3$–5 Hz) C_{4H}/C_{5H} coupling constants of the two diastereoisomers established the *erythro* (*cis*) and *threo* (*trans*) stereochemistries of the corresponding intermediates [457].



The stereochemistries of amino alcohols **689** and **691**, which are useful intermediates for the synthesis of an unusual isomer of statine (3*S*,4*R* configuration), were determined by forming the corresponding cyclic carbamates **690** and **692** with **CDI** [458]. Thus, treatment of the protected amino alcohols **689** and **691** with trifluoroacetic acid (30 equiv.) in dichloromethane at 0 °C, followed by warming to ambient temperature and removal of the solvent, produced the crude ammonium salt, which was diluted with dichloromethane and treated sequentially with triethylamine (2 equiv.) and **CDI** (2.5 equiv.) to produce, after work-up and purification, cyclic carbamates **690** and **692** in 66% yield.

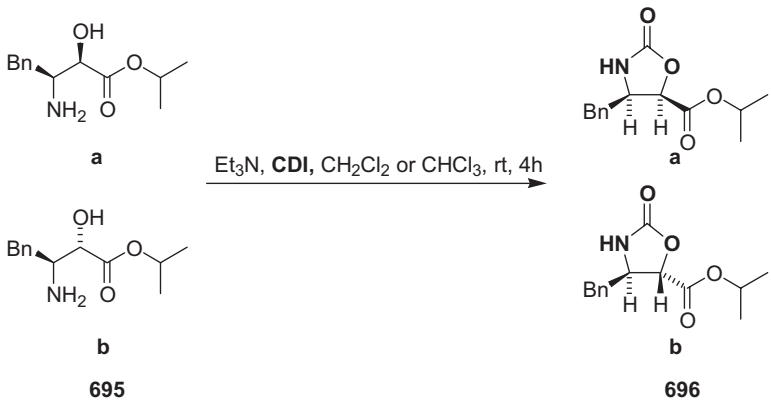


693

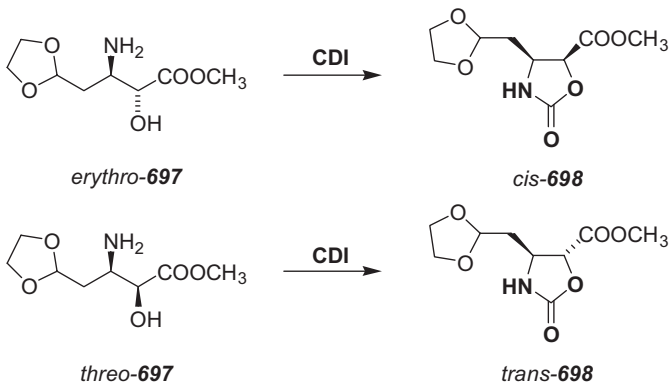


694

The relative stereochemistry of both 2-amino and 3-hydroxy groups in Leucettamols A and B, two antimicrobial lipids, has been defined by analysis of nuclear Overhauser enhancements in bis(oxazolone) **694**, which was formed by treatment of **693** with **CDI** [459]. The absolute stereochemistry of *sphingosine*-related polyunsaturated 2-amino alcohols isolated from marine organisms as secondary metabolites was also assigned by transformation to the oxazolidin-2-one and examination of the NMR data [460].

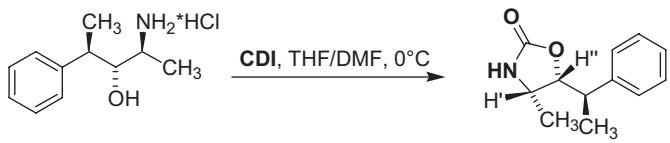


The isopropyl esters of optically active 1,2-amino alcohols **695a**,**b** were converted to the corresponding cyclic carbamates **696a**,**b** with **CDI** [461, 462].



Typical procedure. *cis- and trans-4-Carbomethoxy-5-(dioxol-2-yl-methyl)-2-oxazolidone* **698** [463]: A solution of **CDI** in dry THF (0.47 mL, 0.30 M, 0.14 mmol) was added dropwise to an *erythro*/*threo* mixture of amino alcohol ester **697** (28.3 mg, 0.14 mmol) in dry THF (3 mL). The mixture was stirred under argon at 20 °C until TLC analysis (EtOAc as eluent; less polar product $R_f = 0.68$; starting material $R_f = 0.10$) indicated complete reaction (24 h). Removal of the solvent and flash chromatography (4 g of silica gel, 10 mm o.d. column; hexanes/ethyl acetate/methanol,

12:7:1) of the residue gave a single fraction containing the diastereomeric oxazolidones **698** as a 1:1 *cis*/*trans* mixture, obtained as a clear, colorless oil (17.6 mg, 55%).



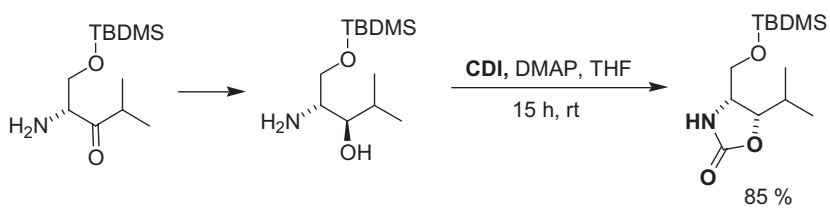
699 a **700 a**

H': δ = 3.9 ppm
H'': δ = 4.6 ppm
$J_{H',H''}$ = 10.6 Hz

699 b **700 b**

H': δ = 3.58, 3.66 ppm
H'': δ = 4.16, 4.28 ppm
$J_{H',H''}$ = 8.5, 5.9 Hz

Typical procedure for the synthesis of *cyclic carbamates* **700a,b** [464]: To a solution of (2*S*,3*S*,4*R*)-2-amino-4-phenyl-3-pentanol **699a** and (2*S*,3*S*,4*S*)-2-amino-4-phenyl-3-pentanol **699b** (70 mg, 0.47 mmol) in THF/DMF (3:1; 4 mL) at 0 °C was added **CDI** (175 mg, 1.08 mmol). The reaction vessel was flushed with nitrogen, stoppered, and the contents were stirred for 14 h at 0 °C. Water (4 mL) was added to the suspension and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried, and concentrated to an oil, which was chromatographed (radial chromatography) with a gradient of 25–50% EtOAc in hexane as eluent. Concentration of the collected fraction yielded 40 mg (50%) of **700b** as a 2:1 mixture of diastereomers; TLC (EtOAc/hexane, 3:1): $R_f = 0.39$. Carbamate **700a** was prepared in a similar manner and purified on a plate of silica gel (100 μm thickness); $R_f = 0.35$.



701 **702** **703**

Typical procedure. *(4R,5S)-4-[(tert-Butyldimethylsilyl)oxymethyl]-5-isopropyloxazolidin-2-one* **703** [465]: A solution of compound **701** (1.03 g, 2.41 mmol) in methanol was hydrogenated in the presence of 10% of Pearlman's catalyst [$Pd(OH)_2$] at 1 atm. After stirring vigorously for 1 h, the reaction mixture was filtered through a short pad of Celite, which was thoroughly washed with methanol. The methanol was evaporated from the combined filtrate and washings to leave compound **702**, which was used without further purification. To a solution of the thus obtained amino alcohol in THF were added **CDI** (507.5 mg, 3.13 mmol) and a catalytic amount of DMAP (29.4 mg, 0.24 mol). After stirring at room temperature for 15 h, the reaction mixture was diluted with saturated aqueous NH_4Cl solution. The aqueous solution was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography on silica gel (eluent: heptane/EtOAc, 3:1 then 2:1) afforded the *oxazolidinone* **703** (559.2 mg, 85%).

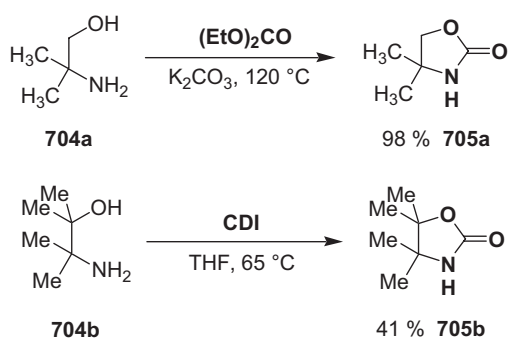
A similar procedure for the synthesis of 4-(*tert*-butyl-dimethylsilyl)oxymethyl-5-phenyl-oxazolidin-2-one with **CDI** has been described by Mitchell [466].

Similar syntheses of oxazolidin-2-one with **CDI**, starting from various substituted 1,2-amino alcohols, have also been reported [461–463, 467–484].

4.3.2.4 Carbamates by Aminolysis of Carbonate or Dithiocarbonate Esters

Diethyl carbonate has been employed for the cyclocarbamation of various amino alcohols. The reaction is catalyzed by basic substances, such as sodium methoxide, magnesium methoxide, potassium hydroxide, or sodium or potassium carbonates. Sodium methoxide in xylene [485–487], or potassium or sodium carbonate under reflux [488–493] are the preferred reaction conditions. The reaction has wide scope and synthetic utility.

4,4-Dimethyl-2-oxazolidone **705a** and 4,4,5,5-tetramethyl-2-oxazolidone **705b** have been prepared with **diethyl carbonate** [494] and **CDI** [494, 495], respectively.



704a 98 % **705a**

704b 41 % **705b**

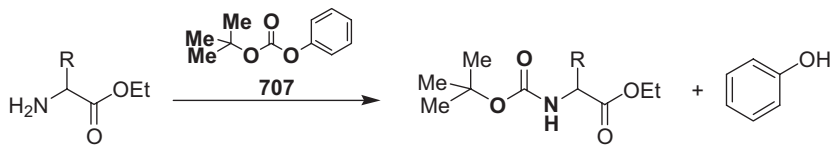
Typical procedure. *4,4-Dimethyl-2 oxazolidone* **705a** [494]: A mixture of 2-amino-2-methyl-1-propanol (4.00 g, 45 mmol), **diethyl carbonate** (10.9 mL, 90 mmol), and anhydrous potassium carbonate (0.100 g, 0.72 mmol) was heated at 120 °C for 2 h with stirring. After removal of the resulting ethanol and excess diethyl carbonate in

vacuo, the residue was diluted with 1 M HCl (8.0 mL) and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. Filtration and concentration in vacuo gave *4,4-dimethyl-2-oxazolidone* **705a** as colorless crystals (5.07 g, 98%).

Typical procedure. *(4R,5S)-4-Methyl-5-phenyloxazolidin-2-one* [487]: To a solution of (*1S,2R*)-norephedrine (40 g, 0.26 mol) in toluene (400 mL) was added **diethyl carbonate** (37 mL, 0.32 mol). The mixture was heated to reflux (under Ar) while 40 mL of solvent was removed through the use of a Dean–Stark apparatus. The mixture was allowed to cool for 20 min, and then sodium methoxide (1 g) was added. Upon reheating, an EtOH/toluene azeotropic mixture was removed at 75–77 °C. After 3 h, the reaction was complete and the temperature of the mixture had increased to 125 °C. The mixture was left to stand at room temperature for 16 h, whereupon *(4R,5S)-4-methyl-5-phenyloxazolidin-2-one* (40.6 g) crystallized and could be collected. The solvent was removed from the filtrate in vacuo and the residue was redissolved in EtOAc (250 mL). This solution was washed with brine (50 mL) and a precipitate was removed by filtration. The solvent was then removed in vacuo and toluene (50 mL) was added to the residue. Removal of the toluene by distillation yielded oily crystals of the oxazolidinone, which were washed with Et_2O to afford 4.5 g (total 45 g, 97%).

As a variant, the cyclic carbonate, **ethylene carbonate**, has been used [496, 497], giving ethylene glycol in addition to the oxazolidinone.

A former approach to Boc-amino acids was based on the instability of **alkyl aryl carbonates** to base. Thus, by using a mixed carbonate such as **707**, one should be able to replace the aryloxy group by an amine.



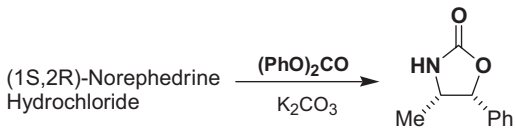
706 **708** **709**

The reaction yields are poor. Even the carbonylisopropoxy and carbonylisobutoxy groups could only be introduced in yields of 20–30%. Neither the use of thiophenol in place of phenol nor transesterification using *tert*-butyl alcohol gave the desired results [498].

Alkyl phenyl carbonates have recently been used for the highly selective synthesis of carbamate protected *polyamines* [508] (for a preparation of **benzyl phenyl carbonate** see section 4.3.3.1).

It has been claimed that **benzyl 4-nitrophenyl carbonate** [499] and **dibenzyl dicarbonate** [500] avoid the side-reaction in acylation, but their applicability has not yet been fully studied. Any practical improvement gained from using a carbonate is at the expense of much slower reaction rates.

Diphenyl carbonate has been chosen as the most convenient *phosgene equivalent* for the laboratory-scale synthesis (up to 3 mol) of oxazolidin-2-one **711** starting from (1*S*,2*R*)-norephedrine **710** [501]. Direct fusion of a 3-amino-D-altritol derivative with diphenyl carbonate to furnish the corresponding oxazolidinone has also been reported [502].



710 **711**

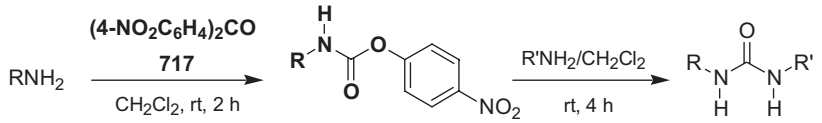
Typical procedure. *(4R,5S)-4-Methyl-5-phenyl-2-oxazolidinone* [501]: A mechanically stirred mixture of (1*S*,2*R*)-norephedrine **710** (151 g, 1.00 mol) ($[\alpha]_{589} = +33.4$ ($c = 7$, water)), as the hydrochloride salt, **diphenyl carbonate** (236 g, 1.10 mol), and anhydrous potassium carbonate (152 g, 1.10 mol) was heated at 110 °C for 4–6 h. The resultant mixture was then cooled to <60 °C. Excess diphenyl carbonate was hydrolyzed by adding methanol (600 mL) and heating the mixture under reflux for 0.5 h. Sufficient water (400–600 mL) was then added to dissolve the potassium carbonate. Methanol was removed in vacuo. The product and phenol were extracted into dichloromethane (3 × 1 L). The combined extracts were washed with 2 M aqueous sodium hydroxide (3 × 1 L) to remove the phenol, 1 M aqueous hydrochloric acid (1 × 1 L), and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 195 g (110% mass balance) of a light-yellow solid. Recrystallization from toluene (600 mL) afforded 145–165 g (82–93%) of oxazolidinone **711** as a white crystalline solid.

Aminolysis of carbonate esters is most successful with symmetrical carbonates or when there is a large difference in leaving group ability between $^{-}OR^1$ and $^{-}OR^2$ (e.g. $R^2 = Ph$, $R^1 = Me$). The method is ineffective for the preparation of carbamates **714** with good leaving groups (e.g. $R^1 = Ph$) since in these cases the carbamate is more reactive than the starting carbonate.

712 **713** **714** **715**

Bis(4-nitrophenyl) carbonate

Bis(4-nitrophenyl) carbonate 717, a very stable reagent, can be converted into carbamates **718** by reaction with equimolecular amounts of primary aliphatic or aromatic amines within 2 h in dichloromethane [503]. Intermediates **718** react further with different primary amines to give the unsymmetrical ureas **719** in good yields.



716 **718** (44 -78 %) **719** (50 -96 %)

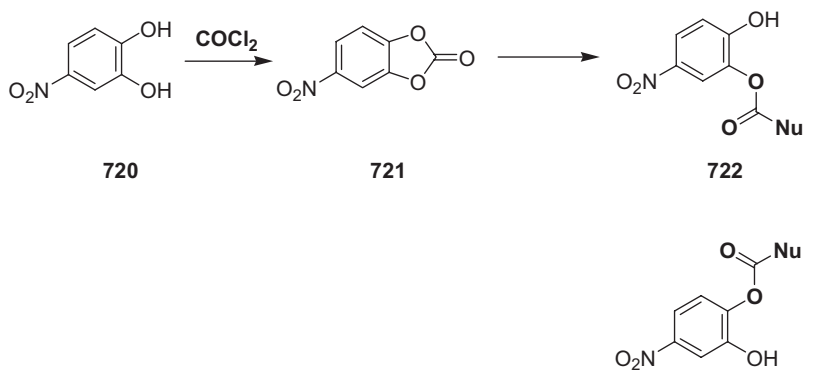
R = alkyl, cycloalkyl, aryl
R' = alkyl, cycloalkyl

The second step is considerably slower than the first and requires a longer reaction time of ca. 4 h. By reacting **717** with an excess of amine (1:2 ratio), symmetrical ureas are formed directly in high yield (50–95%).

General procedure. *4-Nitrophenyl N-alkylcarbamates* [503]: To a stirred solution of **bis(4-nitrophenyl) carbonate 717** (for a preparation of **717**, see Section 4.3.3 "Carbonates") (3.04 g, 10 mmol) in dichloromethane (50 mL), a solution of the amine (10 mmol) in dichloromethane (10 mL) was added dropwise. Following the addition, the mixture was allowed to stand for 2 h. The orange-yellow mixture was then washed with 10% aq. $NaHCO_3$ (4 × 30 mL) and brine (30 mL). The solution was dried with anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crystalline residue was recrystallized from *i*PrOH, MeOH, or Et_2O.

o-(4-Nitrophenylene) carbonate, NPC

***o*-(4-Nitrophenylene) carbonate**, **NPC** (5-nitrobenz-1,3-dioxol-2-one) **721**, has been reported as an activated ester of carbonic acid [504]. Addition of one equivalent of aniline in benzene led to a single adduct in 78% yield following overnight stirring at room temperature.



720 **721** **722**

Nu = PhNH, Et_2N, *cyclo*-$C_6H_{11}NH$ **723**

Although infrared and elemental analyses are consistent with two possible structures, product **722** is the more likely alternative because the 4-nitro group would be expected to stabilize a transient negative charge at the 1-phenoxy position more effectively than at the 2-phenoxy position through a *para* resonance interaction. Since harsher conditions are necessary for the preparation of *N,N′*-diphenylurea, a method for the synthesis of asymmetric ureas by the stepwise addition of amines has been suggested [504].

Typical procedure. *N-Phenyl-2-(1-hydroxy-4-nitrophenyl) carbamate* **722** (Nu = PhNH). [504]. [For a synthesis of **NPC 721**, see Section 4.3.3. ''Carbonates'']

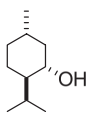
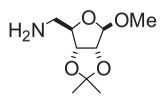
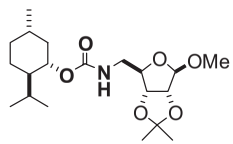
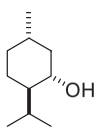
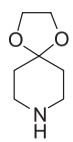
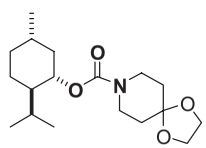
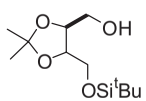
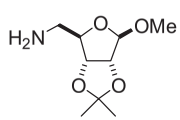
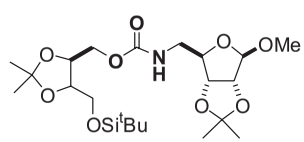
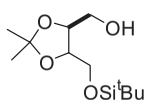
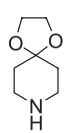
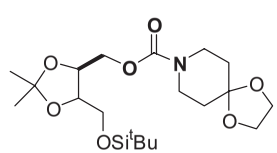
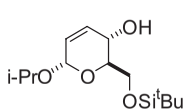
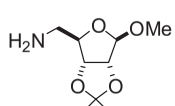
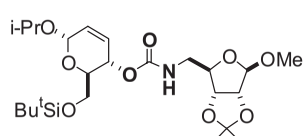
To a solution of **NPC** (0.91 g, 5.0 mmol) in benzene (50 mL), a solution of aniline (0.47 g, 5.0 mmol) in benzene (20 mL) was added dropwise with stirring. After stirring overnight at room temperature, a white precipitate formed, which was collected by filtration and crystallized from benzene to yield 1.07 g (78%) of *N-phenyl-2-(1-hydroxy-4-nitrophenyl) carbamate*.

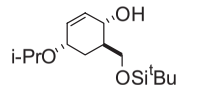
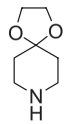
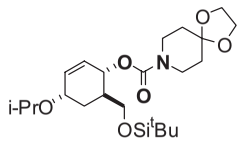
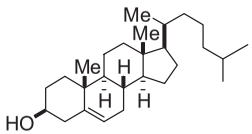
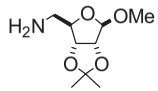
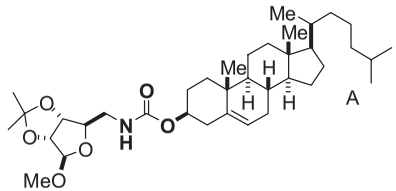
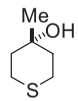
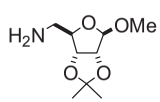
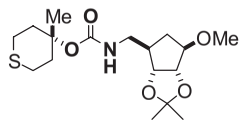
N,N′-Diethyl-2-(1-hydroxy-4-nitrophenyl) carbamate **722** (Nu = Et_2NH). A solution of **NPC** (0.91 g, 5.0 mmol) in chloroform (100 mL) was treated with a solution of diethylamine (0.37 g, 5.0 mmol) in chloroform (25 mL) in a single portion and the reaction mixture was stirred overnight at room temperature. The solvent was then removed in vacuo to yield an oil, which was washed with boiling hexane (2 × 50 mL) leaving a brown residue. This was crystallized from EtOAc/hexane to give yellow needles, which were dried at 80 °C in vacuo to yield 0.78 g (61%) of *N,N′-diethyl-2-(1-hydroxy-4-nitrophenyl) carbamate* **722**.

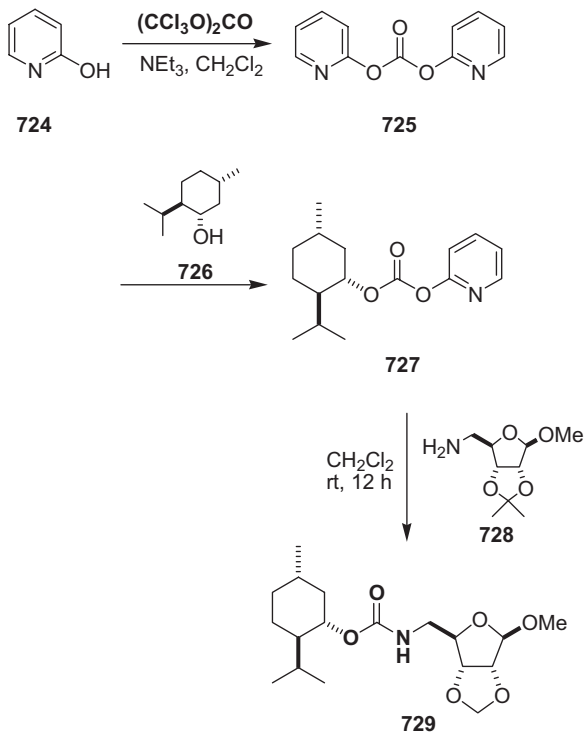
Di(2-pyridyl) carbonate (DPC)

The reaction of **di(2-pyridyl) carbonate** (**DPC**) **725** with a variety of alcohols, including hindered secondary, tertiary, and protected glycols, afforded the corresponding mixed carbonates, which were efficiently transformed into various carbamates in high yield under mild conditions. **DPC** is quite stable and can be stored at room temperature for several months without any noticeable decomposition. This method has allowed the preparation of a variety of functionalized carbamates (Table 4.24), overcoming many of the limitations associated with the alkoxycarbonylation methodologies [505].

Tab. 4.24. Synthesis of carbamates with **DPC** [505].

Entry	*Alcohols*	*Amines*	*Carbamates*	*Method*	*Yields (%)*
1				A	81
2				A	70
3				A	79
4				A	87
5				A	77

6				A	83
7				A	81
8				B	72

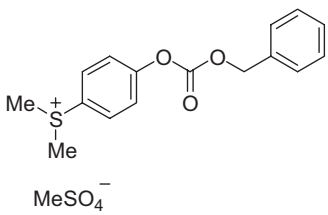


Typical procedure. *Preparation of carbamate* **729** (***Method A***) [505]: To a stirred solution of (+)-menthol **726** (1.0 mmol, 0.16 g) in dichloromethane (5 mL) at 23 °C were added **DPC** (0.32 g, 1.5 mmol) and triethylamine (0.2 mL, 1.5 mmol). The mixture was stirred for 12 h and then diluted with dichloromethane (25 mL). It was washed with saturated aq. $NaHCO_3$ solution (10 mL) and brine (10 mL), and dried over Na_2SO_4. The solvent was evaporated and the residue was used directly for the next reaction. The residue was dissolved in dichloromethane (2 mL) and this solution was added to a stirred solution of amine **728** (0.24 g, 1.2 mmol) in the same solvent (5 mL). The mixture was stirred for 12 h and then diluted with more dichloromethane (20 mL). The resulting mixture was washed with 10% aqueous citric acid (10 mL) and saturated aq. $NaHCO_3$ (10 mL), and dried over Na_2SO_4. Removal of the solvent, followed by chromatography on silica gel (EtOAc/hexanes, 1:3) afforded carbamate **729** (0.28 g, 81%) as a white solid; mp 68–70 °C.

Preparation of carbamate **729** (***Method B***): To a stirred suspension of KH (0.05 g, prewashed, 1.2 mmol) in THF (2 mL) at 0 °C, a solution of alcohol **726** (0.11 g, 0.83 mmol) in THF (2 mL) was added dropwise over a period of 5 min. The mixture was stirred (while warming from 0 °C to 23 °C) for 1 h, and then **DPC** (0.27 g, 1.2 mmol) was added. The resulting mixture was stirred for 4 h and then the reaction was cautiously quenched with saturated NH_4Cl solution. The solvent was

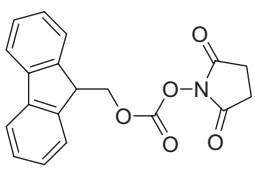
removed under reduced pressure, and the residue was diluted with saturated aq. $NaHCO_3$ solution (5 mL) and extracted with EtOAc (2 × 10 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The residue was then redissolved in dichloromethane (2 mL) and this solution was added to a stirred solution of amine **728** (0.14 g, 1.0 mmol) in dichloromethane (3 mL). After stirring for 12 h (23 °C), the reaction mixture was worked-up and purified according to above procedure to afford **729** (0.17 g, 68%) as a white solid; mp 76–78 °C.

A water-soluble *benzyloxycarbonylation reagent*, **dimethylsulfoxonium salt 730**, has been proposed [506], although this has not found widespread use.



730

9-Fluorenylmethyl *N*-succinimidyl carbonate (**Fmoc-ONSu**) **731** is particularly recommended for the preparation of *Fmoc* derivatives of amino acids, since it avoids the problems arising from the formation of mixed anhydrides [155].



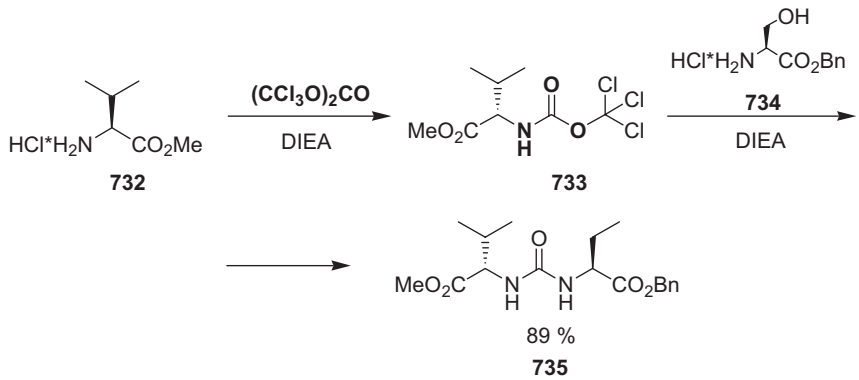
731

Bis(trichloromethyl)carbonate (Triphosgene)

Bis(trichloromethyl)carbonate (**Triphosgene**) [53] is successfully utilized in the sequential synthesis of carbamates and unsymmetrical ureas also bearing chiral amino acid derivatives, without having to purify the intermediates [507].

Thus, in a model reaction, valine methyl ester hydrochloride **732** was reacted with triphosgene in the presence of diisopropylethylamine (DIEA) in dichloromethane at room temperature for 30 min to give the intermediate **733**. Serine benzyl ester hydrochloride **734** and DIEA in dichloromethane were then added over a period of 10 min. Product **735** was obtained in 89% yield as a result of a typical sequential, three-component reaction. The reaction can be successfully applied to various other amines bearing multiple functionalities, and exhibits high selectivity for *N*-nucleophiles; amines (primary and/or secondary) bearing an unprotected primary or secondary hydroxy group can be used directly (85–88% yield).

Methyl, benzyl, and even acid-sensitive *tert*-butyl esters are unaffected. The less sensitive amino component is always chosen for the first step of the synthesis. Products resulting from racemization at the α-center are not detected.

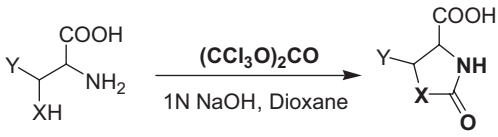


Typical procedure. *Unsymmetrical urea* **735** [507]: **Triphosgene** (110 mg, 0.37 mmol) was dissolved in dichloromethane (2 mL). A mixture of valine methyl ester hydrochloride **732** (167.5 mg, 1 mmol) and diisopropylethylamine (DIEA, 378 μL, 2.2 mmol) in dichloromethane (3.5 mL) was slowly added to the stirred solution of **triphosgene** over a period of 30 min using a syringe pump. After stirring for a further 5 min, a solution of serine benzyl ester hydrochloride **734** (231.5 mg, 1 mmol) and DIEA (378 μL, 2.2 mmol) in dichloromethane (2 mL) was added in a single portion. The reaction mixture was stirred for 10 min at room temperature, concentrated to dryness, and the residue was taken up in ethyl acetate. This solution was washed with 10% aqueous $KHSO_4$, 5% aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated to give pure unsymmetrical urea **735** (314 mg, 89%), which was crystallized from petroleum ether/ethyl acetate.

An important application of the above strategy is illustrated by the use of *O*-trimethylsilyl-protected amino acid hydrogen chlorides to produce half-acid/half-ester urea dipeptides in 45–49% yield [322], which represent starting materials for a variety of pharmacologically active compounds. Addition of the selected *O*-trimethylsilyl-protected amino acid hydrogen chloride to a solution of **triphosgene** in chloroform in the presence of DIEA results in the formation of the *isocyanate intermediate*, which is converted *in situ* to the urea dipeptide upon reaction of a second amino acid methyl ester in methanol.

Since optically active 2-oxazolidinones and 2-thiazolidinones are versatile compounds as chiral auxiliaries [509, 510], much work has been done to find a simple one-step synthesis of oxazolidin-2-one and thiazolidin-2-one derivatives of L-serine, L-threonine, and L-cysteine. In this context, their reaction with **triphosgene** at room temperature has been reported [511, 512].

The procedure has the advantage of avoiding **phosgene** [513–517] as a reagent, and is preferable to that using **CDI** [518, 519], which only gives satisfactory yields with cysteine.



736 **737**

Y = H, Me
X = O, S

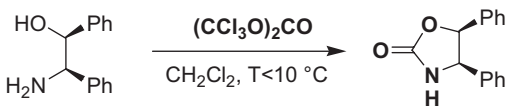
a Y = H, X = O
b Y = Me, X = O
c Y = H, X = S

General procedure. *4-Carboxyoxazolidin-2-ones and 4-carboxythiazolidin-2-one* **737** [511]: To a 1 N solution of NaOH (15 mL, 15 mmol) was added L-serine, L-threonine, or L-cysteine (5 mmol), followed by a solution of **triphosgene** (1.5 g, 5 mmol) in dioxane (10 mL). The reaction mixture was stirred at room temperature until a clear solution was obtained and then stirred for a further 1–2 h. The solvent was then evaporated and the solid residue was extracted with hot acetonitrile (10–15 mL). The extract was filtered, and the filtrate was concentrated to leave an amorphous solid, which was crystallized from acetone or acetone/diethyl ether as a cyclohexylamine salt (starting from L-threonine, a yield of 72% was reported).

L-2-Oxothiazolidine-4-carboxylate is a non-toxic precursor of cysteine proposed as a prodrug capable of penetrating into living cells. Therefore, its oral or parenteral administering to humans provides a method of restoring the glutathione level of numerous tissues in which 5-oxoprolinase is present, especially in the liver [520]. In HIV-seropositive patients, it was shown to increase the levels of glutathione, the lack of which is suspected to be a factor in their immunodeficiency [521].

The reaction of vicinal amino alcohols with **triphosgene**, in dichloromethane or tetrahydrofuran in the presence of triethylamine or Hunig's base at ambient temperature, has been reported elsewere [522–528].

A mild procedure for the synthesis of (4*R*,5*S*)-4,5-diphenyl-2-oxazolidinone **739** has been described [529]. Compound **739** has been used for the synthesis of optically active amines [530] because of its high stereoselectivity and easy deprotection by hydrogenolysis after the reaction. The procedure can also be used to prepare 2-oxazolidinones from various 2-amino-ethanol derivatives.



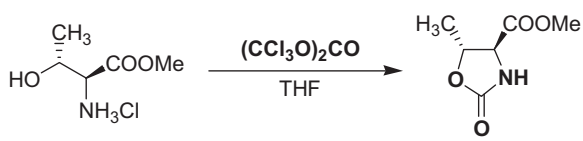
738 **739**

Typical procedure. *(4R,5S)-4,5-Diphenyl-2-oxazolidinone 739* [529]: A 1-L three-necked, round-bottomed flask, equipped with a magnetic stirrer, a thermometer, a reflux condenser, and a dropping funnel, was charged with (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (20.0 g, 94 mmol) and dichloromethane (140 mL), and cooled in an ice/water bath. After the addition of triethylamine (28.4 mL, 204 mmol), a

solution of **triphosgene** (9.8 g, 33 mmol) in dichloromethane (20 mL) was added dropwise over a period of 1 h, keeping the temperature below 10 °C (this is an extremely exothermic reaction). After completion of the addition, the mixture was stirred for 2 h at the same temperature. Water (40 mL) and methanol (20 mL) were added to the resulting suspension, and the mixture was stirred for 30 min. It was then concentrated under reduced pressure in a rotary evaporator. Water (100 mL) was poured onto the residue and the resulting suspension was stirred vigorously for several minutes. The precipitate obtained was collected by filtration, and washed with 1 M hydrochloric acid (10 mL) and water (50 mL) to give *(4R,5S)-4,5-diphenyl-2-oxazolidinone* as colorless crystals. The combined organic phases were washed with brine, and then concentrated under reduced pressure. A small amount of water was added to the residue, and the precipitate was collected by filtration and washed with a small amount of water to obtain additional *(4R,5S)-4,5-diphenyl-2-oxazolidinone* as colorless crystals. The two batches of crystals were air-dried, and then completely dried in a desiccator over phosphorus pentoxide under reduced pressure for 24 h. A total of 22.3 g of *(4R,5S)-4,5-diphenyl-2-oxazolidinone* **739** was obtained (yield 99.2%).

Lower-yielding and more complicated methods for the synthesis of the above compound have been reported [531–533].

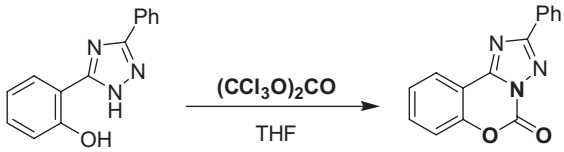
Methyl (*4S*)-2-oxazolidine-4-carboxylate **741**, which is used as a ligand for a dirhodium(II) catalyst employed in metal carbene transformations, was prepared from L-threonine and **triphosgene** [534].



740 **741**

Typical procedure. *Methyl (4S)-2-oxazolidine-4-carboxylate* **741** [534]: To a suspension of L-serine methyl ester hydrochloride (1.56 g, 10.0 mmol) in freshly distilled THF (20 mL), a solution of **triphosgene** (1.9 g, 6.4 mmol) in THF (5 mL) was added in small aliquots. The resulting mixture was heated under reflux for 1 h until the hydrochloride salt had completely reacted and the reaction solution was clear. After cooling, the solution was concentrated under reduced pressure to a volume of approximately 3 mL, ethyl acetate (3 mL) was added, and the resulting solution was passed through a short plug of silica. After washing the silica plug with ethyl acetate and removal of the solvent from the combined filtrate and washings, 1.40 g of a pale-yellow oil identified as compound **741** was obtained (96% yield).

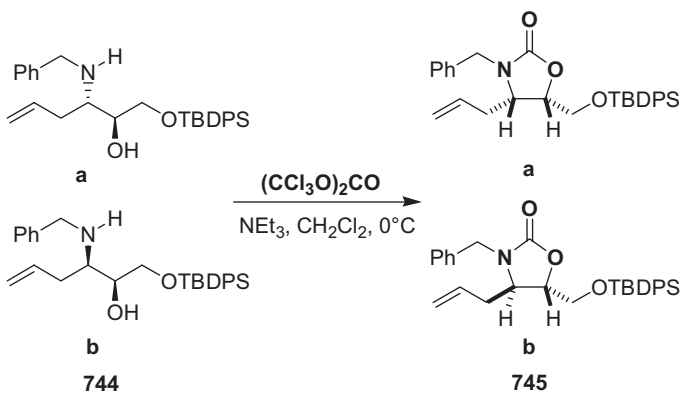
2-Phenyl-1,2,4-triazolo[1,5-*c*][1,3]benzoxazin-5-one **743**, which exhibits benzodiazepine receptor affinity, has been prepared by cyclizing the 3-phenyl-5-(2-hydroxyphenyl)-1,2,4-triazole **742** [535].



742 **743**

Typical procedure. *2-Phenyl-1,2,4-triazolo[1,5-c][1,3]benzoxazin-5-one* **743** [535]: Triethylamine (0.42 mL) and **triphosgene** (0.15 g) were added to a solution of 3-phenyl-5-(2-hydroxyphenyl)-1,2,4-triazole (1.26 mmol) in anhydrous tetrahydrofuran (10 mL). The mixture was stirred at room temperature for 9 days. On the third and sixth days further triethylamine (0.42 mL) and triphosgene (0.15 g) were added. The mixture was eventually diluted with water and the resulting solid was collected and washed with water. Yield 93%.

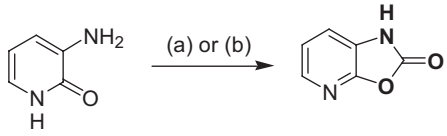
The relative *syn*/*anti* stereochemistry of amino alcohols **744a**,**b** has been assigned by analysis of the $J_{4,5}$ coupling constants of the oxazolidin-2-ones prepared with **triphosgene**, thereby allowing the configuration of the nitrogen-substituted stereogenic center to be unambiguously established [536].



744 **745**

TBDPS = $tBuPh_2Si$-

The preparation of oxazolo[5,4-*b*]pyridin-2(1*H*)-one **747** from the readily available 3-amino-2-pyridone **746** with **triphosgene** or **CDI** at −78 °C has been reported [537].

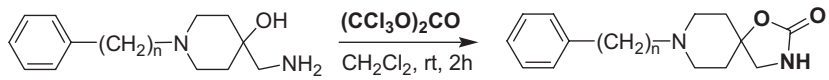


746 **747**

(a) **$(CCl_3O)_2CO$**, CH_2Cl_2/THF (1:1 v/v), 6 h, Et_3N, 78 % or DBU

(b) **CDI**, CH_2Cl_2/THF (1:1 v/v), 6 h, DBU, 50 %

The synthesis of 1-oxa-3,8-diazospiro[4,5]decan-2-ones **749** from 4-pyridones by addition of trimethylsilyl cyanide, reduction with LAH, and cyclization of the thus obtained amino alcohol with **triphosgene** has been reported [538]. 1-Oxa-3,8-diazospiro[4,5]decan-2-ones are structurally related to the antihypertensive agent *Indoramine*, a known postsynaptic α_1 adrenoceptor blocker.

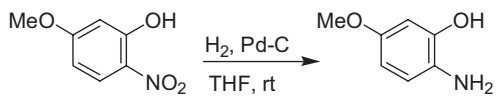


748 **749**

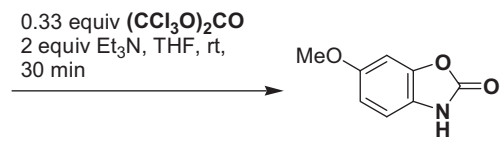
n = 1 yield 72 %
n = 2

Typical procedure. *8-Benzyl-1-oxa-2-oxo-3,8-diazospiro[4,5]decane* **749** ($n = 1$) [538]: **Triphosgene** (0.12 g, 4.0 mmol) in dry dichloromethane (10 mL) was added dropwise to a stirred solution of amino alcohol **748** ($n = 1$) (0.99 g, 4.1 mmol) in dichloromethane (25 mL) at room temperature over a period of 2 h. The reaction was then quenched by the addition of 1% aq. NaOH (20 mL), and the organic layer was washed with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave **749** as a solid (0.801 g, 72%).

6-Methoxybenzoxazolin-2(3*H*)-one **752** (*MBOA*; 6-methoxy-2-oxo-2,3-dihydrobenzoxazole) has been found in extracts of plant tissues from gramineous plants such as *Coix lachryma-jobi*, wheat, and maize, and is implicated as a chemical resistance factor against fungi and insects. Because MBOA is only available in rather small amounts by plant extraction, several methods have been developed for its chemical synthesis. The most representative synthetic route involves the insertion of a C=O unit between the amino and hydroxy groups of 2-amino-5-methoxyphenol **751**, a very easily oxidizable substance.



750 **751**



75 %
752

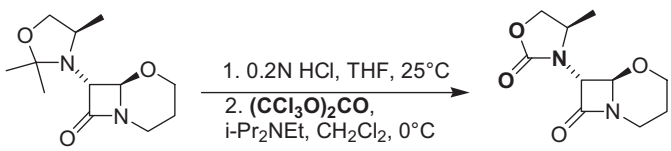
Compounds used for delivering the C=O unit have included **phosgene** (only 15% yield) [539], **ethyl chloroformate** [540, 541], **urea** at elevated temperatures [542–

545], **potassium cyanate** (only 5% yield) [546], **CDI** [547], the use of which results in the formation of an undesired by-product [548], and **triphosgene** [549].

The employment of **triphosgene** has the particular advantage that it can be directly applied to deoxygenated THF solutions of 2-amino-5-methoxyphenol **751** derived from the reduction of the corresponding nitro derivative **750** [549].

Typical procedure. *6-Methoxy-2-oxo-2,3-dihydrobenzoxazole* (*MBOA*) [549]: A solution of 5-methoxy-2-nitrophenol **750** (3.38 g, 20 mmol) in absolute THF (80 mL) containing 10% Pd/C catalyst (100 mg) was hydrogenated at ambient temperature and pressure until the calculated amount of H_2 (1344 cm^3) had been taken up. The resultant colorless solution was treated, with stirring and external cooling under N_2 atmosphere, with triethylamine (4.04 g, 40 mmol) in a single portion, followed rapidly by a solution of **triphosgene** (2.0 g, 6.7 mmol) in THF (20 mL). After 30 min, $Et_3N{\cdot}HCl$ and the catalyst were removed by suction, and THF was completely removed from the filtrate under reduced pressure. The pale-brown crystalline residue was redissolved in boiling benzene (200 mL) and the solution was filtered while hot through a filter pad of 4 cm silica gel (0.063–0.200 mm). The filter pad was then washed with hot benzene (150 mL). Cooling of the filtrate afforded the product *6-methoxy-2-oxo-2,3-dihydrobenzoxazole* **752** as colorless needles, which were isolated by suction filtration; yield 2.5 g (75%).

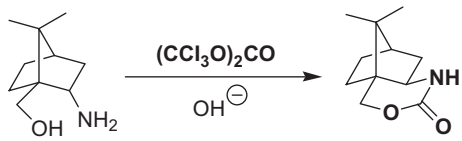
An interesting transformation of the *β*-lactam acetonide **753** into the oxazolidinone **754** has been accomplished by simple hydrolysis followed by recyclization with **triphosgene** [550].



753 **754** 91 %

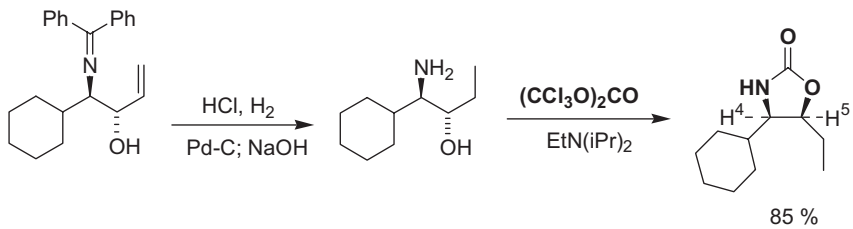
Typical procedure. *(6R,7R)/(6S,7S)-7-[(4R/4S)-2-Oxo-4-phenyl-1,3-oxazolidin-3-yl]-1-aza-5-oxabicyclo[4.2.0]octan-8-one* **754** [550]: A solution of *β*-lactam acetonide **753** (2.30 g, 7.6 mmol) in THF/0.2 N HCl (1:1; 120 mL) was stirred at 25 °C for 45 min. After removal of the THF under reduced pressure, the mixture was neutralized with saturated aq. $NaHCO_3$ solution, extracted with dichloromethane (4 × 100 mL), and the combined extracts were dried over $MgSO_4$, filtered, and concentrated to afford 2.07 g of crude product containing the free amino alcohol. The crude product was redissolved in dichloromethane (150 mL) and this solution was cooled to 0 °C. Diisopropylethylamine (3.71 g, 28.7 mmol) was added and, after 5 min at 0 °C, **triphosgene** (1.9 g, 6.4 mmol) was added portionwise with a spatula. After stirring for 45 min at 0 °C, the mixture was filtered through a short pad of silica gel and the filtrate was concentrated. Chromatography (SiO_2, 150 g; eluent CH_2Cl_2/EtOAc, 3:1) afforded *(6R,7R)/(6S,7S)-7-[(4R/4S)-2-oxo-4-phenyl-1,3-oxazolidin-3-yl]-1-aza-5-oxabicyclo[4.2.0]octan-8-one* **754** (2.0 g, 91%).

Triphosgene under basic conditions [551] was used for the synthesis of oxazinone auxiliary **756** starting from the *exo* amino alcohol **755** [552].



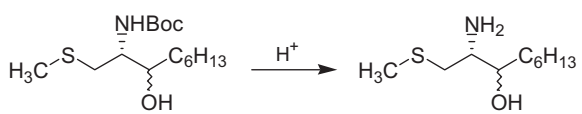
755 **756**

The relative stereochemistry of compound **757** was determined by converting the amino alcohol **758** into the oxazolidinone **759** using **triphosgene** and Hunig's base [553]. The conversion of some vinyl amino alcohols into *cis*-oxazolidinones with the aim of assigning their relative stereochemistry has also been reported [554].

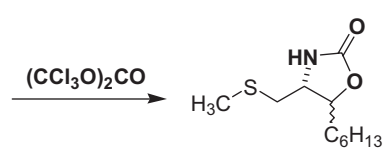


757 **758** **759**

The relative configuration of the diastereomeric alcohols **761** was established after transformation into the corresponding oxazolidines **762**. Generally, the coupling constants of the *cis* isomers (*erythro*) of such 4,5-disubstituted oxazolidinones are greater than those of the *trans* isomer (*threo*). Measured coupling constants $J_{4H,5H}$ showed that **761** exists predominantly as the *erythro* isomer with a coupling constant of 7.4 Hz, whereas the *threo* isomer showed a coupling constant of 5.1 Hz [555].



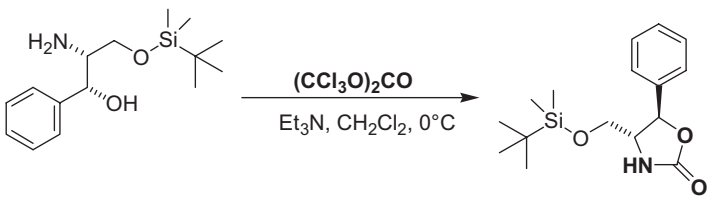
760 **761**



762

Typical procedure. *Oxazolidinone* **762** [555]: The amino alcohol **761** (1 equiv.) was dissolved in dichloromethane (10 mL/mmol) and **triphosgene** (0.3 equiv.) and triethylamine (1 equiv.) were added. After 1 h, the reaction mixture was hydrolyzed with H_2O. The organic layer was separated, washed successively with saturated aq. $NaHCO_3$ solution and saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate, 1:1); *threo* isomer **762**: 54.6 mg (67%) from 85 mg (0.35 mmol) of *threo*-**761** as a pale oil; *erythro* isomer **762**: 124 mg (91%) from 100 mg (0.26 mmol) of *erythro*-**761**.

The synthesis of 4-[(*tert*-butyldimethylsilanyl)oxymethyl]-5-phenyl-oxazolidin-2-one **764** with **CDI** or **triphosgene** in dichloromethane and triethylamine has been described [556].

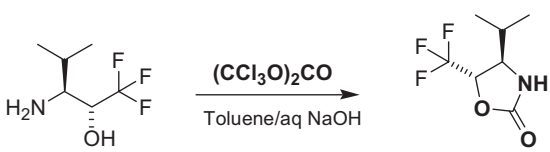


72.8 %

763 **764**

Typical procedure. *(4R,5R)-(+)-4-(tert-Butyldimethylsilyloxymethyl)-5-phenyloxazolidin-2-one* **764** [556]: Amino alcohol **763** (1.92 g, 6.82 mmol) was dissolved in dry dichloromethane (20 mL) under argon and the solution was cooled to 0 °C. Triethylamine (2.87 mL, 20.6 mmol) was then added in one portion at 0 °C. A solution of **triphosgene** (682.5 mg, 2.3 mmol, 0.33 equiv.) in dichloromethane (20 mL) was added dropwise over a period of 60 min. After 4 h, the reaction was complete, and all volatiles were removed in vacuo. The residue was then redissolved in diethyl ether, and this solution was filtered, washed with concentrated $NaHCO_3$ (3×100 mL), and dried over $MgSO_4$. Flash chromatography (hexanes/EtOAc, 3:2; $R_f = 0.57$) yielded 1.52 g (72.8%) of **764** as a waxy solid.

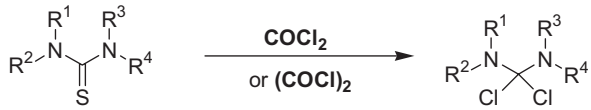
A high yield of 2-oxazolidinone **766** has been obtained from *threo*-(2*R*,*S*,3*S*,*R*)-3-amino-4-methyl-1,1,1-trifluoro-2-pentanol **765** with **triphosgene** in toluene/aq. NaOH [557].



89 %

765 **766**

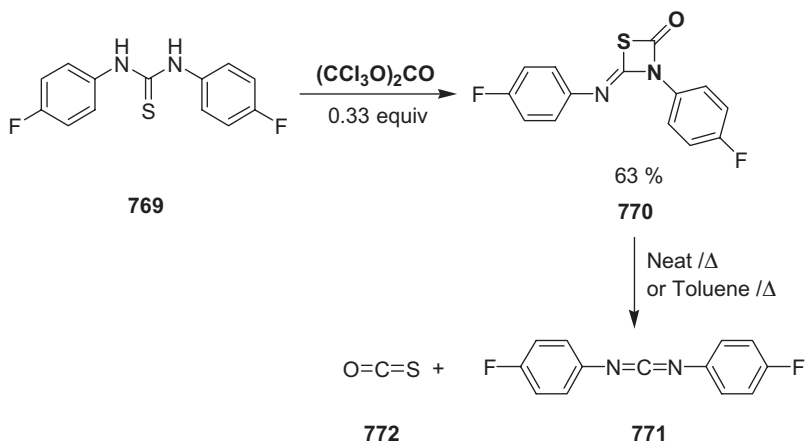
Treatment of thioureas **767** with either **phosgene** or **oxalyl chloride** is known to give amido chlorides **768** in good yields [558].



767 **768**

Attempts to convert *N,N′*-bis(4-fluorophenyl)thiourea into the corresponding amido chloride with **phosgene** [560] were not successful. It has been observed [559] that *N,N′*-diaryl-substituted thioureas, when treated with **phosgene**, give the amido chloride along with some thiazetidinone as a by-product.

Although neither the use of **triphosgene** nor of **oxalyl chloride** afforded the desired amido chlorides, the thiazetidinone has been found [561] to be a highly versatile intermediate allowing the facile conversion of thioureas into either carbodiimides or isoureas in good yields. 3-(4-Fluorophenyl)-1,3-thiazetidin-4-one-2-(4-fluorophenyl)imine **770** was obtained in 63% yield as the main product from the reaction of *N,N′*-bis(4-fluorophenyl)thiourea **769** with one-third of an equivalent of **triphosgene**.

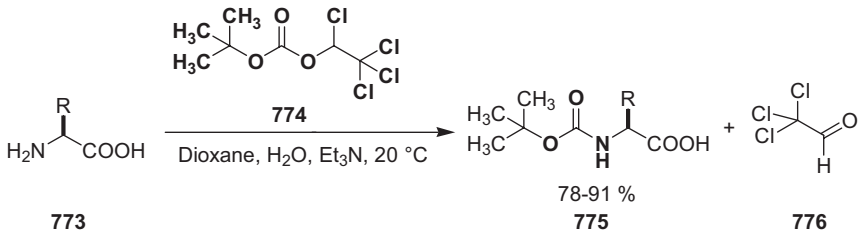


769 **770** **772** **771**

Heating the 3-(4-fluorophenyl)-1,3-thiazetidin-4-one-2-(4-fluorophenyl)imine **770** either neat or in refluxing toluene affords the expected carbodiimide **771** [562] as the sole product (presumably with evolution of O=C=S).

1,2,2,2-Tetrachloroethyl-*tert*-butyl carbonate

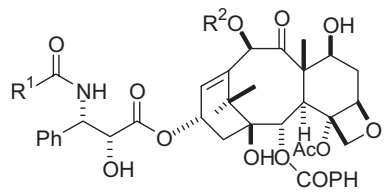
As part of a research program aimed at developing synthetic applications of 1-chloroalkyl chloroformates, *1,2,2,2-tetrachloroethyl-tert-butyl carbonate* (*CN-916*) **774** was introduced as a simple and efficient reagent for the Boc-protection of amino acids, as shown in the scheme below [563–565].



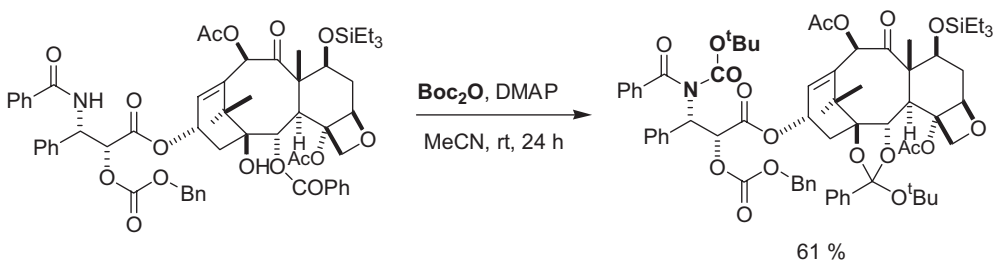
773 **775** **776**

Di-*tert*-butyl dicarbonate (Boc_2O)

Protection of amidic nitrogen with **di-*tert*-butyl dicarbonate** (**Boc_2O**), in acetonitrile at room temperature, as part of an efficient and regioselective method for the *N*-debenzoylation of *Paclitaxel* (*Taxol*®) **777** to 10-acetyldocetaxel and to *Docetaxel* **778**, has been reported [566]. *Paclitaxel*®, and its semisynthetic analogue *Docetaxel* (*Taxotere*®), are among the most important new antitumor agents of last decade.



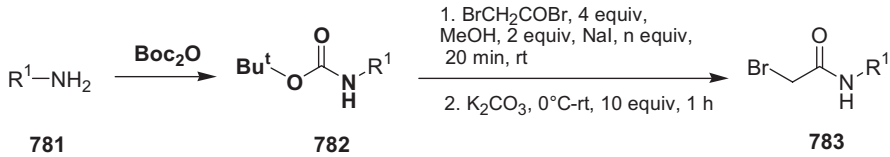
Paclitaxel R^1 = Ph, R^2 = Ac, **777**
Docetaxel R^1 = ^{t}BuO, R^2 = H, **778**



779 **780**

Deprotection and further selective *N*-debenzoylation is accomplished by treatment with magnesium methoxide in methanol [566].

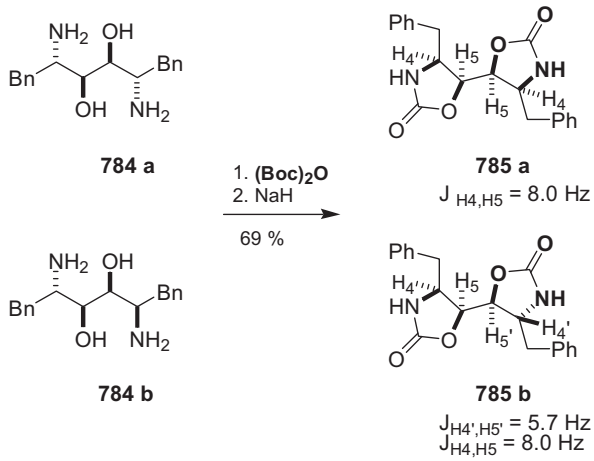
The preparation of *tert*-butyl carbamates **782** with **Boc_2O**, and their one-pot conversion to amides **783** with an acyl halide/methanol mixture, has recently been reported [567].



781 **782** **783**

R^1 = $PhCH_2$ (92 %), *n*-C_8H_{17} (100%), *i*-PrOC(O)CH_2 (100 %)

Bis(oxazolidinone)s **785a**,**b** have been prepared from the corresponding amino alcohols **784a**,**b** with **Boc_2O** [568].



Typical procedure. *(4S,5S,4′S,5′S)-5,5-Bis(4-benzyloxazolidin-2-one* **785a** [568]: To a solution of **784a** (20.0 mg, 0.07 mmol) in dioxane (2.0 mL) was added **Boc_2O** (34.0 mg, 0.15 mmol). The solution was stirred at room temperature for 18 h and then concentrated. The residue was dissolved in THF (2.0 mL) and treated with NaH (60% dispersion in oil, 6.0 mg, 0.15 mmol). The resulting suspension was refluxed for 3 h, treated with MeOH (2 drops), and concentrated. Chromatography of the residue on silica gel eluting with $CHCl_3$/EtOAc (3:2) afforded **785a** (17.0 mg, 69%) as a white solid.

Boc_2O (1.1 equiv.) has been employed to prepare the corresponding 4,5-diphenyloxazolidin-2-one in 80% yield from (1*S*,2*R*)-2-amino-1,2-diphenylethanol in acetonitrile at room temperature [569].

(4*R*)-4-Methyl-5-phenyl-oxazolidin-2-one, a chiral auxiliary for an electrochemical approach to the preparation of α-arylpropionic acids, has been obtained in one step by fusing above the melting point (*R*)-2-phenylglycinol with **urea** [570]. The urea first decomposes to free cyanic acid, which then reacts with the amino group to form a β-hydroxyethylurea derivative. This subsequently cyclizes with loss of ammonia to afford the product [571].

tert-Butoxycarbonylation of amino acids is best accomplished with **Boc_2O** as the reagent. This is for the simple practical reason of stability of the reagent, the use of which in more than one protocol is described in this book. A reagent advocated in earlier times for *tert*-butoxycarbonylation, **$Bu^tO{-}CO{-}N{=}C(CN)Ph$** [573], is rarely used now. Well defined and optimized protocols for the synthesis of *Boc*-amino acids using **Boc_2O** have been published [368]. Some of these are presented below.

Typical procedure. *N-tert-Butoxycarbonyl-L-proline* [574]. *Caution! Carry out all procedures in an efficient fume cupboard, wear latex gloves and chemical-proof safety goggles.* Triethylamine (16.5 mL, 0.12 mmol) was added dropwise over a period of 10 min to a stirred, ice-cold suspension of L-proline (10.0 g, 8.7 mmol) in dichloromethane (200 mL) in a 500-mL three-necked, round-bottomed flask. A solution of **Boc_2O** (28.3 g, 0.13 mmol) in dichloromethane (100 mL) was then added over a period of 10 min and the mixture was stirred for 2.5 h. Thereafter, 10% aqueous citric acid (50 mL) was added, and the dichloromethane layer was washed with saturated brine (2×50 mL) and with water (50 mL). After drying the organic phase over magnesium sulfate, the solvent was evaporated and the residue was taken up in hot ethyl acetate. Dilution of this solution with hexane gave the product, *N-tert-butoxycarbonyl-L-proline* (17.8 g, 95%); mp 138–140 °C; TLC (silica gel): $R_f = 0.36$ (EtOAc/MeOH, 1:1).

Typical procedure. *N-tert-Butoxycarbonyl-L-phenylalanine* [368] (modified from [573]). *Caution! Carry out all procedures in an efficient fume cupboard, wear latex gloves and chemical-proof safety goggles.* Sodium hydroxide (4.4 g, 0.11 mol) was placed in a flask, and dissolved in water (110 mL). Phenylalanine (16.5 g, 0.1 mol) was added, the suspension was stirred until a solution was obtained, and then *tert*-butanol (75 mL) was added. **Boc_2O** (22.3 g, 0.12 mol) was then added with stirring over a period of 1 h, keeping the mixture near 0 °C. A white precipitate was produced, and at the end of the addition the pH had dropped to 7.5–8.5. The mixture was then carefully acidified by the slow, continuous addition of saturated citric acid to give the product *N-tert-butoxycarbonyl-L-phenylalanine* (21.5 g, 81%); mp 85 °C; $[\alpha]^{21}_D = +25.5$ ($c = 1$, ethanol).

Typical procedure. *N-tert-Butoxycarbonyl-L-phenylalanine under non-aqueous conditions* [368]: *Caution! Carry out reaction procedures in an efficient fume cupboard; wear latex gloves and chemical-proof safety goggles.* The amino acid (L-phenylalanine, 0.16 g, 0.1 mmol) is dissolved in a 10% solution of triethylamine (0.10 g, 0.1 mmol) in dimethylformamide (in this case and with tyrosine; a 10% solution in methanol is used with most other amino acids). This solution is vigorously stirred and **Boc_2O** (0.23 g, 0.12 mol) is added. The mixture is kept at 40–50 °C for 5 min (or for 10 min when using dimethylformamide as solvent; glycine in dimethylformamide requires 30 min and glycine in methanol requires heating under reflux for 30 min). It is then diluted with a chilled aq. solution of citric acid [prepared by dissolving citric acid (146 g) in water (100 mL) at 25 °C], and stirred with a glass rod until

there is permanent turbidity. The product is recovered in the form of its triethylammonium salt after extraction and work-up as in the previously described aqueous protocol. *N-tert*-Butoxycarbonyl-L-phenylalanine has mp 85 °C.

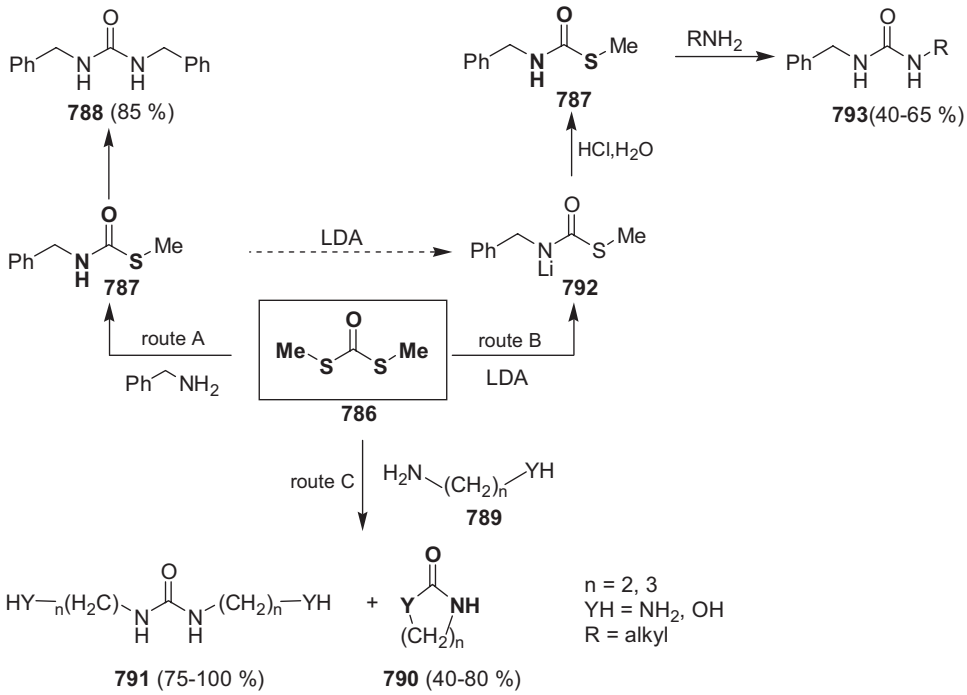
When the *N-tert*-butoxycarbonylation of sterically hindered α-amino acids is carried out under normal conditions, yields of just 40–60% are obtained. The use of excess **Boc_2O** (3–5 equiv.) over 3–4 days gives slightly faster reaction rates, but the competing hydrolysis means that there is no overall benefit in terms of yield. However, the use of tetramethylammonium hydroxide leads to enhanced solubility of the amino acid in dry acetonitrile, and hence *tert*-butoxycarbonylation under these conditions leads to excellent yields of the derivatized products [368].

Typical procedure. *N-tert-Butoxycarbonylation of α,α-disubstituted glycines* [368]. *Caution! Carry out all procedures in an efficient fume cupboard; wear gloves and chemical-proof safety goggles.* The reaction flask is charged with equimolar amounts of the amino acid (α,α-disubstituted glycine, 10 mmol) and solid tetramethylammonium hydroxide pentahydrate (1.81 g, 10 mmol). Dry acetonitrile (freshly distilled from calcium hydride; 5–10 mL $mmol^{-1}$) is added, and the mixture is stirred at room temperature until a solution is obtained (usually within 30 min). **Boc_2O** (0.12 mmol) is then added and the resulting mixture is stirred at room temperature for 2 days. On the third day, a further portion of **Boc_2O** (1.2 g, 0.6 mmol) is added and the mixture is stirred for another day. The acetonitrile is then removed in vacuo, the residue is partitioned between diethyl ether and water, and the aqueous layer is acidified to pH 3–4 with saturated aqueous citric acid [prepared by dissolving citric acid (146 g) in water (100 mL) at 25 °C]. The aqueous layer is washed with a further portion of diethyl ether, separated, and extracted three times with ethyl acetate. The combined organic extracts are washed with water, dried (magnesium sulfate), and concentrated. Pure material is usually obtained; when necessary, the product can be recrystallized from diethyl ether.

S,S-Dimethyldithiocarbonate (DMDTC)

***S,S*-Dimethyldithiocarbonate** (**DMDTC**) **786** represents a mild and safely handled reagent structurally similar to **phosgene**, which is useful in the synthesis of ureas. **DMDTC** can be prepared from methanol, carbon disulfide, and dimethyl sulfate by a two-step sequence [575, 576]. Although dimethyl sulfate is a suspected human carcinogen, it is relatively non-volatile and with due care can be handled safely in the laboratory.

In a representative example, **DMDTC 786** is allowed to react with 2 equivalents of benzylamine **787** at 60 °C for 24 h in methanol or ethanol to give the symmetrical dibenzylurea **788** in 85% yield (route A) [577]. Aliphatic amines **789** bearing a hydroxy or an amino substituent at the β- or γ-position react with **786** in dilute solution to predominantly afford cyclic ureas or *carbamates* **790** (40–80% yield) (route C). By increasing the concentration of the starting reagent **789** with respect to **DMDTC**, the symmetrical ureas **791** are obtained in high yield (75–100%) without any need for protection and deprotection procedures.

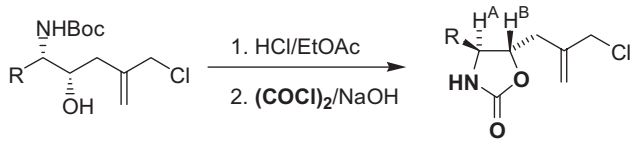


By carrying out the reaction under basic conditions (LDA), the intermediate **787** is deprotonated immediately after its formation, giving the corresponding lithium salt **792** in quantitative yield. The latter is relatively stable toward nucleophilic substitution at ambient temperature and will not react further to give dibenzylurea (route B). Unfortunately, this method cannot be employed with amino acids due to the requirement for LDA, which would racemize any stereogenic center.

Typical procedure. *S-Methyl N-alkylthiocarbamates*. *S-Methyl N-benzylthiocarbamate* **787** [577]: To a solution of benzylamine (0.93 g, 0.87 mmol) and diisopropylamine (0.89 g, 8.8 mmol) in THF (20 mL) at −78 °C under nitrogen was added a solution of *n*-BuLi (1.6 M, 10.9 mL, 17.5 mmol) in hexane. Following the addition, the solution was stirred at −78 °C for 0.5 h, and then a solution of **DMDTC** (1.07 g, 8.8 mmol) was added. The resulting mixture was allowed to react at room temperature for 20 h. Thereafter, the reaction was quenched by pouring the mixture into ice/dilute aq. HCl. The crude solid obtained was dissolved in EtOAc, and this solution was washed with aqueous Na_2CO_3 solution and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was recrystallized from hexane to provide *S-methyl N-benzylthiocarbamate* **787** as colorless crystals (0.95 g, 62%).

Oxalyl chloride

The stereochemistry of products **794** was found to be (*S*,*S*), and was confirmed by the chemical correlation described in the following scheme [578].



794

a R = $PhCH_2$
b R = CH_3
c R = $iPrCH_2$
d R = $C_2H_5(CH_3)CH$

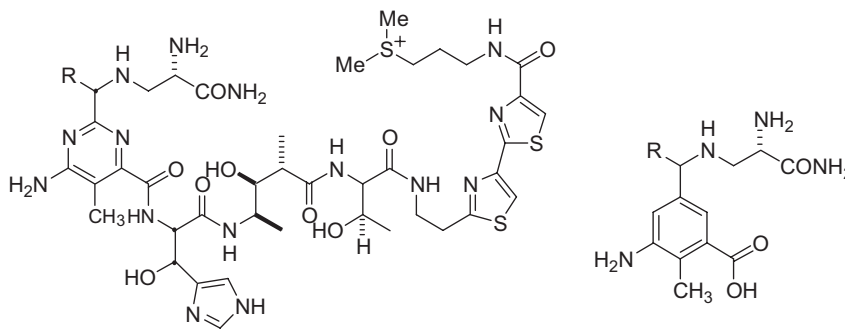
795

a J_{AB} = 4.5 Hz
b J_{AB} = 4.2 Hz
c J_{AB} = 5.0 Hz
d J_{AB} = 4.8 Hz

The assignment of the stereochemistry of products **795** was based on the well-established values of the coupling constants for *trans*-oxazolidinones [579–581].

4.3.2.5 Enol Carbamates

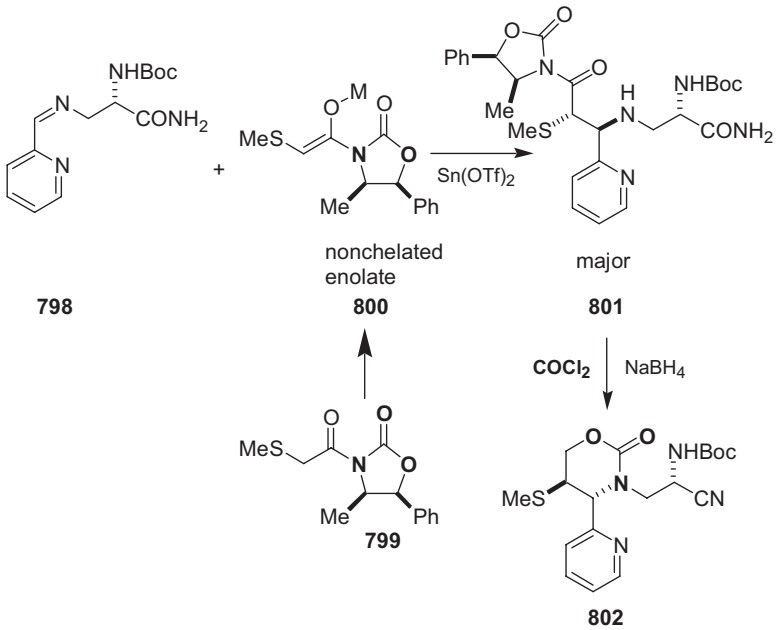
A study of the diastereoselective addition of the tin(II) (*Z*)-enolates of optically active *N*-acyloxazolidinones **799** with a prototype imine **798** led to an approach for the stereocontrolled introduction of the C2-acetamido side chain of the pyrimidoblamic subunit **797** of bleomycin A_2 **796** [582].



796
Bleomycin A_2
R = CH_2CONH_2
R = H

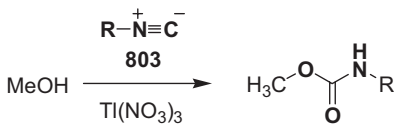
797
Pyrimidoblamic acid
R = CH_2CONH_2
R = H

The tentative relative and absolute stereochemistry of the imine addition products **801**, as well as their conversion to the cyclic carbamate **802** by reduction with $NaBH_4$ and cyclic carbonylation with **phosgene**, has been reported [582].



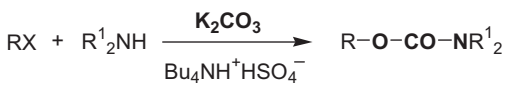
4.3.2.6 Carbamates from Isocyanides

An interesting general synthesis of carbamates is the direct reaction of **isocyanides** with alcohols in the presence of thallium(III) nitrate, which offers advantages over the preliminary oxidation of the isocyanide to an isocyanate prior to reaction with the alcohol [583].



4.3.2.7 Potassium Carbonate as a Carbonylating Reagent

Alkyl halides can be converted to carbamates by treatment with a secondary amine and K_2CO_3 under phase-transfer conditions [584, 585].

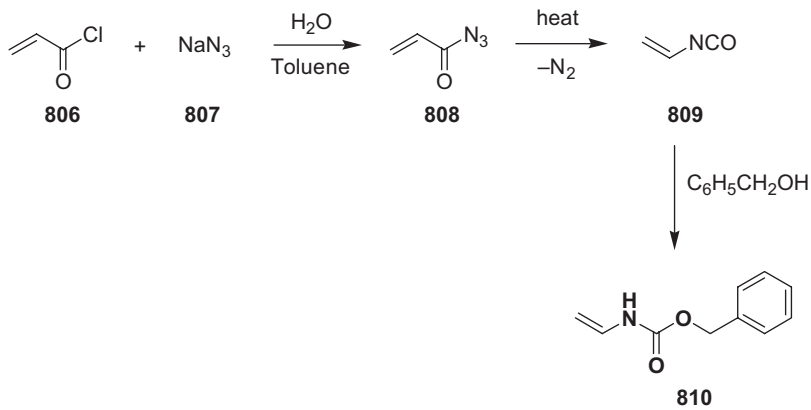


When alkyl halides are treated with cyanate ion, the corresponding acyl isocyanates are formed [586]; for alternative procedures, see Section 4.3.1. If the reaction is

carried out in the presence of ethanol, carbamates can be prepared directly [587, 588].

4.3.2.8 Carbamates Prepared with Acryloyl Azide

An improved method that can be easily scaled-up has been developed for the preparation of benzyl-*N*-vinyl carbamate **810** (Z-vinylamine), a valuable synthetic intermediate in the synthesis of *β-lactam antibiotics* [589]. In this method, vinyl isocyanate **809**, formed by the Curtius rearrangement of **acryloyl azide 808**, is co-distilled with a solvent such as toluene into benzyl alcohol containing a catalyst and an inhibitor. The product thus obtained can be purified by crystallization, thereby avoiding purification by high-vacuum distillation or chromatography. Potential safety issues associated with the process are important [590, 591].



The thermal stability of **acryloyl azide** has been studied in some detail. Solutions of this compound in toluene appear to be stable at sub-ambient temperatures. However, it can undergo polymerization when stored for long periods, and the crystals formed can undergo rapid decomposition when dry. Care should be exercised to avoid this polymerization by storing the solutions below 5 °C. It is strongly recommended that solutions of **acryloyl azide** be used soon after their preparation.

Typical Procedure. *Benzyl N-vinyl carbamate* **810** [590]. *Note! Some of the chemicals described below can undergo rapid decomposition and polymerization, with evolution of gaseous products.* ***Acryloyl azide*** *in neat form may be dangerously explosive, and vinyl isocyanate is probably very toxic. All experiments should be carried out behind a safety shield in a well-ventilated hood. Extreme care should be taken to avoid injury.*

Acryloyl azide **808**: A 1 l reactor was charged with 68.4 g (1.05 mol) of sodium azide, 200 ml of water, 200 ml of toluene, and 0.09 g of Adogen 464 (methyltrialkylammonium chloride). The mixture was cooled with stirring in ice-water bath, and 90 g (1 mol) of acryloyl chloride was added dropwise over a period of 1.5 h at 0–5 °C. After the addition, the mixture was stirred for 45 min. The organic phase was separated and stored at 0–5 °C.

Benzyl N-vinyl carbamate **810**: A 1-L flask was equipped with a variable speed pump, a mechanical stirrer, a temperature controller, a 4″ (10 cm) column packed with ceramic saddles, a distillation head, a spiral condenser (cooled with water at 10–15 °C), and a receiver. The flask was charged with toluene (150–200 mL) and phenothiazine (0.5 g) and the solution was heated to 105–110 °C. The receiver was charged with benzyl alcohol (86 g, 0.8 mol), phenothiazine (0.05 g), and triethylamine (0.1–0.3 g). This mixture was cooled in ice and stirred. A solution of **acryloyl azide** (1 mol), prepared as described above, was pumped into the distillation flask over a period of 4–5 h, maintaining the pot temperature at 105–110 °C with a heating mantle. The vapor temperature varied, depending on the rate of addition of the azide, but was in the range 80–100 °C. The distillate was passed directly into the benzyl alcohol mixture. After the addition of **acryloyl azide**, the distillation continued, generating a further 10–20 mL of toluene. The receiver was then removed from the distillation set-up, and its contents were stirred at 0–5 °C for 1–2 h. The product mixture was then allowed to gradually warm to room temperature and was stirred until HPLC analysis indicated complete reaction. The mixture was then concentrated in vacuo to a weight of 200–250 g. The residue was treated with heptane (300–350 mL) and cooled to 15 °C with stirring. A few seed crystals of *benzyl N-vinyl carbamate* **810** were added, and the mixture was stirred for 2–3 h. The product was collected by filtration, washed with heptane, and dried in vacuo. Yield 115–128 g (65–72%); mp 41–44 °C.

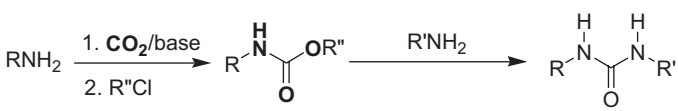
4.3.2.9 **Carbon Monoxide**

Carbamates can be obtained from primary or secondary amines by treating these with **CO**, $\mathbf{O_2}$, and an alcohol in the presence of a catalyst [592, 593]. Carbamates can also be obtained from nitroso compounds by treatment with **CO**, ROH, $Pd(OAc)_2$, and $Cu(OAc)_2$ [594] and from nitro compounds [595, 596].

4.3.2.10 **Carbon Dioxide**

Carbon dioxide reacts with aromatic amines and iodoethane, under electrolysis conditions, to give the corresponding carbamate [597].

More conveniently, carbamate **811** can be synthesized by reaction of amines with **carbon dioxide** ($\mathbf{CO_2}$) and alkyl halides in the presence of bases [286].



811 **812**

The use of sterically hindered guanidine bases gives the best results (80–99% yields with virtually 100% selectivity). Amino acids and diamines are efficiently converted into the corresponding carbamates, which can be utilized as intermediates en route to ureas. However, the need for stoichiometric amounts of base represents a serious limitation to the large-scale application of the process. A fur-

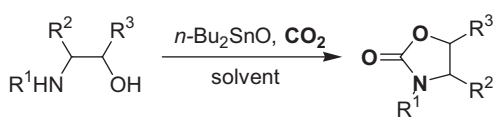
ther drawback of this methodology is that alkylation of the amine affords unwanted by-products. This side reaction can be avoided by performing the alkylation on alkylammonium *N*-alkylcarbamates; these are easily obtained from primary amines and **CO_2** in the presence of 18-crown-6, which can be quantitatively recovered at the end of the reaction [598].

An advantage that increases the industrial interest in this methodology is the possibility of reducing the production of chloride wastes. In fact, alkylating agents other than alkyl chlorides can also be employed. The entire process occurs with yields close to 100% [599].

CO_2 has been used as a cyclocarbamating agent in a limited number of cases, described only in patents. The reaction of 2-(methylamino)ethanol with **CO_2** gave solely 1,4-dimethylpiperazine in aqueous solution without any catalyst [600], while 1-methylamino-2-propanol reacted with **CO_2** to give 3,5-dimethyl-2-oxazolidinone in 58% yield under similar conditions [601].

It has been reported, on the other hand, that by using triphenylstibine oxide as catalyst, even 2-(methylamino)ethanol reacted with **CO_2** to give 3-methyl-2-oxazolidinone in 48% yield [602]. Unfortunately, this catalyst failed to promote the reaction of 2-aminoethanols lacking an *N*-substituent, giving only small amounts of 2-oxazolidinones. The addition of some dehydrating reagents, such as phosphorus compounds [603] or carbodiimides [604], was found to promote the reaction, although this strategy inevitably led to increased costs and by-product formation. This was also the case in relation to the utilization of aziridines, the dehydrated form of 1,2-amino alcohols, in their cycloaddition reactions with **CO_2** to form 2-oxazolidinones [605].

It has been found that NMP is an excellent solvent and that *n*-Bu_2SnO can be used as a catalyst for the dehydrative condensation of 1,2-aminoethanols **813** with **CO_2** to give 2-oxazolidinones **814** [606].

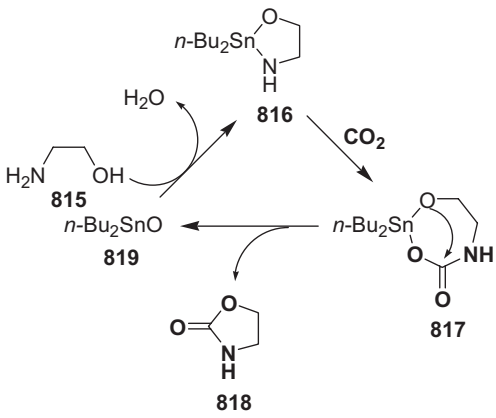


813 **814**

R^1 = Me, R^2 = R^3 = H, NMP, 94%
R^1 = Et, R^2 = R^3 = H, NMP, 76%
R^1 = R^2 = R^3 = H, NMP, 53%
R^1 = R^2 = H, R^3 = Me, NMP, 73%
R^1 = H, R^2 = R^3 = Me, NMP, 85%

It may be noteworthy that this catalyst is commercially available in the form of a powder, and is easy to handle because of its stability in air.

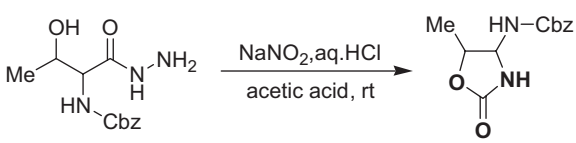
A proposed reaction mechanism involves **CO_2** insertion to form a cyclic tin carbamate **817**, and subsequent intramolecular nucleophilic attack of an alkoxy group on a carbonyl carbon atom leading to elimination of 2-oxazolidinone **818** and regeneration of the starting tin oxide **819**.



Typical procedure. *Synthesis of oxazolidinone* **818** [606]: The 1,2-amino alcohol (10.0 mmol), solvent (8.0 mL), and *n*-Bu_2SnO (1.0 mmol) were placed in a 50 mL autoclave. **CO_2** was then introduced at an initial pressure of 5 MPa, and the autoclave was heated at 180 °C for 16 h. The reaction solution obtained was then analyzed by GLC. The products were isolated by fractional distillation of the reaction solution under reduced pressure. When necessary, i.e. for characterization, they could be further purified by preparative GLC. The products were identified by comparing their FT-IR-, mass-, and ^{1}H NMR spectra with those of corresponding authentic samples.

4.3.2.11 **Sodium Nitrite/HCl**

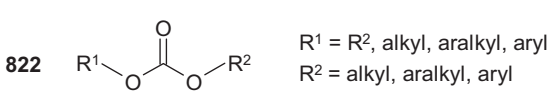
4-Amino-2-oxazolidinones **821** have been prepared by treating **Cbz**-protected amino acid *hydrazides* **820** with sodium nitrite/HCl in glacial acetic acid [607].

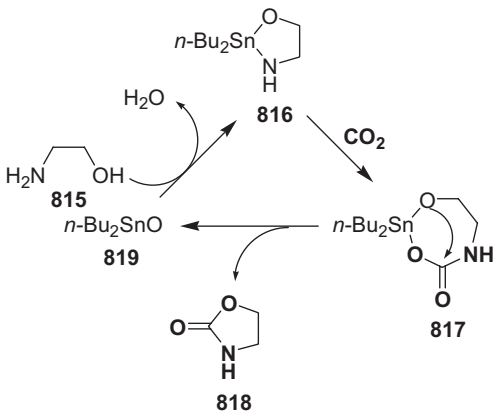


820 **821**

4.3.3 **Carbonates**

Two types of carbonates **822** can be produced in carbonylation reactions of alcohols with **phosgene** or *phosgene equivalents or substitutes*, namely *symmetrical* ($R^1 = R^2$) and *asymmetrical* ($R^1 \neq R^2$).

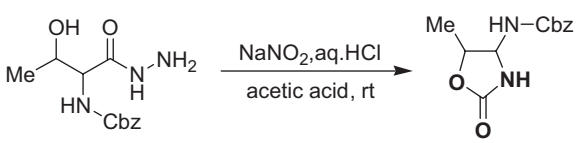




Typical procedure. *Synthesis of oxazolidinone* **818** [606]: The 1,2-amino alcohol (10.0 mmol), solvent (8.0 mL), and *n*-Bu_2SnO (1.0 mmol) were placed in a 50 mL autoclave. **CO_2** was then introduced at an initial pressure of 5 MPa, and the autoclave was heated at 180 °C for 16 h. The reaction solution obtained was then analyzed by GLC. The products were isolated by fractional distillation of the reaction solution under reduced pressure. When necessary, i.e. for characterization, they could be further purified by preparative GLC. The products were identified by comparing their FT-IR-, mass-, and ^{1}H NMR spectra with those of corresponding authentic samples.

4.3.2.11 **Sodium Nitrite/HCl**

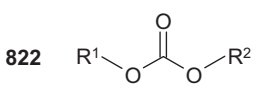
4-Amino-2-oxazolidinones **821** have been prepared by treating **Cbz**-protected amino acid *hydrazides* **820** with sodium nitrite/HCl in glacial acetic acid [607].



820 **821**

4.3.3 **Carbonates**

Two types of carbonates **822** can be produced in carbonylation reactions of alcohols with **phosgene** or *phosgene equivalents or substitutes*, namely *symmetrical* ($R^1 = R^2$) and *asymmetrical* ($R^1 \neq R^2$).



$R^1 = R^2$, alkyl, aralkyl, aryl
R^2 = alkyl, aralkyl, aryl

Phosgenations – A Handbook. L. Cotarca, H. Eckert

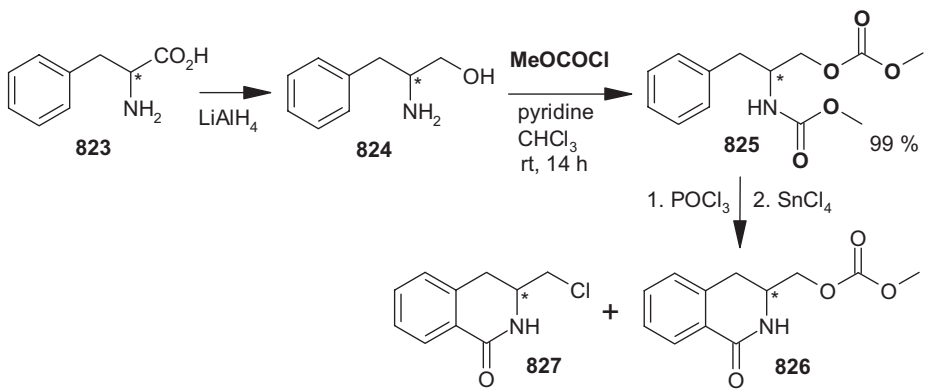
ISBN: 3-527-29823-1

Carbonates are rather reactive compounds and thus can be used for syntheses of *carbamates* and ureas, particularly *asymmetrical ureas*. Reviews on carbonates are given in [608–611]. Preparations of carbonates described herein are performed with **chloroformates** [612–632], **phosgene** [503, 634–649], **diphosgene** [650, 651], **triphosgene** [652–657], **CDI** [658–663], **acyl carbonates** [664–675], **carbonates** interchanges [633, 676–701], **CO** [702, 703], **CO_2** [704–714], and **ureas** [715–718], or under **enzymes** catalysis [719–721].

4.3.3.1 Chloroformates

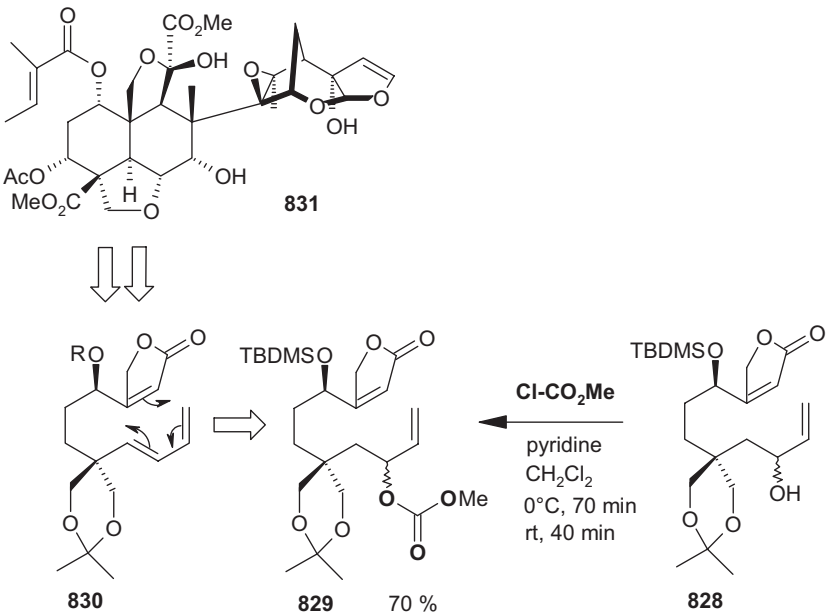
Carbonates **822**, particularly asymmetrical carbonates, with at least one *simple* group R^1, can be easily obtained by reaction of an *alcohol* R^2–OH with **chloroformates** of the type **$R^1O-CO-Cl$** (R^1 = alkyl, aralkyl, aryl), most of which are commercially available and cheap products (see also Section 4.2.1 "Chloroformates").

Enantiospecific synthesis of 1,2,3,4-tetrahydroisoquinoline derivatives **826** and **827** can be accomplished from the amino acid L-phenylalanine **823**. During the synthesis, both the amino and alcohol functions of phenylalaninol **824** are carbonylated with **methyl chloroformate**, leading to the carbonate **825** in 99% yield (together with carbamate) [612].



Typical procedure. *(R)-(+)-N,O-Bis(methoxycarbonyl)-2-amino-3-phenylpropanol* **825** [612]: A solution of the alcohol **824** (5.60 g, 37 mmol) in dry chloroform (75 mL) and pyridine (15 mL) was cooled to 0 °C. **Methyl chloroformate** (5.80 mL, 74.0 mmol) was then added dropwise from an addition funnel. After the addition, the solution was stirred at room temperature for 14 h. Iced water (50 mL) was then slowly added to the reaction mixture and the resulting mixture was stirred for 15 min. The organic phase was separated and the aqueous phase was extracted with chloroform (2 × 50 mL). The combined organic phases were washed with 3 N HCl (2 × 50 mL), 5% $NaHCO_3$ (50 mL), and brine (50 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Bulb-to-bulb distillation (140–150 °C, 0.5 mmHg) yielded carbonate **825** as a white solid (14.3 g, 99%); mp 83–84 °C; $[\alpha]^{20}_D = +3.9°$ ($c = 0.38$, EtOH).

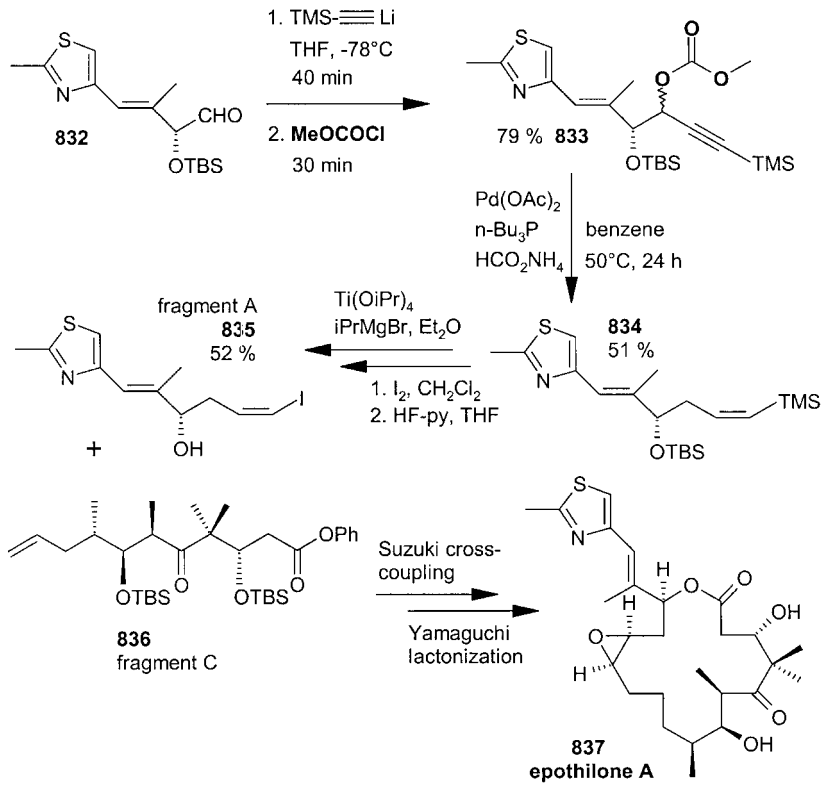
A key intermediate **829** in the construction of the decalin part of *azadirachtin* **831**, an antifeedant insect growth regulatory and reproductive effective substance from the Neem tree *Azadirachta indica*, has been prepared by carbonylation of the alcohol with **methyl chloroformate**, affording carbonate **829** in 70% yield [613].



Typical procedure. *5-{3′-tert-Butyldimethylsilyloxy-3′-[furan-2″(5″H)-on-4″-yl]propyl}-5-(2‴-methoxycarbonyloxybut-3‴-en-1⁗-yl)-2,2-dimethyl-1,3-dioxane* **829** [613]: To a cooled (0 °C) solution of alcohol **828** (758.5 mg, 1.70 mmol) and pyridine (0.70 mL, 8.65 mmol) in dichloromethane (10 mL), **methyl chloroformate** (0.52 mL, 6.73 mmol) was carefully added over a period of 16 min. The mixture was stirred at 0 °C for 70 min, and then allowed to warm to room temperature over a period of 40 min. The reaction was subsequently quenched with saturated aq. NH_4Cl solution (10 mL), and the mixture was extracted with diethyl ether (3 × 30 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (230–400 mesh, 23 g, hexane/EtOAc, 4:1 → 1:1) afforded carbonate **829** as a 1:1 mixture of diastereomers (604.0 mg, 1.20 mmol, 70%) as a pale-yellow oil, followed by recovered **828** (233.0 mg, 0.53 mmol, 30%). IR (neat): $\nu_{max} = 1780$, 1754 cm^{-1}.

An enantioselective total synthesis of *epothilone A* **837** using multifunctional asymmetric catalysis has been achieved [614]. Suzuki cross-coupling of fragment A **835** with fragment C **836** followed by Yamaguchi lactonization as key steps leads to an enantiocontrolled synthesis of epothilone A **837**. During the synthesis of fragment A, reaction of an aldehyde **832** with TMS-acetylide affords an alcohol, which

is immediately methoxycarbonylated with **methyl chloroformate** resulting in the carbonate **833** (yield 79%), which is removed by catalytic reduction to compound **834** [614].



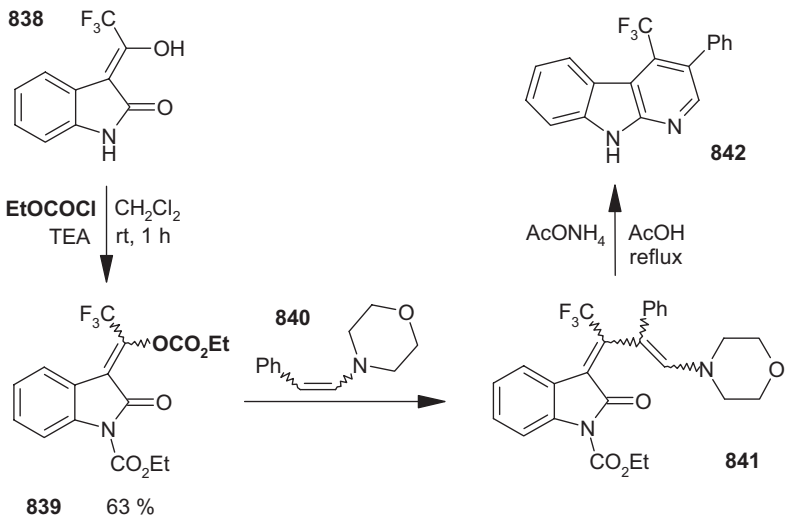
Typical procedure. *(1E,3S)-3-tert-Butyldimethylsilyloxy-2-methyl-6-trimethylsilyl-1-(2-methyl-1,3-thiazol-4-yl)-1-hexen-5-yne* **834** (via carbonate **833**) [614]: Trimethylsilylacetylene (198 μL, 1.4 mmol) was dissolved in THF (5 mL) and the solution was cooled to −78 °C. Butyllithium (903 μL, 1.55 M in hexane, 1.4 mmol) was added, and the reaction mixture was stirred at the same temperature for 20 min. Then, a solution of aldehyde **832** (218 mg, 0.7 mmol) in THF (1 mL) was added, followed, after 40 min, by **methyl chloroformate** (216 μL, 2.8 mmol). The resulting mixture was stirred for a further 30 min. Saturated aqueous $NaHCO_3$ solution (30 mL) was then added, followed by EtOAc (30 mL). The organic layer was separated, and the aqueous phase was further extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated; the residue was purified by flash chromatography on silica gel (EtOAc/hexane, 1:10) to

give a diastereomeric mixture of carbonate **833** (259 mg, 0.55 mmol, 79%) as a colorless oil.

To a solution of carbonate **833** (65 mg, 0.14 mmol), palladium acetate (6.2 mg, 0.028 mmol), and ammonium formate (35 mg, 0.56 mmol) in benzene (2 mL) was added tributylphosphine, and the mixture was heated to 50 °C. After 24 h, the mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/hexane, 1:100) to give alkyne **834** (28 mg, 0.07 mmol, 51%) as a colorless oil; $[\alpha]^{24}_{D} = +31.3$ ($c = 0.5$, $CHCl_3$) (99% *ee*).

Methyl chloroformate has also been employed in the synthesis of *rosefuran* [615], in a general and facile method for determining the configuration of steroid-17-yl methyl glycolates at C-20 [T. Suzuki, H. Tada, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3831–3836], and in a novel method for the stereospecific generation of natural C-17 stereochemistry [616].

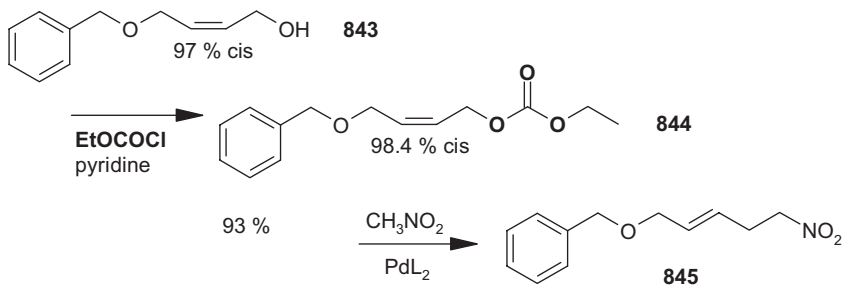
Functionalized *pyrido[2,3-b]indoles* **842** have recently attracted great interest by virtue of their cytotoxic activity toward L1210 leukemia cells. An approach to their synthesis involves a cyclization reaction of the 3-(ethoxycarbonyloxymethylene)-indol-2-one **839** with enamine **840** and ammonium acetate [617]. The carbonate **839** is prepared from the corresponding enol **838** with **ethyl chloroformate** in 63% yield.



Typical procedure. *1-Carbethoxy-3-(1-trifluoromethyl-1-ethoxycarbonyloxy-methylene)indol-2-one* **839** [617]: Compound **838** (2.29 g, 10 mmol) was dissolved in dichloromethane (30 mL) and triethylamine (5.5 mL, 40 mmol) was added. The stirred reaction mixture was cooled to 0 °C and a solution of **EtOCOCl** (2.9 mL, 30 mmol) in dichloromethane (20 mL) was slowly added. After 1 h at room temperature, the mixture was washed with water (50 mL). The organic layer was dried (Na_2SO_4),

filtered, and concentrated and the residue was purified by column chromatography on silica gel (eluent: hexane/CH_2Cl_2 (2:1) → CH_2Cl_2) to give 2.35 g of **839**; yield 63%; mp 37–38 °C (light-yellow crystals from pentane). IR: $\nu_{max} = 1763$, 1728 cm^{-1}.

Homoallylic nitro compounds **845** are accessible by conversion of allylic alcohols to carbonates followed by their palladium-catalyzed solvolysis in nitromethane [618]. Ethoxycarbonylation of the alcohols **843** with **ethyl chloroformate** provides the corresponding allylic ethyl carbonates in high yields (99% in the case of **844**). Exposure of these substrates to catalytic palladium(0) in nitromethane initiates a reaction sequence of ionization – decarboxylation – nitromethylation, which culminates in the formation of nitroalkenes **845**.

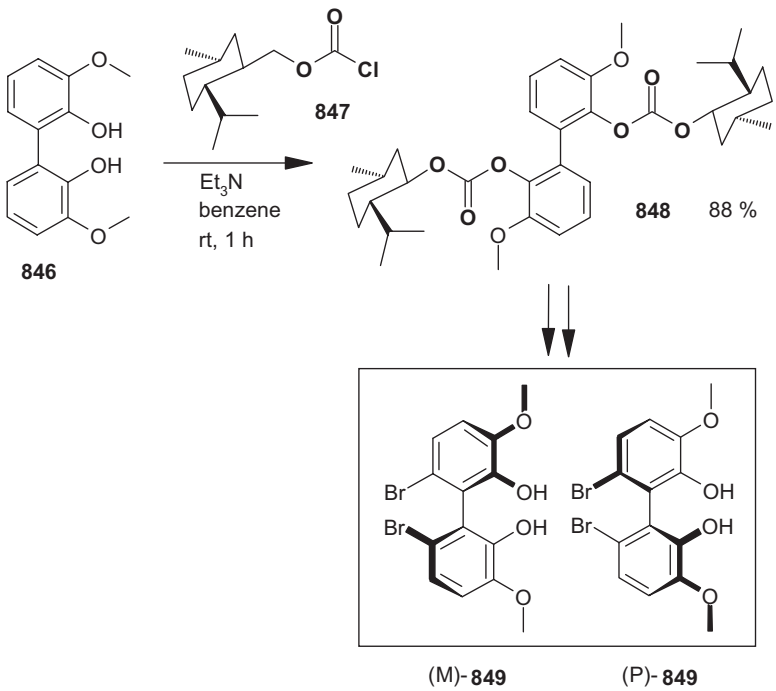


Typical procedure (small scale). *cis-4-Benzyloxy-2-butenyl ethyl carbonate* **844** [618]: A flask purged with N_2 was charged with pyridine (7.0 mL). Then, *cis*-4-benzyloxy-2-buten-1-ol **843** (97% *cis*, 0.47 mL, 500 mg, 2.81 mmol) was injected into the flask by means of a syringe. The solution was cooled to 0 °C with an ice/water bath, and cold **ethyl chloroformate** (0.34 mL, 4.21 mmol) was added dropwise over a period of 5 min. After completion of the addition, the ice/water bath was removed and the reaction was monitored by TLC analysis (hexanes/EtOAc, 6:1; R_f of product = 0.63). The reaction was subsequently quenched by diluting with diethyl ether, and the organic layer was washed with saturated aq. NH_4Cl solution (3 × 8 mL), 1 N HCl (3 × 8 mL), and saturated aq. $NaHCO_3$ solution (3 × 8 mL). The organic phase was then dried over $MgSO_4$ and concentrated under reduced pressure. Radial chromatography (4 mm plate; hexanes/EtOAc, 12:1) was performed on 760 mg of the crude product. Removal of the solvent in vacuo afforded 659 mg (93% yield) of **844** as a colorless oil; 98.4% *cis* by GC.

Ethyl chloroformate has also been employed in a stereochemical study on the palladium(0)-catalyzed carbonylation of 3-alkoxycarbonyloxy-2-methylenealkanoates [619]. **Isobutyl chloroformate** is used in the synthesis of 17α-hydroxy-20-oxo-pregnanes from 17(20)-dehydro-23,24-dinorcholan-22-oic acids [620]. **Phenyl chloroformate** is employed in a cyclocarbonylation reaction to prepare an intermediate in synthesis of *solanoeclepin A* [621].

A practical route for preparing the biphenyl (M)-**849**, (P)-**849** starting from

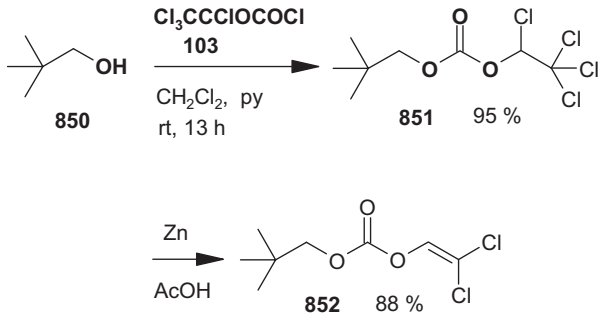
3,3′,2,2′-tetramethoxy-1,1′-biphenyl and proceeding via **846** has been described. Carbonylation of **846** using **(1*R*,2*S*,5*R*)-(−)-menthyl chloroformate 847** affords the dicarbonate intermediate **848** in 88% yield [622].



(M)-**849** (P)-**849**

Typical procedure. *1,1′-Biphenyl-2,2′-diyl-O,O′-bis[5-methyl-2-(1-methylethyl)cyclohexyl)] carbonic ester* **848** [622]: A solution of **846** (2.10 g, 8.50 mmol) and triethylamine (2 mL) in benzene (15 mL) was added dropwise to a solution of **(−)-(1*R*,2*S*,5*R*)-menthyl chloroformate 847** (4.10 g, 18.76 mmol) in benzene (15 mL) at room temperature under N_2. The solution was stirred at room temperature for 1 h, washed with 10% aq. HCl and water, and the organic phase was diluted with dichloromethane. After drying over Na_2SO_4, evaporation of the solvent left a colorless solid, which was purified by flash chromatography using CH_2Cl_2/petroleum ether (1:1) as eluent to give **848** (4.57 g, 88%); mp 202–204 °C.

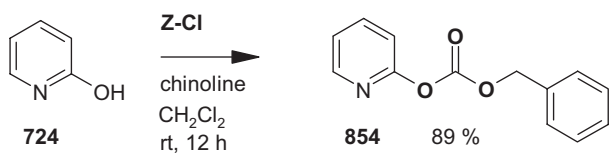
Modern generations of insecticides continue to take advantage of the toxicity to insects of a particular halogen substitution pattern in the molecule and also contain functionalities guaranteeing ready degeneration by environmental agents. An example is the 2,2-dichlorovinyl unit in pyrethrin analogues [623, 624]. In this context, *2,2-dichlorovinyl neopentyl carbonate* **852** has been prepared via 1,2,2,2-tetrachloroethyl neopentyl carbonate **851** by reaction of neopentyl alcohol **850** with **1,2,2,2-tetrachloroethyl chloroformate** and reduction of the resulting product **851** with zinc dust [58].



Typical procedures. *2,2-Dichlorovinyl neopentyl carbonate* **852** [58]: *1,2,2,2-Tetrachloroethyl neopentyl carbonate* **851**: Pyridine (4.75 g, 0.06 mol) was added over 20 min to a stirred, ice-bath cooled solution of neopentyl alcohol **850** (5.05 g, 0.06 mol) and **1,2,2,2-tetrachloroethyl chloroformate 103** (17.0 g, 0.07 mol; for a preparation, see Section 4.2.1) in dichloromethane (40 mL). After 13 h at room temperature, the mixture was washed with water, concentrated, and distilled; the product (bp 98–101 °C at 1 mmHg) solidified on standing; mp 40.5–42 °C; 16.2 g (95% yield) of **851**; IR (CCl_4): $\nu_{max} = 1775\ cm^{-1}$.

2,2-Dichlorovinyl neopentyl carbonate **852**: A mixture of **851** (3.5 g, 0.012 mol) and zinc dust (1.00 g, 0.015 mol) in anhydrous AcOH (5 mL) was refluxed for 1 h, cooled, diluted with dichloromethane, washed with water, dried (Na_2SO_4), concentrated, and distilled (bp of product 58–60 °C at 1 mmHg); this gave 2.4 g (88% yield) of **852**; IR ($CHCl_3$): $\nu_{max} = 1765\ cm^{-1}$.

Benzyl chloroformate (**Z-Cl**) is employed to prepare *benzyl 2-pyridyl carbonate* **854** from 2-hydroxypyridine **724** in 89% yield [625]. Benzyl 2-pyridyl carbonate is a reagent for introducing the Z-residue on amino functions of amino acids.



Typical procedure. *Benzyl 2-pyridyl carbonate* **854** [625]: To a solution of 2-hydroxypyridine **724** (3.80 g, 40.0 mmol) and chinoline (5.16 g, 40 mmol) in abs. dichloromethane (80 mL), **Z-Cl** (6.82 g, 40 mmol) was added dropwise with stirring under exclusion of moisture at −10 °C. The mixture was stirred for 12 h at room temperature and then washed with ice-cold 0.1 N HCl (3 × 20 mL), saturated aqueous $NaHCO_3$ solution (2 × 20 mL), and water (2 × 20 mL), dried over Na_2SO_4, and concentrated. The residue was recrystallized from abs. diethyl ether/*n*-pentane. Yield 8.14 g (89%) of **854**; mp 59–61 °C.

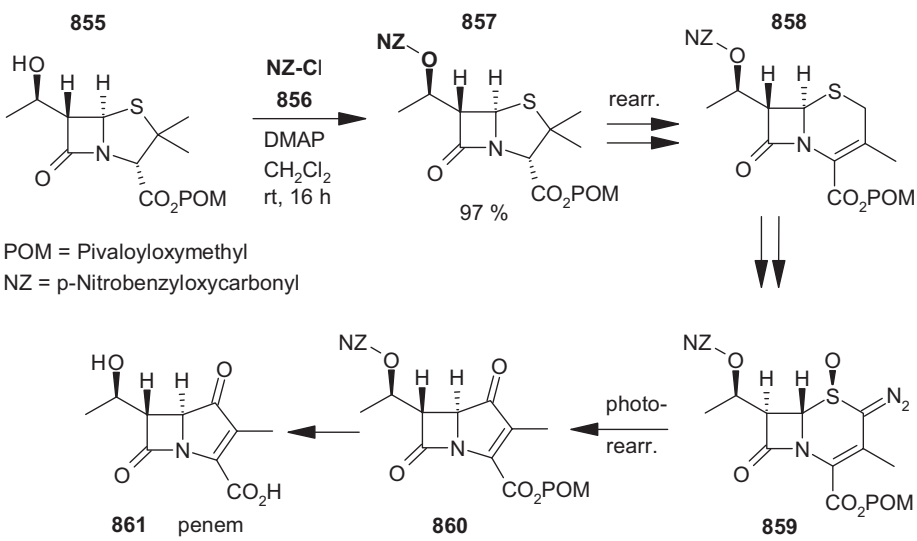
Phenyl chloroformate has been employed to produce *benzyl phenyl carbonate* in 79% yield [508]. With benzyl phenyl carbonate highly selective syntheses of carbamate protected polyamines have been accomplished [508] (see section 4.3.2.4).

Typical procedure. *Benzyl phenyl carbonate* [508]: To a mixture of benzyl alcohol (108.0 g, 1.0 mol), pyridine (100 ml) and CH_2Cl_2 (175 mL) in a 500 ml 3-necked flask equipped with a condenser, mechanical stirring and an addition funnel was added **phenyl chloroformate** (156.0 g, 1.0 mol) over a period of 1 h. The reaction mixture was stirred for an additional 3 h, and H_2O (250 mL) was added. The organic phase was washed with aq H_2SO_4 (2 M; 2×250 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was distilled in vacuum to give benzyl phenyl carbonate. Yield: 180.2 g (79%); colorless oil; bp 146–150 °C/0.2 mmHg (127–131 °C/0.1 mmHg). ^{1}H-NMR ($CDCl_3$): $\delta = 5.37$ (s, 2 H), 7.18–7.48 (m, 10 H).

O-Protective groups of the carbonate type

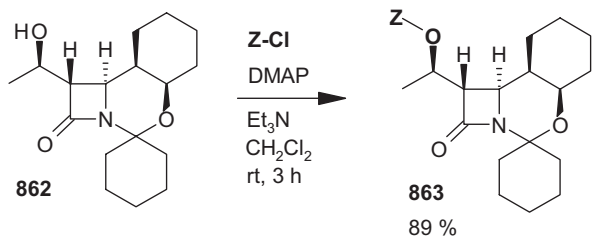
Widely used protective groups for amino functions (see Section 4.3.2 "Carbamates"), such as *Z* or *Fmoc residues*, are also employed for the protection of alcohol functions.

β-Lactam antibiotics *carbapenems* and *carbapenams* can be prepared from readily available *cephalosporins*, allowing facile access to a ring system previously accessible only by total synthesis, lengthy semisynthesis, or fermentation [626]. The photo "Wolff" rearrangement of 2-diazoceph-3-em oxides **859** leads directly to carbapen-2-ems **860**. The chirality of the cephalosporin is wholly preserved in the corresponding carbapenem. **858** can be obtained by a rearrangement from the corresponding hydroxyethyl penicillin precursor **855**, which has to be fitted with protecting groups in order to avoid side reactions in further steps. Thus, the key intermediate of the synthesis is **857**. The *p*-nitrobenzyloxycarbonyl residue is introduced at the alcohol function with ***p*-nitrobenzyl chloroformate** (**NZ-Cl**, **856**), affording **857** in 97% yield [626].

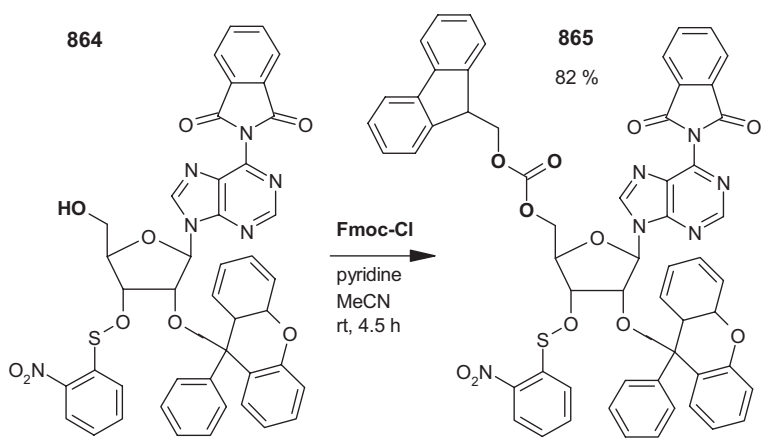


Typical procedure. *Pivaloyloxymethyl 6α-[1(R)-(p-nitrobenzyloxycarbonyloxyethyl)]penicillanate* **857** [626]: Pivaloyloxymethyl 6α-[1(*R*)-hydroxyethyl]penicillanate **855** (3.2 g, 9.54 mmol) was dissolved in dichloromethane (100 mL) and the solution was cooled to 0 °C. Diisopropylethylamine (2.19 mL, 12.7 mmol), DMAP (1.28 g, 10.5 mmol), and ***p*-nitrobenzyl chloroformate 856** (2.72 g, 12.6 mmol) were added. The reaction mixture was stirred for 16 h at room temperature, then was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated to leave the crude product, which was chromatographed on silica gel eluting with chloroform/ethyl acetate (15:1) to yield purified *penicillanate* **857** (5 g, 97%, oil); $R_f = 0.7$ (diethyl ether); ^{1}H NMR ($CDCl_3$): $\delta = 1.0$ (s, 9 H), 1.5 (s, 3 H), 1.6 (s, 3 H), 4.4 (s, 1 H), 7.4 (d, 2 H, $J = 8$ Hz), 8.2 (d, 2 H, $J = 8$ Hz).

During a synthesis of *trinem antibiotics* (also β-lactams) a temporary Z-protective group was introduced on the secondary alcohol **862** with **benzyl chloroformate** (**Z-Cl**), affording **863** in 89% yield [627].

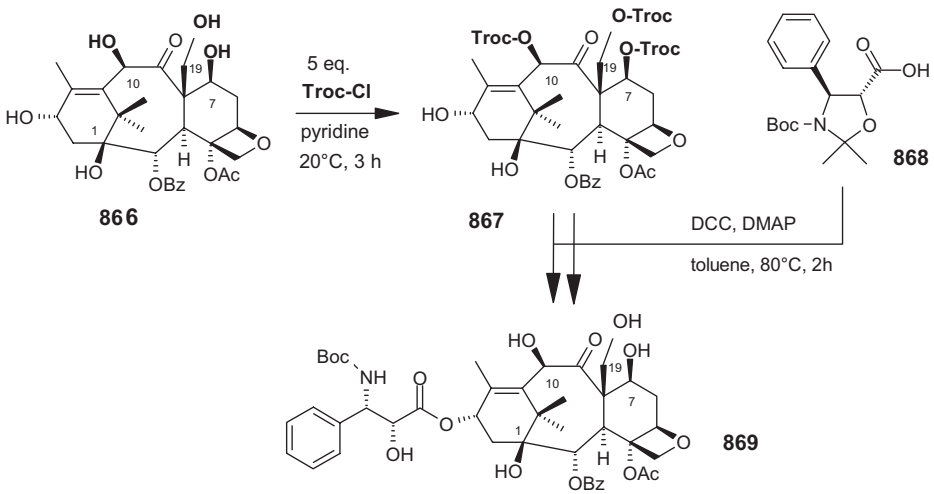


In a study on the reaction of arenesulfenyl chlorides with hydroxyl functions of ribonucleosides, the *Fmoc residue* was employed as a protective group for the 5′-hydroxy function in an *adenosine derivative* [628]. Reaction of **864** with **Fmoc-Cl** afforded the 5′-*O*-Fmoc-adenosine derivative **865** in 82% yield.



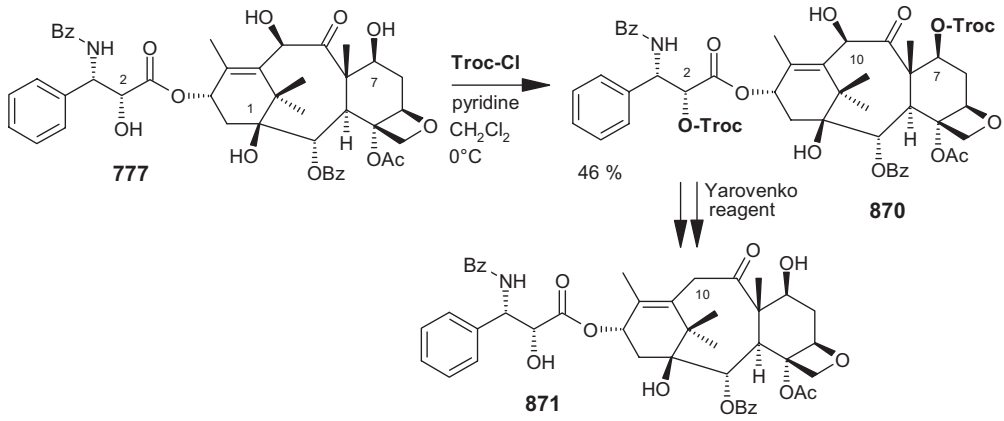
Typical procedure. *6-N-Phthaloyl-2′-O-(9-phenylxanthen-9-yl)-5′-O-(fluoren-9-yl-methoxycarbonyl)adenosine* **865** [628]: To a solution of **864** (635 mg, 1 mmol) in dry pyridine (10 mL) was added dropwise a solution of **Fmoc-Cl** (336 mg, 1.3 mmol) in dry acetonitrile (5 mL). The reaction mixture was stirred for 4.5 h at room temperature and was then poured into cold, saturated sodium hydrogen carbonate solution (100 mL). The resulting mixture was extracted with chloroform (2 × 50 mL), the combined organic layers were concentrated in vacuo, and the residue was dried by co-evaporation with toluene (4 × 25 mL). It was then dissolved in dichloromethane, and precipitation from cyclohexane gave **865**; yield (717 mg, 82%); $R_f = 0.77$ (chloroform/methanol, 9:1, *v*/*v*).

Several publications deal with the protection of various primary and secondary alcohol functions at the scaffold of cytotoxic and antileukemic *taxol*, at positions C-7, C-10, C-19, and C-2′, using the 2,2,2-trichloroethyloxycarbonyl-[Troc]-residue as protecting group [629–632].

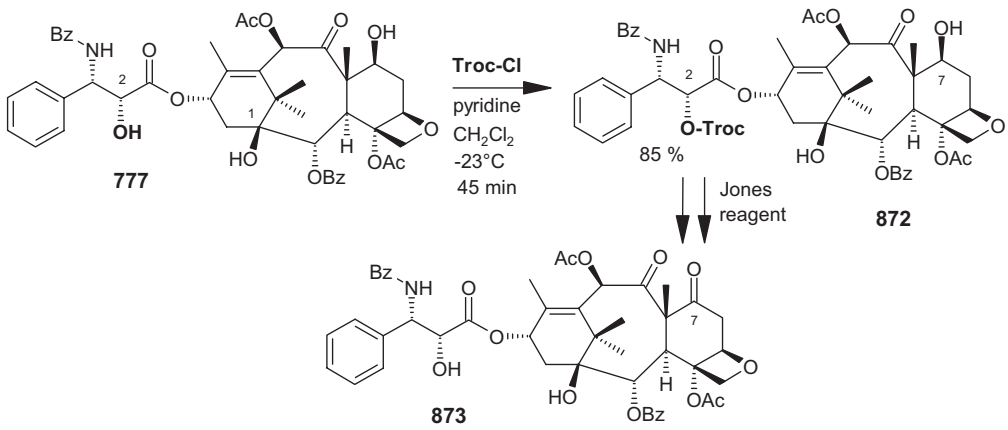


A semisynthesis of the 19-hydroxy taxol derivative, 19-hydroxy docetaxel **869**, was accomplished by semisynthesis of a new baccatin derivative, 10-deacetyl-19-hydroxybaccatin III **866**, which, after temporary protection at positions C-7, C-10, and C-19 with Troc groups using **2,2,2-trichloroethyl chloroformate** (**Troc-Cl**) (to give **867**), was coupled with *N*-Boc-*N*,*O*-isopropylidene-phenylisoserine **868** to yield **869** [629]. Analogue **869** exhibits a high level of *in vitro* cytotoxicity and thus the results demonstrate that chemical modifications at C-19 can be made without significant loss of biological activity.

The following three examples deal with modifications on the preformed taxol molecule. *10-Deoxytaxol* **871** can be prepared from taxol **777** in four steps. Dehydration of the alcohol function at C-10 requires protection of the hydroxy functions at C-2′ and C-7, which is accomplished using **Troc-Cl**, thereby affording the corresponding 2,2,2-trichloroethyl carbonate **870** in 46% yield [630].



Oxidation of taxol **777** with Jones' reagent yields 7-oxotaxol **873**, 2′,7-dioxotaxol, or 2′-oxo-7-acetyl taxol. In order to selectively obtain 7-oxotaxol, it is necessary to block the C-2′ hydroxy function. This is accomplished using the Troc group, introduced with **Troc-Cl**, affording 2′-O-Troc-taxol **872** in 85% yield [631].



Typical procedure. *2′-O-(2,2,2-Trichloroethyloxycarbonyl)taxol* **872** [631]: A solution of taxol **777** (50 mg) in dichloromethane (1.0 mL) and pyridine (0.1 mL) was cooled to −23 °C and treated with **Troc-Cl** (0.008 mL) over a period of 45 min. Work-up by standard methods yielded a mixture of *2′-O-Troc-taxol* **872** ($R_f = 0.34$; EtOAc/hexane, 1:1) together with small amounts of taxol, $R_f = 0.11$, and a product assumed to be 2′,7-bis-Troc-taxol, $R_f = 0.74$. The product was isolated by PTLC with EtOAc/hexane (1:1) as solvent, yield: 51 mg (85%); FAB-MS: $m/z = 1028$ [MH^+], 509; IR: $\nu_{max} = 1780, 1740, 1690, 1675, 1530, 1505, 1390, 1290, 1255$ cm^{-1}.

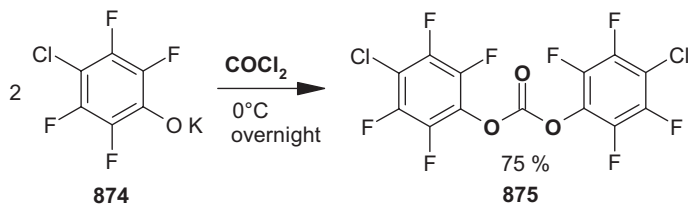
A similar, more detailed procedure for the preparation of **872** has been elaborated in order to synthesize the tritiated derivative [^{3}H]-7-acetyl-taxol [632].

Typical procedure. *2′-O-(2,2,2-Trichloroethyloxycarbonyl)taxol* **872** [632]: In a microreactor (Pierce), taxol **777** (195 mg, 228 μmol) was dissolved in dichloromethane (6 mL) containing pyridine (86 μL, 1066 μmol). The solution was cooled to −30 °C using an acetone/dry-ice mixture. Then, a solution of **Troc-Cl** (225 mg, 1006 μmol) in dichloromethane (2 mL) at room temperature was slowly added to the taxol solution and the mixture was gently stirred for 1 h at −30 °C. Water (5 mL) was then added, and the mixture was allowed to warm to room temperature. Water was added before the temperature increase in order to minimize the formation of 2′,7-di-Troc-taxol. The crude product was extracted into dichloromethane and the mixture of unreacted taxol, 2′-Troc-taxol **872**, and 2′,7-di-Troc-taxol was applied to a column of silica gel (100 × 1.2 cm), allowed to equilibrate, and eluted with dichloromethane/methanol (98:2). The recovery of 180 mg of pure 2′-Troc-taxol **872** represented a 76% yield.

4.3.3.2 **Phosgene**

Symmetrical carbonates are synthesized by carbonylation of the alcohols 4-chlorotetrafluorophenol and 4-nitrophenol with **phosgene**. In this way, "active esters" of carbonic acids, such as *di(p-chlorotetrafluorophenyl) carbonate (di-Tfc-carbonate)* **875** [634] and *di(p-nitrophenyl) carbonate (di-Dnp-carbonate)* **717** [503], are produced. *Di-Tfc-carbonate* **875** is used to prepare *p-chlorotetrafluorophenyl esters* of *N*-protected amino acids and offers an advantageous alternative to *pentafluorophenyl esters*, because pentafluorophenol is too stable in waste.

Di-Dnp-carbonate **717** is employed to prepare *symmetrical* and *unsymmetrical N,N′-disubstituted ureas* [503].

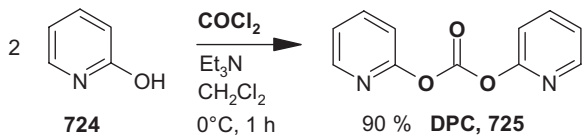


Typical procedure. *Di-Tfc-carbonate* **875** [634]: *p*-Chlorotetrafluorophenol **874** (54.5 g, 0.27 mol) was dissolved in 0.5 M KOH (1.0 L), and the solution was cooled to 0 °C. **Phosgene** (for a *safe source*, see Chapter 7) was then passed through this solution with vigorous mixing. The pH of the reaction mixture was kept at no lower than 6.0. Sometimes, *di-Tfc-carbonate* **875** crystallized from the solution, but more often an oily precipitate was formed. The reaction mixture was kept at 0 °C

overnight. The solidified residue was collected by filtration, washed with water, and redissolved in chloroform (300 mL). This solution was dried over anhydrous sodium sulfate, filtered, and concentrated. 48 g of the crude crystalline product, with a strong, chloroformate-like odor due to an impurity, was crystallized from hexane. The yield of *di-Tfc-carbonate* **875** was 43 g (75%); mp 61–63 °C.

Typical procedure. *Di-Dnp-carbonate* **717** [503]: To a stirred solution of **phosgene** (for a *safe source*, see Chapter 7) (178 g, 1.8 mol) in toluene (520 mL), dry sodium 4-nitrophenolate **876** (645 g, 4 mol) was added in portions from a flask attached by a rubber tube. The reaction flask was cooled during the addition to keep the temperature of the reaction mixture below 40 °C. Then, the mixture was heated by means of a water bath at 60 °C for 3 h. The precipitate formed was filtered off, washed with acetone (500 mL), and the combined filtrate and washings were concentrated to dryness. The crystalline residue was recrystallized from toluene, and then from CCl_4; yield 428 g (78%) of **717**; mp 140–141 °C; IR (KBr): $\nu_{max} = 1775\ cm^{-1}$ (CO).

A versatile reagent for a convenient synthesis of various functionalized carbamates (see Section 4.3.2), ureas, interchanged carbonates, and active esters for activation in forming peptide bonds, as well as for the direct esterification of carboxylic acids [635–637] (see also Section 4.3.3.7), is *di-2-pyridyl carbonate*, **DPC**, **725**. It is prepared from commercially available 2-hydroxypyridine and **phosgene** in 90% yield [638].



724 90 % **DPC, 725**

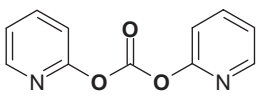
Typical procedure. *Di-2-pyridyl carbonate*, **DPC**, **725** [638]: A solution of **phosgene** (for a *safe source*, see Chapter 7) (2.5 M in toluene, 2 mL, 5.0 mmol) was diluted with dichloromethane (8 mL) and then a solution of 2-pyridinol **853** (950 mg, 10 mmol) and triethylamine (1.214 g, 10.2 mmol) in dichloromethane (20 mL) was added at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then washed with cold 5% $NaHCO_3$ solution (20 mL) and cold saturated brine (20 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated to dryness to give *di-2-pyridyl carbonate*, **DPC**, **725** (972 mg) in 90% yield. It was recrystallized from dichloromethane/petroleum ether (811 mg, 75%); mp 84–86 °C.

DPC has also been produced as its hydrochloride salt **877**, in a more facile procedure on a larger scale, in 97% yield [639].

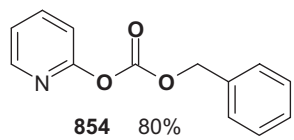
Typical procedure. *Di-2-pyridyl carbonate hydrochloride*, **DPC·HCl**, **877** [639]: *Avoid sunlight (2-hydroxypyridine is light-sensitive) and work in a well-ventilated fumehood.* In a 2-L three-necked flask equipped with a gas inlet tube, stirrer, and reflux condenser, 2-hydroxypyridine **724** (47.5 g, 500 mmol) was dissolved in absolute THF (750 mL) with stirring and mild warming. **Phosgene** (for a *safe source*, see Chapter 7) (12.4 g, 8.9 mL, 125 mmol) was passed into the solution, and then nitrogen was

bubbled into the reaction mixture for 2–3 h at room temperature with stirring. 2-Hydroxypyridinium hydrochloride was then filtered off under exclusion of moisture and the filtrate was concentrated to dryness in vacuo at 20–30 °C to afford fine, pale-yellow crystals of **DPC·HCl**, **877**; yield 26.2 g (97%).

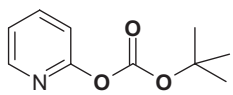
This product is slightly contaminated with 2-hydroxypyridinium hydrochloride, but can be used in most reactions. A very pure product can be obtained by dissolving it in cold absolute THF and reducing the volume of the solution. **DPC·HCl** **877** crystallizes in plates; mp 110–112 °C. It is well soluble in DMF, pyridine, chloroform, and dichloromethane, moderately soluble in benzene, THF, and acetonitrile, and poorly soluble in petroleum ether, cyclohexane, and water.



x 2 HCl **877** 97 %



854 80%

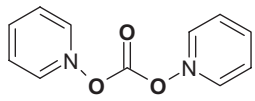


878 70 %

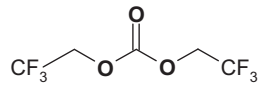
Mixed alkyl carbonates, such as *benzyl 2-pyridyl carbonate* **854** and *t-butyl 2-pyridyl carbonate* **878**, are useful reagents for introducing *Z* or *Boc residues* as protective groups due to the fact that 2-pyridinol is an excellent leaving group [625, 638].

Typical procedure. *t-Butyl 2-pyridyl carbonate* **878** [638]: A solution of **phosgene** (for a *safe source*, see Chapter 7) (2.5 M in toluene, 20 mL, 50 mmol) was diluted with dichloromethane (20 mL), and then a solution of 2-pyridinol (951 mg, 10 mmol) and pyridine (870 mg, 11 mmol) in dichloromethane (40 mL) was slowly added at −10 to 0 °C. After stirring within this temperature range for 15 min, excess phosgene and the solvents were evaporated under reduced pressure (Author's remark: Note: All volatiles should be evaporated into a voluminous dry-ice cooled trap and then treated with sufficient ethanol to immobilize the phosgene). The residue was redissolved in dichloromethane (30 mL), and to this solution was added a solution of *t*-butyl alcohol (815 mg, 11 mmol) and pyridine (830 mg, 10.5 mmol) in dichloromethane (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 5 h and then diluted with dichloromethane (30 mL). The resulting solution was washed with saturated aq. $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated to dryness under reduced pressure. The crude product was purified by filtration through a short column of silica gel using dichloromethane as eluent to afford *t-butyl 2-pyridyl carbonate* **878** (1.37 g, 70%). The product was recrystallized from hexane; mp 48–49 °C.

Symmetrical carbonates derived from **phosgene** and pyridine 1-oxide, *di(1-pyridyl) carbonate* **879** [640], or 2,2,2-trifluoroethanol, *bis(2,2,2-trifluoroethyl) carbonate* **880** [641], have been described.



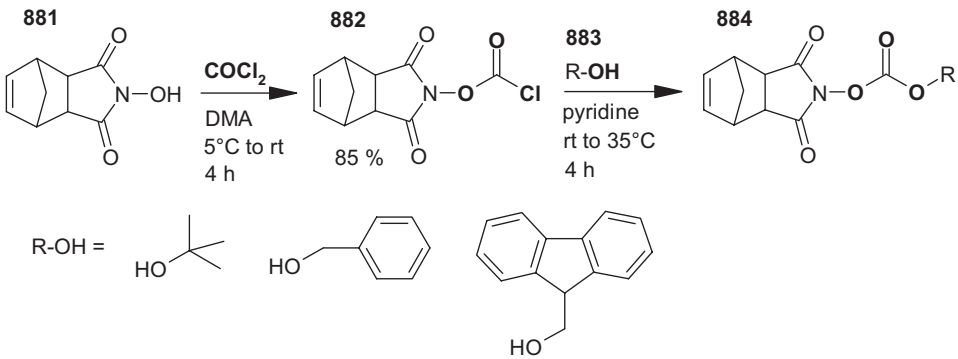
879 80-90 %



880 88 %

Typical procedure. *Bis(2,2,2-trifluoroethyl) carbonate* **880** [641]: A solution of 2,2,2-trifluoroethanol (200 g, 2.0 mol) and pyridine (158 g, 2.0 mol) in dry diethyl ether (1 L) was treated with **phosgene** (for a *safe source*, see Chapter 7) (99 g, 1.0 mol). The reaction mixture was stirred overnight and then filtered. The filtrate was distilled to give 199 g (88%) of *bis(2,2,2-trifluoroethyl) carbonate* **880**; bp 65–66 °C (100 mmHg); IR: $\nu_{max} = 1780\ cm^{-1}$ (C=O).

Unsymmetrical carbonates **884** [642] can be synthesized in *two steps* from *N*-hydroxy-5-norbornene-2,3-dicarboxamide **881**, **phosgene**, and the appropriate alcohols **883**. The activated carbonates **884** are excellent reagents for the introduction of all currently used urethane protecting groups, such as *Z*, *Boc*, and *Fmoc residues*.

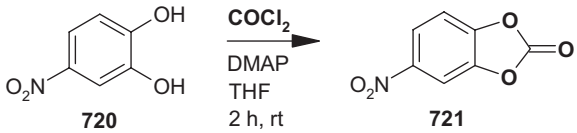


General procedure. *Preparation of carbonates* **884** [642]: A solution of **881** (17.9 g, 0.1 mol) and *N*,*N*-dimethylaniline (12 g, 0.095 mol) in THF/benzene (1:3, 100 mL) was added dropwise to a solution of **phosgene** (for a *safe source*, see Chapter 7) (9.9 g, 0.1 mol) in benzene (50 mL) at 0–5 °C. The mixture was stirred for 1 h at 5 °C and for 3 h at room temperature. The amine hydrochloride was filtered off, and the filtrate was concentrated to dryness in vacuo. The residue was redissolved in dichloromethane (50 mL), and a trace of bis(5-norbornene-2,3-dicarboximido) carbonate was removed by filtration. The solvent was removed in vacuo, and the residue was triturated with diethyl ether (50 mL) to give **882**; yield 20.5 g (85%); mp 98–100 °C (dec.); IR (KBr): $\nu_{max} = 1815, 1795, 1740\ cm^{-1}$ (C=O).

882 (24.1 g, 0.1 mol) was dissolved in an inert solvent (toluene, benzene, THF, or a halogenated hydrocarbon; 150 mL) and a solution of the appropriate alcohol **883** (0.1 mol) and pyridine (8 mL) in an inert solvent (40 mL) was added at 10–15 °C. The reaction mixture was stirred for 1 h at room temperature and for 3 h at 35 °C. The pyridinium hydrochloride precipitate was filtered off and the filtrate was concentrated to dryness. Further purification was carried out either by recrystallization of the solid from 90% aqueous methanol or by extraction of the impurities from a dichloromethane solution first with 5% aqueous sodium hydrogen carbonate so-

lution and then with water at 5 °C, followed by drying with sodium sulfate and evaporation to give the *pure carbonates* **884**.

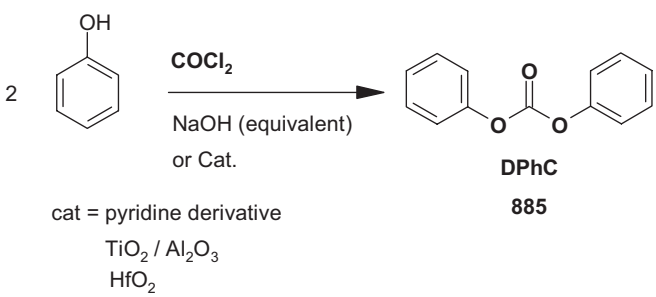
A reagent for synthesizing carbamates and particularly asymmetric ureas (see Sections 4.3.2 and 4.3.4) is ***o*-(4-nitrophenylene) carbonate** (**NPC**) **721** [504], a cyclic carbonate obtained from 4-nitrocatechol and **phosgene** or **triphosgene**.



720 **721**

Typical procedure. *o-(4-Nitrophenylene) carbonate* (**NPC**) **721** [504]: To a stirred solution of 4-nitrocatechol (3.10 g, 20 mmol) in THF (250 mL), a solution of DMAP (2.44 g, 20 mmol) in THF (100 mL) was added in a single portion. To this mixture, a solution of **phosgene** (for a *safe source*, see Chapter 7) (20% in toluene, 50 mL, 84 mmol) was added dropwise with stirring over a period of 2 h and the reaction mixture was stirred for a further 2 h at room temperature. A white precipitate began to form on addition of the phosgene solution. Nitrogen was bubbled through the suspension for 15 min and then the precipitate was removed by filtration. The filtrate was concentrated and the residue was crystallized from hexane to yield **NPC 721** (1.49 g, 41%) as pale-yellow needles; mp 100–101 °C.

Dropwise addition of a solution of **triphosgene** (3.96 g, 13.3 mmol) in THF (150 mL), instead of excess phosgene, over a period of 4 h at room temperature, followed by stirring for 2 h at 50–60 °C and the same work-up, gave 2.92 g (81%) of **NPC 721**.

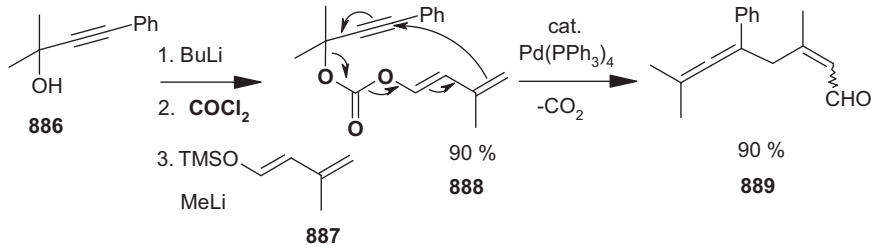


DPhC

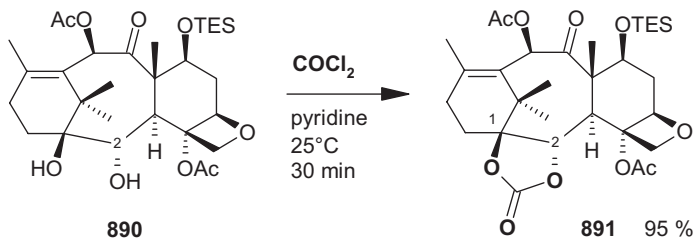
885

Technical processes for the production of diphenyl carbonate (**DPhC**) **885** from phenol and **phosgene** are covered in many patent applications (for the production of polycarbonates on optical storage of electronic data, see Section 4.3.3.7). Such processes are carried out in the presence of sodium hydroxide [643], pyridine derivatives [644], TiO_2 and Al_2O_3 [645], or HfO_2 [646].

A highly interesting synthetic route for forming intermediates en route to *retinal* and their analogues involves a palladium-catalyzed transformation of an *yne-carbonate* **888** into an *allenyl enal* **889**. The carbonate **888** is generated by unsymmetrical carbonylation of propargylic alcohol **886** and silyl enol ether **887** with **phosgene** [647].

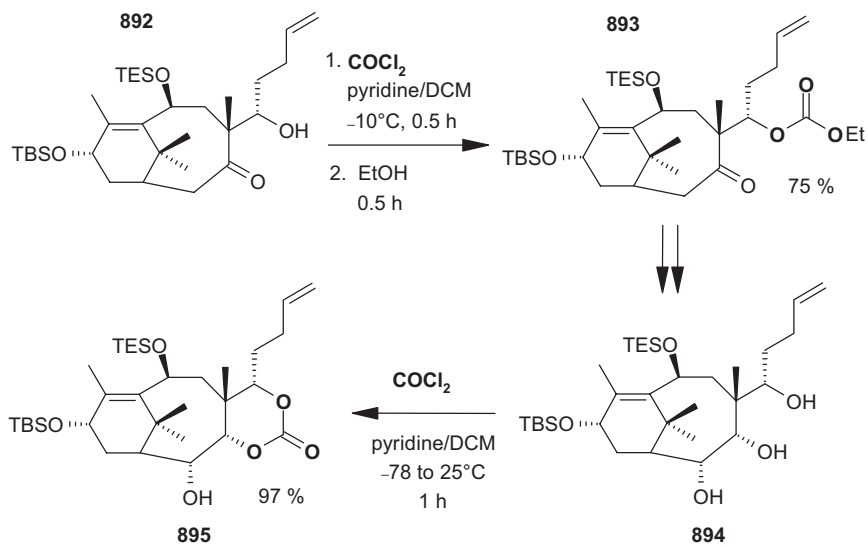


Taxol is a powerful anti-cancer drug with a versatile and widespread medical application. In the synthesis of taxol, *cyclocarbonates* are sometimes useful tools in functionalizing the taxol rings. An intermediate protective group is introduced by cyclocarbonylation of the 1,2-diol of 10-TES baccatin III **890** with **phosgene**, furnishing **891** in 95% yield [648] (see also Section 4.3.3.5).



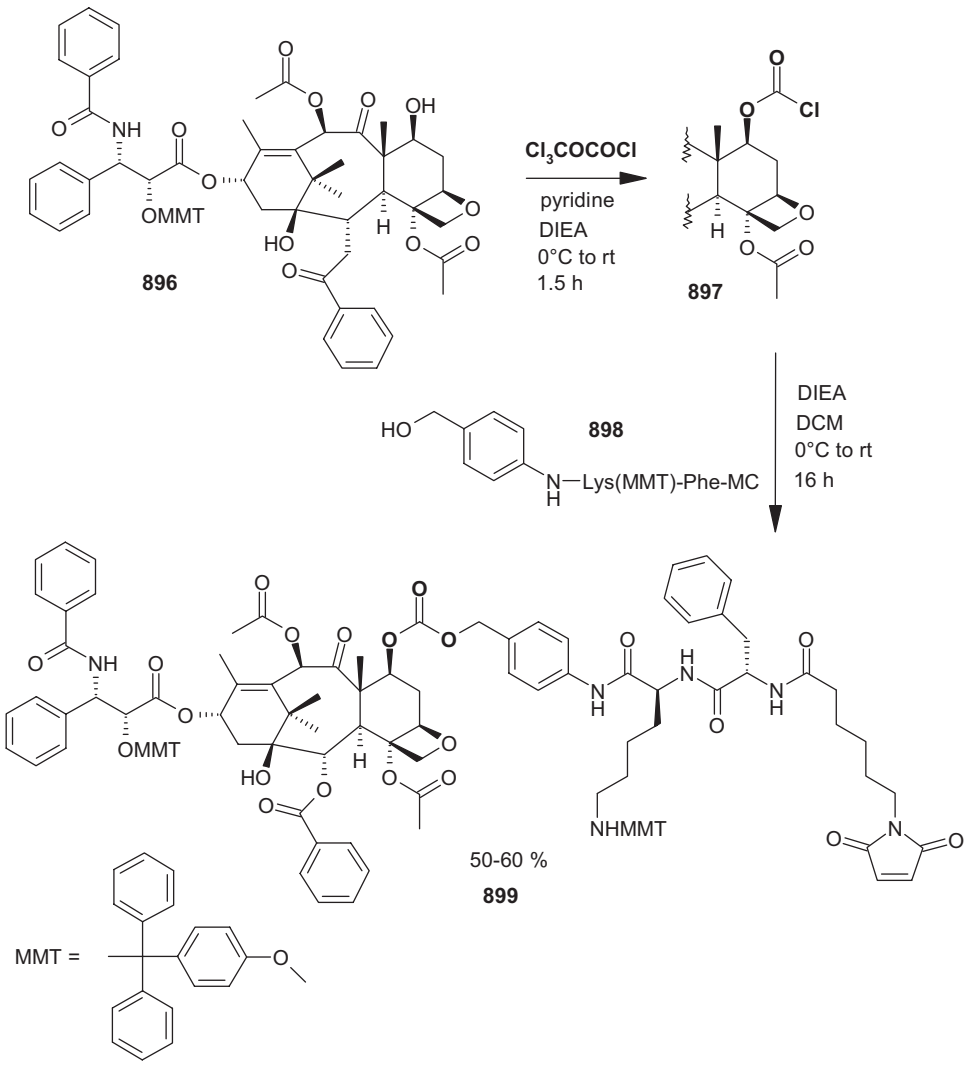
On treating **891** with a variety of nucleophiles, the cyclic carbonate is opened with precise control of regiochemistry to afford new C-2 analogues of taxol in high yield (see Section 4.3.5).

During the first total synthesis of taxol, a sequence of *phosgenation reactions* was used to generate both the carbonate **893** and the cyclocarbonate **895** with **phosgene**;



the yields for these steps were 75% and 97%, respectively [649]. Cyclocarbonylation of the triol **894** is regioselective and yields the six-membered ring.

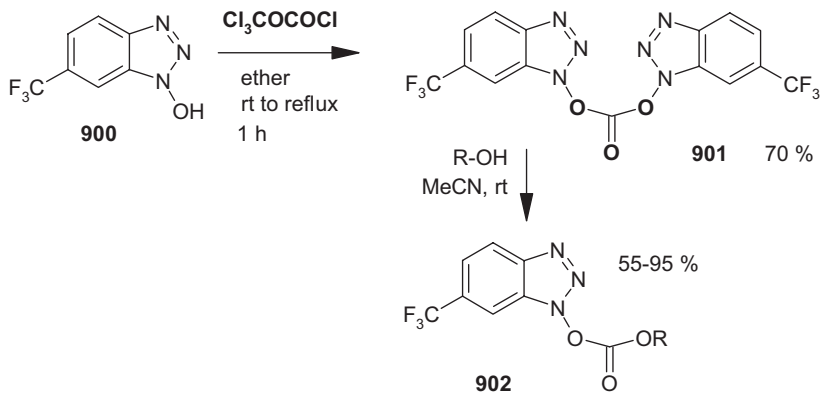
4.3.3.3 **Diphosgene**



To obtain the complex pro-drug **899** of the 2′-blocked anti-cancer drug taxol **896**, the latter has been derivatized at the 7-position using **diphosgene** (intermediate chloroformate **897**) and the dipeptide linker MC-Phe-Lys(MMT)-PABA **898**, forming the *carbonate* **899** in 50–60% yield [650].

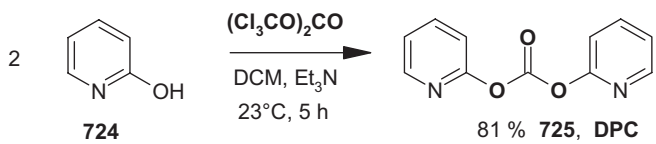
Diphosgene has also been used in the preparation of *1,1-bis(6-trifluoromethylbenzotriazolyl) carbonate (BTBC)* **901** from 1-hydroxy-6-trifluoromethylbenzo-

triazole **900** in 70% yield [651]. The reaction of *BTBC* with alcohols affords the corresponding *active carbonates* **902**, which are useful reagents for the introduction of common protective groups such as *Z*, *Fmoc*, and *Alloc residues*, and can be converted into the corresponding carbamates and carbonates.



Typical procedure. *1,1′-Bis(trifluoromethylbenzotriazolyl) carbonate (BTBC)* **901** [651]: To a stirred solution of **900** (20.3 g, 0.1 mol) in dry diethyl ether (700 mL), **diphosgene** (5.34 g, 0.025 mol) was added at room temperature. After 10 min, a further portion of **diphosgene** (5.34 g, 0.025 mol) was added and the mixture was gently refluxed for 1 h. Thereafter, the precipitate formed was collected by filtration and washed with dry diethyl ether. Almost pure crystals of *BTBC* **901** were obtained; yield: 15.1 g (70%); mp 138–143 °C.

4.3.3.4 Triphosgene

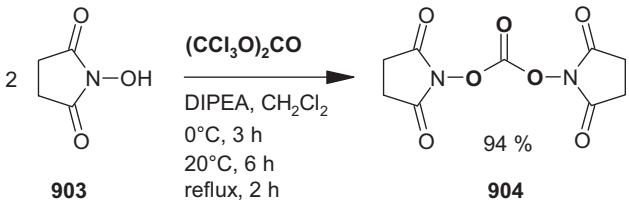


An alternative preparation of *di(2-pyridyl) carbonate* (**DPC**) **725** to that in Section 4.3.3.2 using **phosgene**, is the reaction of commercially available 2-hydroxypyridine and **triphosgene** to afford pure **DPC** in 81% yield [652].

Typical procedure. *Di(2-pyridyl) carbonate* (**DPC**) **725** [652]: To a stirred solution of **triphosgene** (3 g, 10 mmol) and 2-hydroxypyridine (5.7 g, 60 mmol) in dichloromethane (500 mL) at 0 °C, triethylamine (10.5 mL, 75 mmol) was added dropwise over a period of 15 min. The mixture was stirred at 23 °C for 5 h and then the solvent was evaporated under reduced pressure. The residue was redissolved in EtOAc (500 mL), washed with saturated $NaHCO_3$ solution (300 mL) and brine (200 mL), and dried over Na_2SO_4. Removal of the solvent and subsequent re-

crystallization of the residue from diethyl ether/petroleum ether afforded **DPC 725** (5.2 g, 81% yield) as a white solid; mp 76–78 °C.

Another important reagent, particularly used for the coupling of functional groups, such as carboxylic groups, is *N,N′-disuccinimidyl carbonate* (**DSC**) **904**, which has been prepared from *N*-hydroxysuccinimide with **triphosgene** in 94% yield [653].

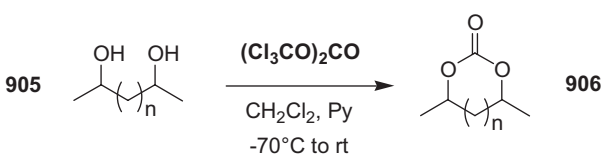


903 **904**

Typical procedure. *N,N′-Disuccinimidyl carbonate* (**DSC**) **904** [653]: In a dry 200-mL flask equipped with an Ar inlet adapter, a rubber septum, and a magnetic stirring bar were placed *N*-hydroxysuccinimide **903** (2.00 g, 17.4 mmol) and a solution of **triphosgene** (7.24 g, 24.4 mmol, 1.4 equiv.) in dry dichloromethane (50 mL). The mixture was cooled to −30 °C, whereupon DIPEA (2.24 g, 17.4 mmol, 1 equiv.) was added dropwise. The resulting mixture was stirred at 0 °C for 3 h, allowed to warm to 20 °C over a period of 6 h, and then refluxed for a further 2 h. It was concentrated under reduced pressure to leave a crystalline solid, which was suspended in THF (20 mL). The precipitate was collected by filtration, washed well with THF (2 × 20 mL), and then crystallized from MeCN. Yield: 94% of **DSC**; mp 209.3–211.5 °C (MeCN).

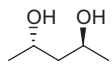
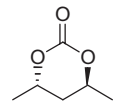
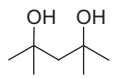
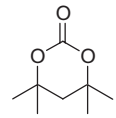
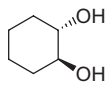
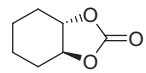
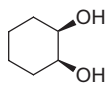
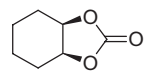
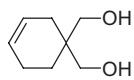
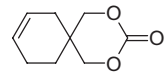
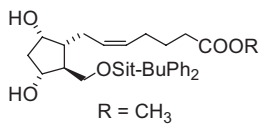
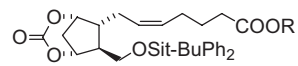
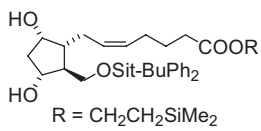
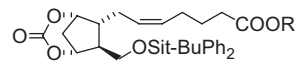
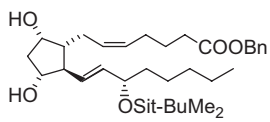
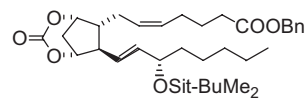
Reaction of **triphosgene** in the presence of pyridine with a variety of 1,2- and 1,3-diols, including hindered tertiary and 1,3-cyclic diols, provides the corresponding cyclic carbonates in high yields. This constitutes a base-labile protecting group in the protection and derivatization of prostaglandin derivatives [654]. Although numerous procedures have been documented for the conversion of 1,2-diols and 1,3-acyclic diols into cyclic carbonates using phosgene, 4-nitrophenyl chloroformate, trichloroacetyl chloride, CDI, or carbon monoxide, employment of these procedures [655] with 1,3-cyclic diols has either proved unsuccessful or very low yielding.

The application of other reported carbonylation methods with **triphosgene** (R_3N; THF, EtOAc or benzene; at 23–50 °C) resulted in either no carbonylation or competing chlorination at the hydroxy positions. Reaction at lower temperatures, which eliminated chlorination side reactions, led to the following general procedure for the carbonylation of diols, as illustrated in Table 4.25.



905 **906**

Tab. 4.25. Synthesis of cyclic carbonates **906** from diols **905** with **triphosgene** [654].

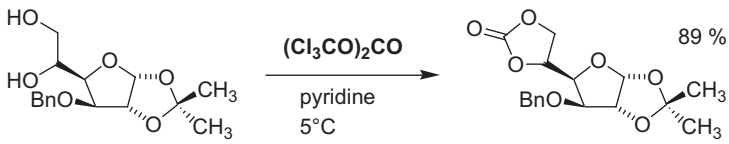
Entry	*Diols 905*	*Carbonates 906*	*Yields (%)*[b]
1			87
2			92
3			84
4			99
5			83
6			85
7			93[c]
8			94

[a] all reactions were conducted under nitrogen atmosphere
[b] yield of pure products after silica gel chromatography and characterization by their ^{1}H NMR, ^{13}C NMR, IR and mass spectra
[c] yield for multigram scale reaction carried out using 10 equiv pyridine and 0.5 equiv triphosgene in dichloromethane (0.08 M)

Typical procedure. *Small-scale carbonylation* of diols [654]: A solution of **triphosgene** (0.5 equiv.) in dichloromethane (1.0 mL) was added dropwise to a solution of pyridine (6.0 equiv.) and the diol **905** (0.5 mmol) in dichloromethane (1.5 mL) cooled to −70 °C. Once the addition was complete, the reaction mixture was allowed to

warm to room temperature. The resulting homogeneous solution was quenched with saturated aq. ammonium chloride solution and the aqueous layer was separated and extracted with dichloromethane. The combined organic extracts were washed with 1 N aq. HCl, saturated aq. $NaHCO_3$ solution, and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Products **906** were purified by flash column chromatography on silica gel.

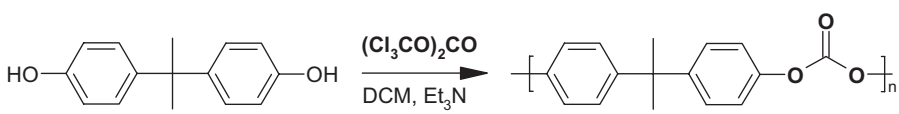
3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose-5,6-carbonate **908** has been synthesized with **triphosgene** in pyridine at +5 °C, whereby the cyclic carbonate was obtained in 89% yield. This method is amenable to scale-up [656].



907 **908**

Typical procedure. *3-O-Benzyl-1,2-O-isopropylidene-α-D-glucofuranose-5,6-carbonate* **908** [656]: A three-necked, round-bottomed flask was charged with 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose **907** (35.94 g, 115.84 mmol) and dry pyridine (110 mL). The solution was cooled to an internal temperature of +5 °C, and then **triphosgene** (11.50 g, 38.76 mmol) was added in portions, using an addition funnel for solids, over a period of 80 min. Stirring was continued for 1 h. The reaction mixture was then diluted with chloroform (550 mL) and washed with water (1 × 220 mL, 1 × 150 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was purified by azeotropic distillation with toluene (2 × 60 mL) and dried in vacuo overnight. The product was purified on a flash chromatography column, eluting with EtOAc/hexanes (25:75 → 100:0). The appropriate fractions were combined and concentrated. The product **908** was isolated in 89% yield.

A *polycarbonate* has been prepared in 75% yield from bisphenol A and **triphosgene** [53]; for literature on polycarbonates, see [657, 687].



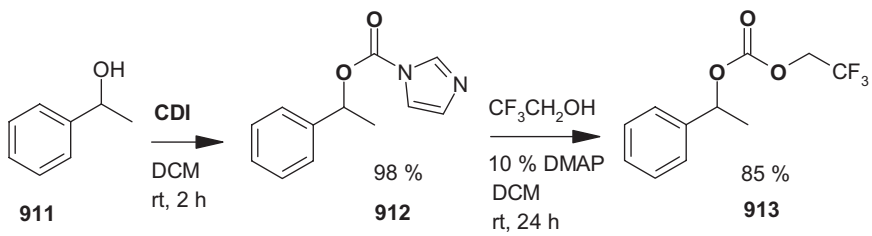
909 **910**

Typical procedure. *Bisphenol A polycarbonate* **910** [53]: To a solution of 2,2-bis-(4-hydroxyphenyl)propane **909** (0.68 g, 3 mmol) in dichloromethane (10 mL) was added triethylamine (0.60 g, 6 mmol), followed by a solution of **triphosgene** (0.30 g,

1 mmol) in dichloromethane (10 mL). The mixture was stirred for 8 h at room temperature, washed with water (3×) and with aq. sodium hydrogen carbonate solution (3×), and dried over sodium sulfate. The solvent was removed in vacuo and the resulting colorless powder was dried under high vacuum; yield 0.74 g (75%) of **910**; IR (KBr): $\nu_{max} = 1770\ cm^{-1}$.

4.3.3.5 Carbonyldiimidazole (CDI)

A simple approach for the resolution of *chiral alcohols* through a lipase-catalyzed transesterification of one enantiomer of the corresponding *trifluoroethyl carbonate* has been described [658]. (*RS*)-*sec*-Phenethyl alcohol is converted to its 2,2,2-trifluoroethyl carbonate with **CDI** in 83% yield.

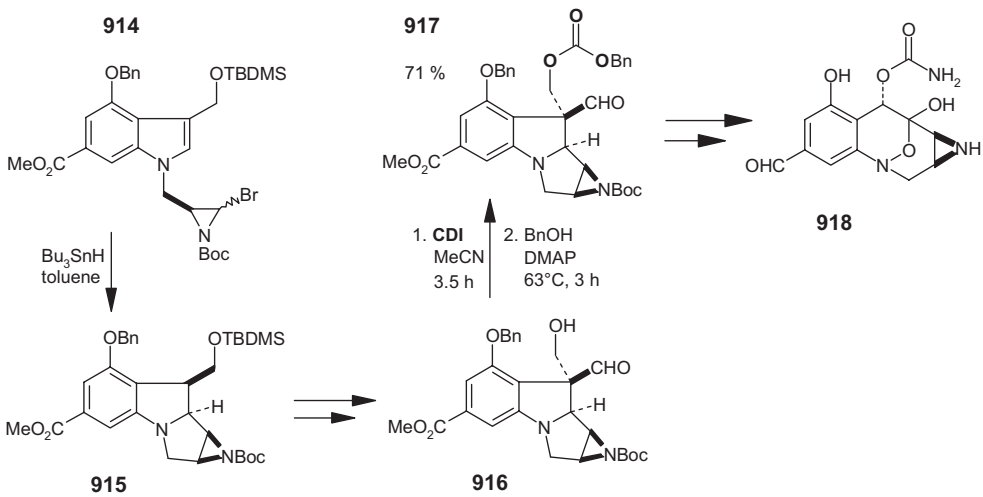


Typical procedure. *(RS)-sec-Phenethyl 2,2,2-trifluoroethyl carbonate* **913** [658]: *(RS)-sec-Phenethyl-1H-imidazole-1-carboxylate* **912**: In a dry 250-mL flask, **CDI** (17.8 g, 110 mmol) was dissolved in dichloromethane (25 mL) with stirring. Further dichloromethane (10 mL) was added, followed by a solution of **911** (12.2 g, 100 mmol) in dichloromethane (10 mL). Upon addition of the alcohol, the solution became light-yellow and boiled for a few minutes. A yellow precipitate of imidazole could be seen in the reaction flask after 10 min. After stirring for 4 h at room temperature, VPC analysis showed that the alcohol had been consumed. The mixture was extracted with distilled water (3 × 20 mL) to remove the imidazole, and then dried (note: if the imidazole is not removed by aqueous extraction, it interferes with the next reaction). Evaporation of the dichloromethane yielded 21.12 g (98%) of **912** as a light-yellow oil, which solidified to a brittle white solid on storage in a freezer.

(RS)-sec-Phenethyl 2,2,2-trifluoroethyl carbonate **913**: Following the procedure described above, **CDI** (8.9 g, 55 mmol) and **911** (6.1 g, 50 mmol) were used to prepare **912**. After extracting with distilled water (3 × 15 mL) and drying, the solution was transferred to a new 250 mL flask, and a solution of 2,2,2-trifluoroethanol (12.31 g, 123 mmol) in dichloromethane (10 mL) was added followed by DMAP (0.61 g, 5 mmol). After 20 h at room temperature, VPC analysis showed that the mixture consisted of >95% carbonate **913**. The mixture was then stirred with 0.05 M HCl (20 mL), and 2.9 M HCl was added dropwise with stirring until pH 2 was reached (17 mL was required). The phases were separated and the organic phase was extracted successively with 20 mL portions of 0.05 M HCl, distilled water, saturated aq. sodium hydrogen carbonate solution, and saturated brine (2 × 20 mL). After

drying, the dichloromethane was evaporated to give 10.52 g (84.8% yield) of a clear liquid, which could be further purified by vacuum distillation; bp 44 °C/ 0.001 mmHg.

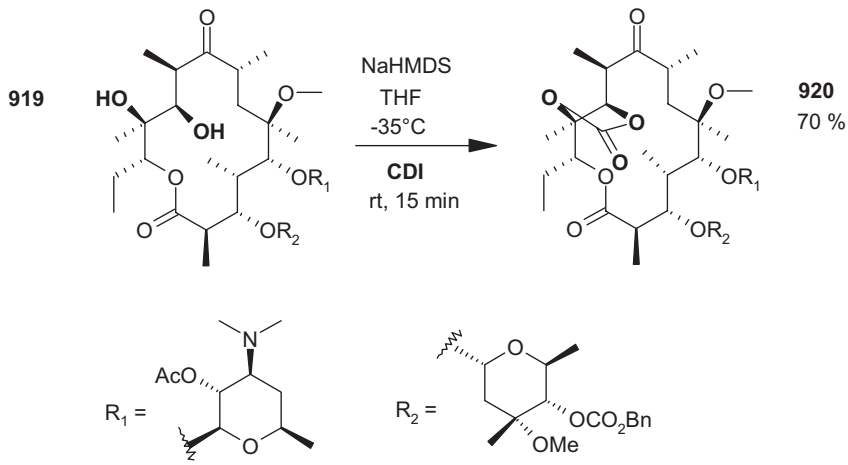
FR-900482 **918**, a *mitomycin*-like antitumor agent, isolated from *Streptomyces sandaensis*, exists as a 2:1 mixture (β:α ether bridge) of stereoisomers at neutral pH, but almost exclusively as the β-isomer in acidic media. An asymmetric route to its core nucleus involves the cyclization of an aziridinyl radical derived from **914** to give a functionalized indole nucleus **915** → **916**. In a further step, a *benzyloxycarbonyl* group is introduced on the primary alcohol function using **CDI** and benzyl alcohol, affording **917** in 71% yield [659].



Typical procedure. *Methyl (1aS,8R,8aS,8bR)-1,1a,2,8,8a,8b-hexahydro-7-benzyloxy-8-(benzyloxycarbonyl)oxymethyl-1-tert-butyloxycarbonyl-8-formylazirino[2′,3′:3,4] pyrrolo-[1,2a]indole-5-carboxylate* **917** [659]: **CDI** (150 mg, 0.925 mmol) was added to a solution of alcohol **916** (385 mg, 0.779 mmol) in acetonitrile (12 mL), and the reaction mixture was stirred for 3.5 h. Benzyl alcohol (600 μL, 5.80 mmol) and DMAP (60.0 mg, 0.491 mmol) were added, and the reaction mixture was heated at 63 °C for 3.0 h. The solvent was then removed, and the residue was submitted to flash chromatography (column prepared with dichloromethane; eluent: 10–25% EtOAc/ hexanes) to give a pale-yellow foam of **917** containing traces of an impurity (349 mg, 71%). This material was suitable for further experiments. A sample of **917** was purified by radial chromatography (EtOAc/dichloromethane, 3:97) for characterization purposes; $[\alpha]^{23}_{D} = +36.0$ ($c = 0.540$, chloroform).

A cyclocarbonate moiety is formed on a macrolide scaffold during the synthesis of an intermediate of *erythromycin A derivatives*. *Erythromycin A* is a safe and effective antibiotic for the treatment of Gram-positive pathogens, and, in particular, it is the drug of choice for the treatment of Legionnaires'disease. *Erythromycin A*, how-

ever, has a short *in vivo* half-life in humans of 2 h. This can be prolonged by its specific derivatization. The intermediate **920** was prepared in 70% yield by cyclocarbonylation of the vicinal diol **919** using **CDI** [660].

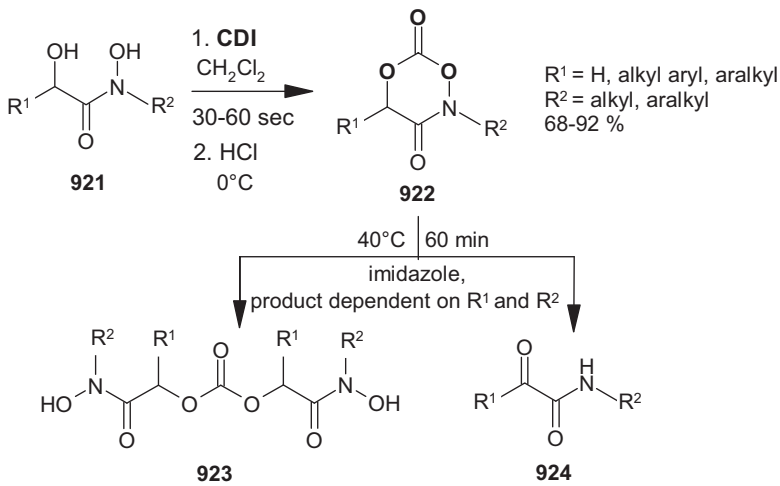


Typical procedure. *2′-Acetyl-4″-O-benzyloxycarbonyl-6-O-methyl-erythromycin A 11,12-carbonate* **920** [660]: A solution of diol **919** (0.51 g, 0.55 mmol) in THF (10 mL) at −35 °C was treated with sodium bis(trimethylsilyl)amide in THF (0.7 mL of a 0.84 M solution; 0.6 mmol). After 10 min, a solution of **CDI** (0.33 g, 2.0 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm to room temperature and kept at this temperature for 15 min. It was then cooled to 0–5 °C (ice/water bath) and 0.5 M NaH_2PO_4 solution was added. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried (magnesium sulfate) and concentrated to a yellow oil. The residue was purified by flash chromatography eluting with acetonitrile/dichloromethane/concentrated ammonium hydroxide (1:1:0.01) to afford 370 mg (70%) of *carbonate* **920**; mp 248–250 °C; IR ($CDCl_3$): $\nu_{max} = 1800\ cm^{-1}$ (cyclic carbonate C=O).

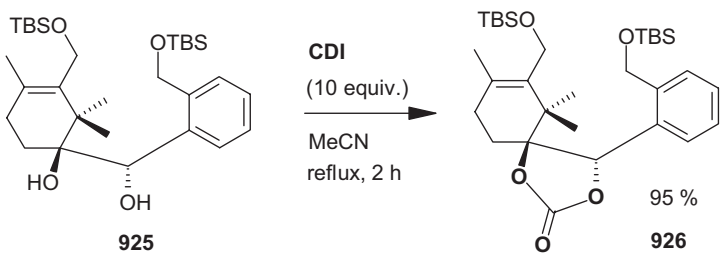
The heterocyclic systems *perhydro-1,5,2-dioxazin-3,6-diones* **922** are synthesized in yields of 68–92% by cyclocarbonylation of hydroxamic acids **921** with **CDI** in very short reaction times of 30–60 s [661]. Prolonged reaction times (60 min) and an increased reaction temperature (40 °C) lead to further reactions forming either linear carbonates **923** or phenylglyoxylamides **924**, depending on the nature of R_1 and R_2.

General procedure. *Preparation of perhydro-1,5,2-dioxazine-3,6-diones* **922** [661]: A solution of **CDI** (10 mmol) in dry dichloromethane (50 mL) is added to a suspension of **921** (10 mmol) in dry dichloromethane (100 mL). After 30–60 s (!), the reaction mixture is extracted with ice-cold 3 N HCl. The organic layer is dried over magnesium sulfate and filtered through silica gel. The solvent is evaporated, the residue

is redissolved in tetrachloromethane/petroleum ether, and the resulting solution is placed in a refrigerator until crystals appear. Yields of **922** are 68–92%.



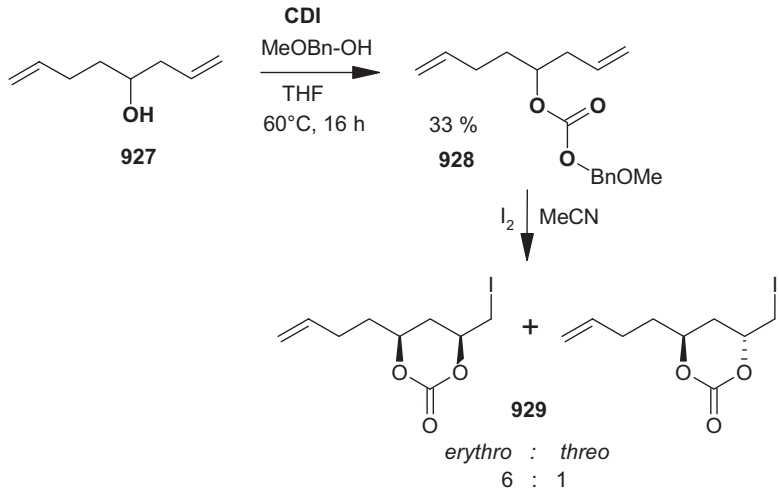
In a taxoid synthesis, a cyclocarbonylation is performed with **CDI** at the 2- and 3-positions of the taxol ring system **925**, prior to closure of the eight-membered B ring, giving **926** in 95% yield [662].



A special type of *iodolactonization* is the *iodocarbonate cyclization* of homoallylic alcohols **927** [663]. *Iodocarbonate cyclization* is an efficient and moderately *erythro*-stereoselective method for the functionalization of homoallylic alcohols with relative 1,3-asymmetric induction.

Typical procedure. *(4-Methoxyphenyl)methyl 1-(2-propenyl)-4-pentenyl carbonate* **928** [663]: A solution of **CDI** (970 mg, 6 mmol) and 4-methoxybenzyl alcohol (830 mg, 6 mmol) in THF (10 mL) was kept at 21 °C for 1 h. 1,7-Octadien-4-ol **927** (768 mg) was then added, and the solution was heated to 60 °C for 16 h. After cooling and dilution with diethyl ether (40 mL), the mixture was washed with water (2 × 40 mL) and saturated NaCl solution (40 mL), dried (magnesium sulfate), concen-

trated, and the residue was chromatographed (hexane/ethyl acetate, 5:1) to give 580 mg (33% yield) of the mixed *carbonate* **928**.

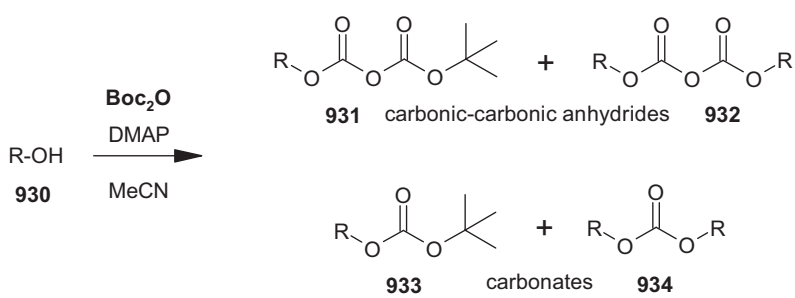


4.3.3.6 Acyl Carbonates

An established method for the activation of carboxylic groups, particularly those of *N*-protected amino acids or peptides, is to form "**mixed anhydrides**" with alkyl chloroformates or dialkyl dicarbonates such as **Boc_2O**. Acyl carbonates can also be essential intermediates in the reactions of anhydrides with carbonates.

Di-*tert*-butyl dicarbonate (Boc_2O)

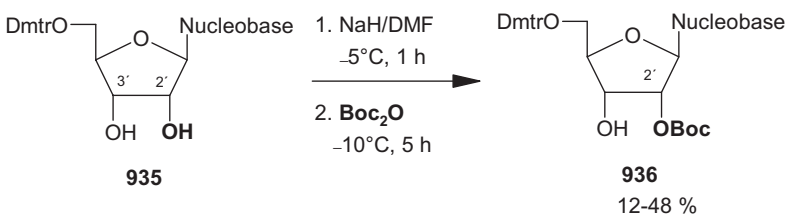
A detailed review on the reactions of **di-*tert*-butyl dicarbonate** (**Boc_2O**), in conjunction with 4-dimethylaminopyridine (DMAP), with amines and alcohols has been given by Hassner and Basel [664]. Many general procedures for reactions of **Boc_2O** with common alcohols **930** are presented therein. In most cases, either *O*-Boc derivatives **933** and/or symmetrical carbonates **934**, or mixed **931** and/or symmetrical carbonic-carbonic anhydrides **932** are formed.



General procedure. *Formation of carbonates* **934** and *O-Boc derivatives* **933** [664]: To a solution of **Boc_2O** (0.8–1.2 equiv.) and an alcohol **930** (0.5 mmol) in MeCN or toluene (5 mL) at room temperature was added DMAP (0.1–0.4 equiv.) or MeIm (1 equiv.). At the end of the reaction, chloroform (10 mL) was added and the solution was washed with 5% aq. HCl (20 mL), dried with $MgSO_4$, and concentrated to give the carbonates.

General procedure. *Formation of mixed and symmetrical carbonic-carbonic anhydrides* **931**, **932** [664]: **Boc_2O** (0.8 equiv.) and an alcohol (0.5 mmol) were dissolved in MeCN (5 mL) at room temperature, and DMAP (0.4 equiv.) was added. The reaction was allowed to proceed for 10–20 min, and then chloroform (10 mL) was added. The solution was washed with 1% aq. HCl (2 × 50 mL) and water, dried with $MgSO_4$, and concentrated to give the carbonic-carbonic anhydrides.

An *O*-protection with **Boc_2O** is performed in the synthesis of 2′-(*tert*-butyloxycarbonyl) ribonucleosides. The Boc residue is a particularly suitable protective group for the 2′-OH position in ribonucleotide syntheses, because it offers increased stability towards bases and resistance to 2′ → 3′ acyl group transfers [665]. Yields range from 12–48% for **936**.

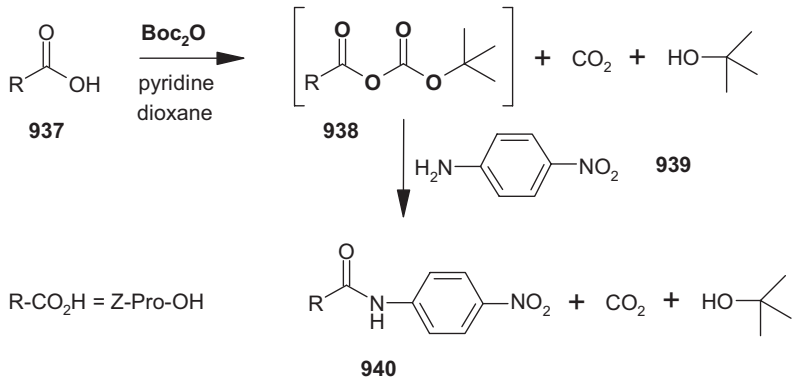


935 **936** 12-48 %

General procedure. *2′-Boc Nucleoside derivatives* **936** [665]: To a stirred solution of the nucleoside derivative **935** (0.6 mmol, 1 equiv.) in dry DMF (6 mL) at −5 °C was added NaH (20 mg, 0.78 mmol, washed 3× with benzene). After 1 h, **Boc_2O** (140 mg, 0.72 mmol, 1.2 equiv.) in DMF (1 mL) was added dropwise at −10 °C over a period of 1 h and the mixture was stirred at this temperature for 4 h (DC control). The reaction was then quenched by adding iced water (1 mL). The mixture was concentrated in vacuo to afford a yellow oil, which was dissolved in dichloromethane (10 mL) and washed with water (2 × 5 mL). The organic layer was dried with Na_2SO_4, the solvent was evaporated in vacuo, and the product was precipitated by trituration with hexane (10 mL). The crude product was purified by column chromatography (20 × 4 cm) on silica gel eluting with CH_2Cl_2/MeOH (99:1). The first fraction contained the by-product 3′-*O*-Boc derivative, while the desired 2′-*O*-Boc nucleoside **936** was eluted with 2% methanol in dichloromethane.

In a convenient one-pot procedure for the preparation of arylamides **940** of *N*-protected amino acids, carboxylic acids **937** are activated with **Boc_2O** in protic solvents in the presence of tertiary amines. Intermediate **938** is an acyl carbonate

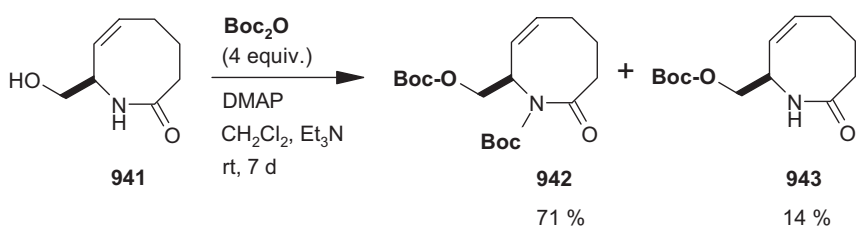
[666, 667]. A wide variety of *N*-protected amino acid arylamides **940** are prepared in this way in good yields.



Typical procedure. *Z-Pro-NHNp* **940** [666]: A solution of Z-Pro-OH **937** (2.7 g, 10.7 mmol), pyridine (0.5 mL), and **Boc_2O** (2.5 g, 11.4 mmol) in dioxane (10 mL) was stirred for 0.5 h (50 mL of CO_2 was evolved). Then, a solution of *p*-nitroaniline **939** (1.5 g, 10.8 mmol) in dioxane (5 mL) was added over a period of 1 h. After stirring for a further 16 h (a small amount of a yellow solid was formed), the mixture was diluted with ethyl acetate, filtered, and washed with water, 5% citric acid, 3% ammonia, water, and brine, dried over $MgSO_4$, and the solvent was evaporated. The residue was crystallized from diethyl ether. Yield 2.6 g (66%) of Z-Pro-NHNp; $R_f = 0.78$ (toluene/chloroform/acetone/isopropanol, 10:6:5:1).

In a similar manner, **Boc_2O** is employed to perform esterifications via highly activated acyl carbonates [668].

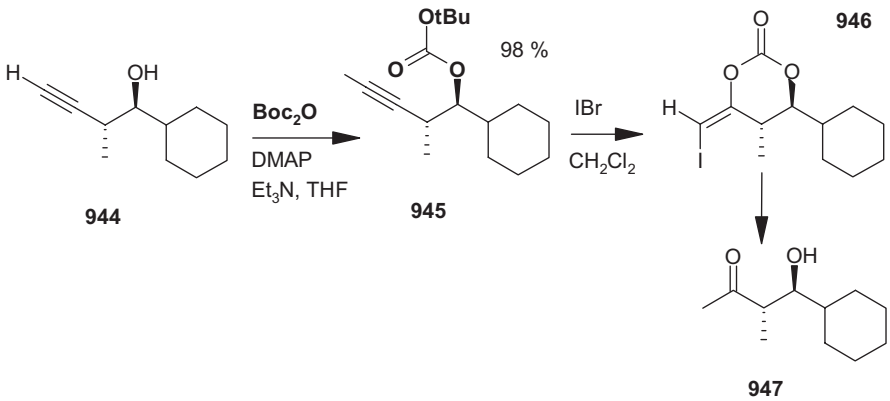
During the synthesis of eight-membered lactam dipeptides, the primary alcohol function is protected with an *O*-Boc residue [669]. The protective group is introduced with **Boc_2O** to afford **942** and **943**.



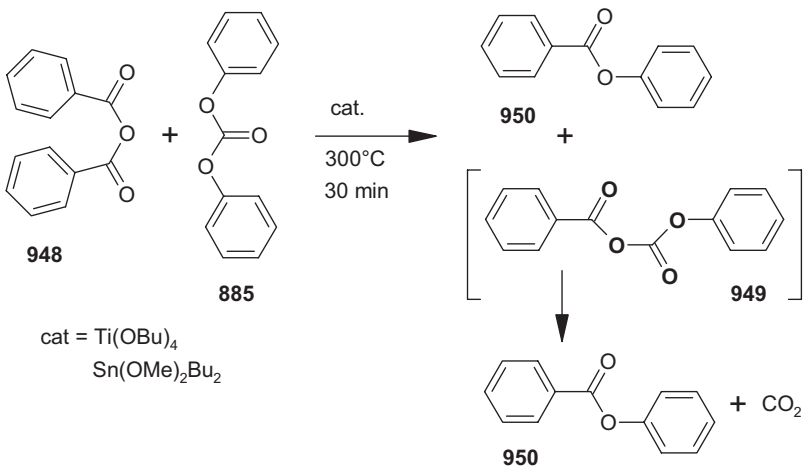
Typical procedure. *(8R)-1-tert-Butyloxycarbonyl-8-tert-butyloxycarbonyloxymethyl-1,2,3,4,5,8-hexahydroazocin-2-one* **942** [669]: A solution of lactam **941** (157 mg, 1.01 mmol), **Boc_2O** (932 mg, 4.14 mmol), DMAP (251 mg, 2.03 mmol), and triethylamine (0.3 mL, 0.138 mmol) in dichloromethane (50 mL) was stirred at room temperature for 7 d. The reaction mixture was then concentrated in vacuo and purified by flash chromatography on silica gel eluting with hexane/ethyl acetate

(10:1 → 0:1) to give bis-Boc-lactam **942** (255 mg, 71%) as colorless crystals; mp 108–110 °C (ethyl acetate/hexane); $R_f = 0.68$ (ethyl acetate/methanol, 10:1); $[\alpha]^{18}_D = -66$ ($c = 0.44$, $CHCl_3$); IR ($CHCl_3$): $\nu_{max} = 1740, 1698\ cm^{-1}$.

An *iodolactonization* reaction of the *iodocarbonate cyclization* type [670], as described in the last example of Section 4.3.3.5, has been performed with homopropargylic alcohols **944** and **Boc_2O**, to afford non-racemic *β*-hydroxy ketones **947** [671]. The *tert*-butyloxycarbonylation reaction with **Boc_2O** furnishes **945** in 98% yield.

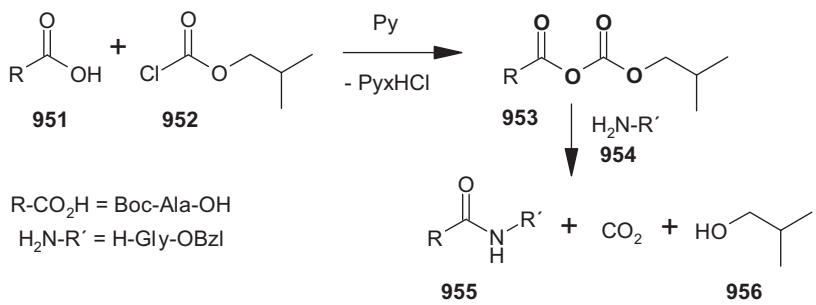


Acyl carbonate **949** is formed as an intermediate in the reaction of anhydride **948** with carbonate **885**. It decomposes to afford the corresponding ester **950**. This exchange reaction between anhydrides and carbonate offers a new, solvent-free method for the synthesis of esters in the presence of Ti- or Sn-based catalysts [672]. Various esters have been synthesized by this method, typically in yields of 80–90%, although the reaction requires high temperatures of about 300 °C, and is thus incompatible with sensitive compounds.



Typical procedure. *Phenyl benzoate* **950** [672]: A glass tube was charged with benzoic anhydride (1.13 g, 5.00 mmol), diphenyl carbonate (1.07 g, 5.00 mmol), and either $Ti(OBu)_4$ (0.020 g, 0.059 mmol) or $Sn(OMe)_2Bu_2$ (0.017 g, 0.059 mmol) as catalyst. The reaction mixture was heated at 300 °C for 30 min. After cooling to room temperature, the crude product obtained was dissolved in dichloromethane (10 mL) and the solution was filtered. The solvent was evaporated and the product obtained after column chromatography (silica gel; CH_2Cl_2/cyclohexane, 4:1) was recrystallized from petroleum ether; yield 95%; mp 69–70 °C; IR (NaCl): $\nu_{max} = 1730\ cm^{-1}$ (ν C=O).

The "mixed anhydride" method is a well-established coupling method in peptide chemistry [673–675]. Activation of the carboxylic group of an *N*-protected amino acid or peptide **951** is achieved by forming an acyl carbonate **953**, the **mixed anhydride**, with an alkyl chloroformate **952**. The acyl carbonate **953** reacts with the amino function of a carboxy-protected amino acid or peptide **954**, forming the peptide bond in **955** in high yield and without racemization. The by-products are gaseous CO_2 and the corresponding low-boiling alcohol **956**, which can easily be evaporated. In contrast, the by-products generated in some other methods are often difficult to remove. This coupling technique using acyl carbonates proved its superiority in the synthesis of analgesic *enkephalin* analogues [675].



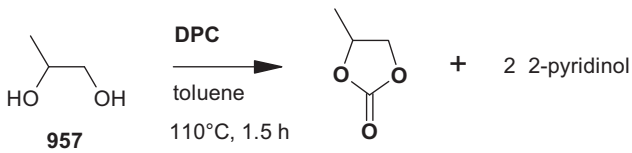
Typical procedure. *Boc-D-Ala-Gly-OBzl* **955** [675]: Boc-D-Ala-OH **951** (2.3 g, 12 mmol) and *N*-methylmorpholine (1.3 mL, 12 mmol) were dissolved in THF (20 mL) and the solution was cooled to −20 °C. **Isobutyl chloroformate 952** (1.6 mL, 12 mmol) was then added, followed, after stirring at −15 °C for 5 min, by a cold solution of H-Gly-OBzl **954**, Ts-OH (4 g, 12 mmol), and further *N*-methylmorpholine (1.6 mL, 12 mmol) in DMF (10 mL). After stirring at −15 °C for 2.5 h, the mixture was diluted with ethyl acetate (250 mL) and extracted with several portions of water, 2 M citric acid, 1 M $KHCO_3$, and 30% NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The residue was recrystallized from ethyl acetate/diethyl ether/petroleum ether (bp 30–60 °C) to give 3.4 g (85%) of Boc-D-Ala-Gly-OBzl **955**; mp 84 °C, $[\alpha]^{20}_D = +11.3$ ($c = 1$, DMF).

4.3.3.7 Carbonates (Interchanges)

Carbonates themselves can be employed to prepare other carbonates by transfer of the carbonyl group to another alcohol function in an interchange reaction.

Di-2-pyridyl carbonate (DPC)

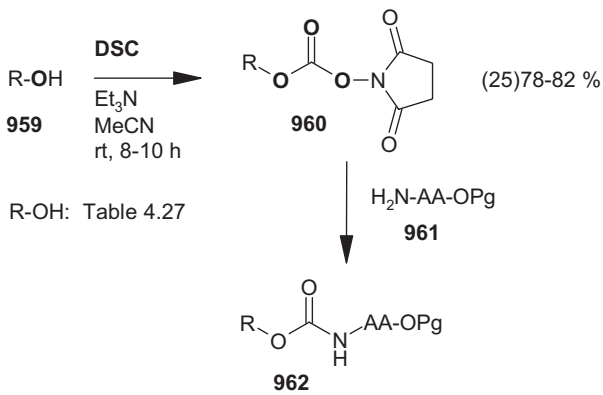
Cyclic carbonates can be conveniently prepared in high yields of 82–96% by the reaction of diols with **DPC**. It is of synthetic significance that the formation of cyclic carbonates in refluxing toluene occurs under essentially neutral conditions [676].



Typical procedure. *4-Methyl-1,3-dioxolan-2-one* **958** [676]: To a stirred solution of 1,2-propanediol **957** (230 mg, 3.0 mmol) in toluene (8 mL) was added **DPC** (670 mg, 3.1 mmol). After stirring at 110 °C for 1.5 h, the reaction mixture was allowed to cool to room temperature, diluted with dichloromethane (40 mL), washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated to dryness under reduced pressure. The crude product was distilled in vacuo in a kugelrohr apparatus to give 4-methyl-1,3-dioxolan-2-one **958** (254 mg) in 83% yield; bp 73–75 °C; IR (film): $\nu_{max} = 1790\ cm^{-1}$.

***N,N′*-Disuccinimidyl carbonate (DSC)**

An efficient method for the synthesis of various mixed succinimidyl carbonates **960**, commonly used for the alkoxycarbonylation of amino acids, has been described. **Disuccinimidyl carbonate** (**DSC**) has been exclusively used as the reagent for the preparation of these carbonates from structurally diverse alcohols [677]. Thus, important reagents for the introduction of *N*-protective groups, such as *Z-OSu*, *Boc-OSu*, and *Fmoc-OSu*, can be prepared (Table 4.26), often in good yields.



Tab. 4.26. Reaction of **DSC** with various alcohols R-OH **959** forming mixed succinimidyl carbonates **960** [677].

Alcohol R-OH 959	*Mixed succinimidyl carbonate 960*	*Yield (%)*
fluoren-9-ylmethanol	Fmoc-OSu	82
benzyl alcohol	Z-OSu	81
2-chlorobenzyl alcohol	2ClZ-OSu	79
2,2,2-trichloroethanol	Troc-OSu	80
2-trimethylsilylethanol	TEOC-OSu	81
cholesterol	ChOC-OSu	78
tert-amyl alcohol	Aoc-OSu	80
tert-butyl alcohol	Boc-OSu	25

General procedure. *Reaction of* ***DSC*** *with alcohols* **959** *forming* **960** [677]: To a solution of the alcohol **959** (1 mmol) in dry acetonitrile (4 mL), **DSC** (for a preparation, see Section 4.3.3.4) (1.5 mmol) and triethylamine (3 mmol) were added. The clear solution was stirred at room temperature for 8–10 h. After completion of the reaction, the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (50 mL), and the solution was washed with 5% aq. $NaHCO_3$ solution (2×8 mL) and water (2×8 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was crystallized from ethyl acetate/light petroleum (bp 40–60 °C) to afford **960** (for yields, see Table 4.26).

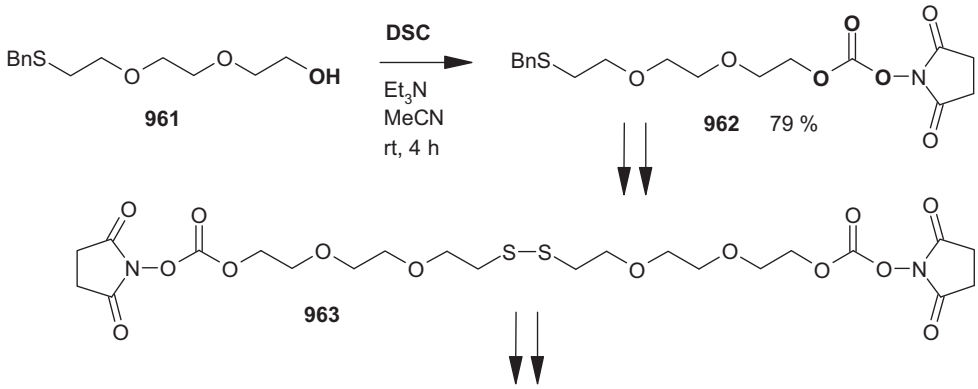
DSC is employed as a coupling agent in the synthesis of thiophospholipids [678]. The attachment of biomembranes to solid supports is important in a variety of areas, from fundamental studies of bilayer structure and function to the creation of biocompatible surfaces and biosensors. **DSC** has been used to couple diacylglycerophosphatidylethanolamine with ω-hydroxypolyethyleneoxydisulfide. The resultant thiophospholipids can be used for anchoring biomembranes to gold surfaces. The reaction of **DSC** with 8-benzylthio-3,6-dioxaoctanol **961** affords **962** in 79% yield [678].

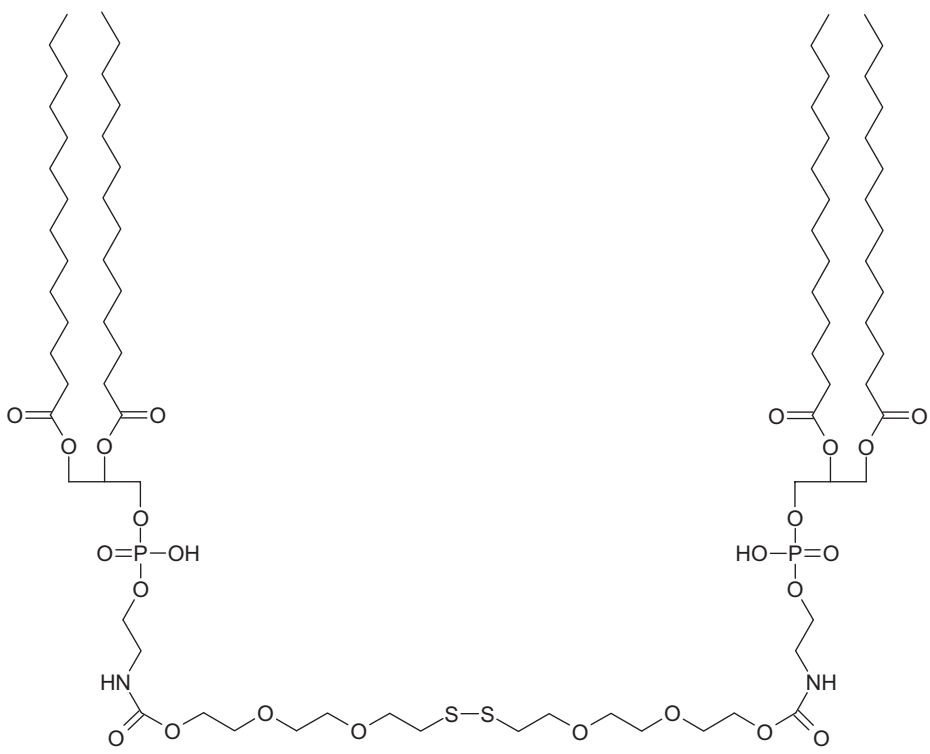
Typical procedure. *N-(8-Benzylthio-3,6-dioxaoctyloxycarbonyloxy)succinimide* **962** [678]: To a stirred solution of 8-benzylthio-3,6-dioxaoctanol **961** (0.52 g, 2.03 mmol) in dry MeCN (5 mL) at room temperature were added **DSC** (for a preparation, see Section 4.3.3.4) (1.04 g, 4.06 mmol) and triethylamine (0.62 g, 0.85 mL, 6.09 mmol). The resulting mixture was stirred at room temperature for 4 h and then the solvent was removed in vacuo. The product was separated by column chromatography on silica gel (ethyl acetate/petroleum ether, 2:1) to give *N*-(8-benzylthio-3,6-dioxaoctyloxycarbonyloxy)succinimide **962** (0.64 g, 1.61 mmol, 79%) as a viscous, pale-yellow oil; MS (EI): $m/z = 396$ [$M^+ - 1$].

Dimethyl carbonate (DMC)

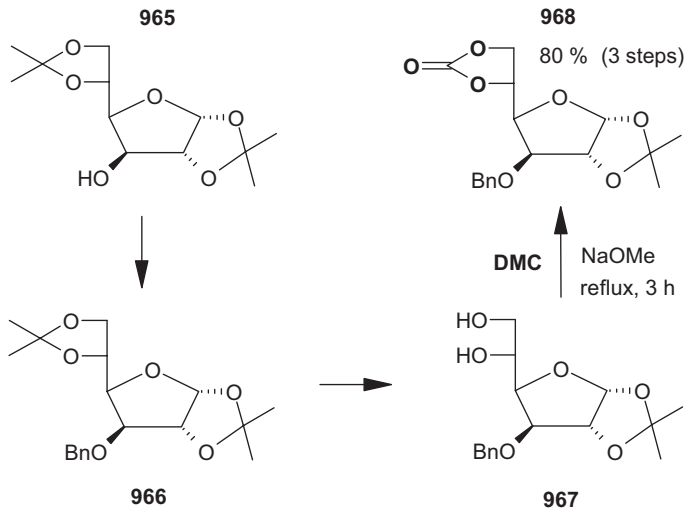
Dimethyl carbonate (**DMC**) has been employed as a carbonyl transfer agent to form a 5,6-cyclocarbonate on 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose

967. Thus, 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose-5,6-carbonate **968** was obtained in 80% yield in three steps on a rather large scale from diacetone glucose **965** [679].

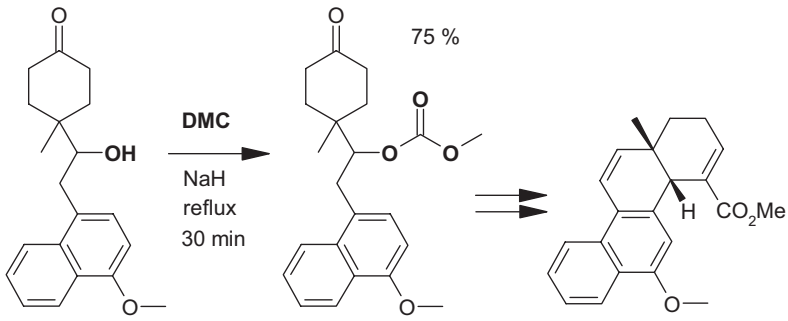




964

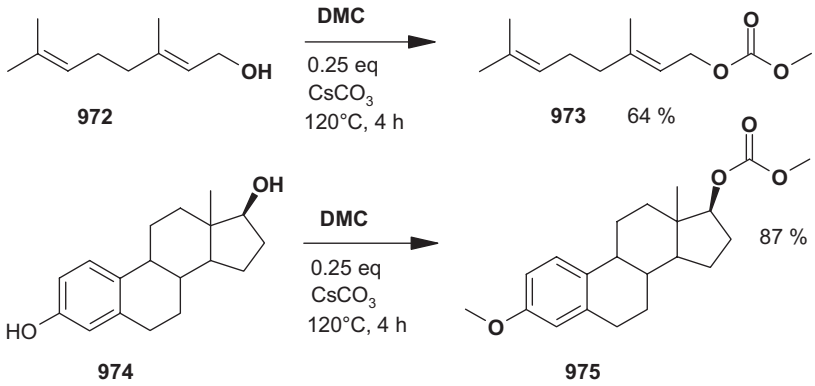


Typical procedure. *3-O-Benzyl-1,2-O-isopropylidene-α-D-glucofuranose-5,6-carbonate* **968** [679]: A solution of diacetone glucose **965** (52 g, 0.2 mol) in dry THF (480 mL) was added dropwise, with cooling and stirring, to a suspension of sodium hydride (50% dispersion in oil, washed with hexane, 10.6 g, 1.1 equiv.) in THF (60 mL). Benzyl bromide (26 mL, 1.1 equiv.) and tetrabutylammonium iodide (0.6 g) were added and the mixture was refluxed for 45 min. The solution was then cooled, filtered through Celite, and concentrated to a yellow syrup (79 g), which was used directly in the next step. The crude **966** (79 g) was dissolved in methanol (400 mL) containing concentrated hydrochloric acid (2.2 mL) and water (40 mL) and stirred at room temperature. After 20 h, TLC (diethyl ether/hexane, 2:1) showed that the starting material ($R_f = 0.9$) had been consumed and that one product ($R_f = 0.2$) had been formed. The solution was neutralized with aq. ammonia (specific gravity 0.88) and concentrated to a syrup, which was dissolved in ethyl acetate (400 mL) and washed with water (2 × 400 mL). Evaporation of the solvent gave a crude syrup of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose **967**, which was dissolved in **DMC** (400 mL) and refluxed for 3 h with sodium methoxide (10 g, 185 mmol). The reflux condenser was then replaced with a stillhead and heating was continued until the stillhead thermometer reached 90 °C (approximately 2 h). Further **DMC** was added at intervals to keep the volume of the reaction mixture constant. At this stage, TLC showed that the conversion to carbonate **968** was complete. The solution was cooled, washed with water (500 mL), and concentrated to a syrup, which crystallized spontaneously upon addition of diethyl ether to afford *3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose-5,6-carbonate* **968** (54 g, 80% yield based on **965**), as colorless crystals; mp 119–120 °C, $[\alpha]^{20}_D = -52.2$ ($c = 1.15$ in $CHCl_3$).



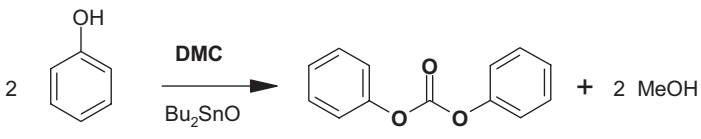
969 970 971

An efficient approach to highly functionalized hydrochrysenes **971** relies on an intramolecular Friedel–Crafts alkylation. The corresponding intermediate is a carbonate **970**, which is prepared in 75% yield from the alcohol **969** using **DMC** as the carbonylating reagent [680].



972 **973** 64 % **974** **975**

DMC has proved to be a reagent capable of accomplishing *two different* reactions at the same time. The aliphatic alcohol groups in geraniol **972** and estradiol **974** are carbonylated affording methyl carbonates **973** (64% yield) and **975** (87% yield), respectively; in the case of estradiol **974** the phenolic hydroxy function is simultaneously methylated to give the ether moiety in **975** [681].



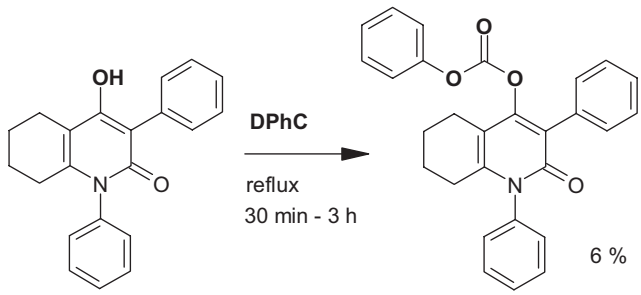
87 % **DPhC**

In a technical process for the production of diphenyl carbonate (**DPhC**), an 87% yield of the product is obtained by employing **DMC** in the presence of Bu_2SnO as catalyst [682–684].

Reviews on **DMC** chemistry are given in [633, 685].

Diphenyl carbonate (DPhC)

In a synthesis of isocoumarins, intermediates **977** are obtained, albeit in modest yields, by carbonylation of pyridones **976** with **diphenyl carbonate** (**DPhC**) [686].



976 **977**

General procedure. *Reaction of phenylmalonyl heterocycles with* **DPhC** [686]: The malonyl heterocycle (for example, **976**) (0.01 mol) and **DPhC** (4.3 g, 0.02 mol) are refluxed for 0.5–3 h and then treated with 10% aq. sodium carbonate solution (200 mL) to remove any remaining starting material. The residue is extracted with boiling ligroin and the extract is filtered. The solvent is evaporated from the filtrate and the residue is triturated with a small amount of cold methanol to crystallize the *carbonate* (for example, **977**).

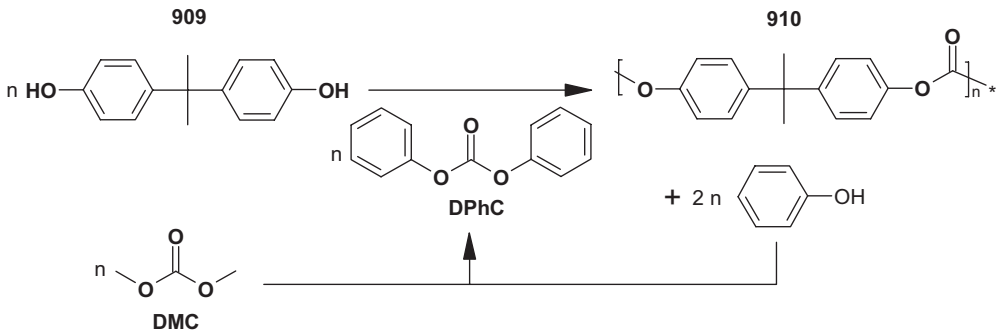
977: mp 141 °C; IR (KBr): $\nu_{max} = 1780, 1640\ cm^{-1}$.

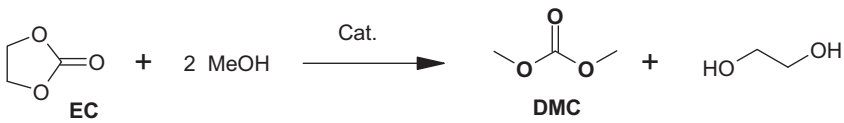
Diphenyl carbonate (**DPhC**) is employed in the production of polycarbonates, for which there is a huge and fast-growing market. Polycarbonates are excellent engineering thermoplastics and substitutes for metals and glass because of their good impact strength, heat resistance, and transparency [687]. A number of synthetic routes for producing polycarbonates have been described in the literature [685]. Two current commercial methods are the interfacial polycondensation of diphenols with **phosgene** and the transesterification of diphenols with **DPhC**. The **DPhC** process for the production of polycarbonates **910** from bisphenol A **909** of Asahi Chemical and Enichem requires no solvent or phosgene, and the by-product phenol can be recycled. In this process, **DPhC** is produced by transesterification from DMC [685, 688].

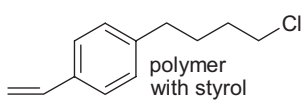
Ethylene carbonate (EC)

The most important cyclic carbonate is **ethylene carbonate** (**EC**). It is employed as a promoter in the curing of phenol-formaldehyde or epoxy resins and, in huge quantities, as a starting material for the production of **DMC** and **DPhC**. Such pro-

cesses feature widely in recent patent literature, whereas in this book only a selection of some of these will be given.



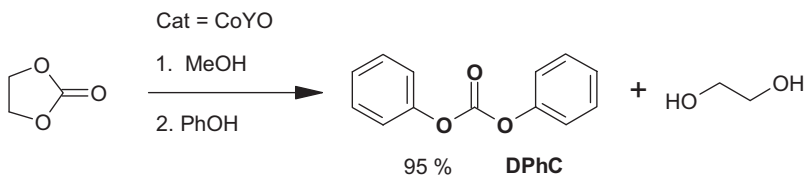


Cat.	yield of **DMC** [%]	patent appl. year
Y_2O_3	-	2001
HO-Al=O (Boehmite)	-	2001
Na_2WO_4	-	2000
MoO_3	-	2000
zeolite	-	2000
 polymer with styrol	82	2000
NaOH	99	1997
CoYO	-	1997
ZnO	73	1996
MnO	69	1996
Dowex MSA 1	99	1992

The catalysts applied include sodium hydroxide [689], polymer-supported catalysts such as Dowex MSA 1 [690] or the polymer from styrol and 4-(4-chlorobutyl)styrol [691], zeolites [692], Boehmite [693], and metal-based catalysts such as Y_2O_3 [694], Na_2WO_4 [695], MoO_3 [696], CoYO [697], ZnO [698], and MnO [699].

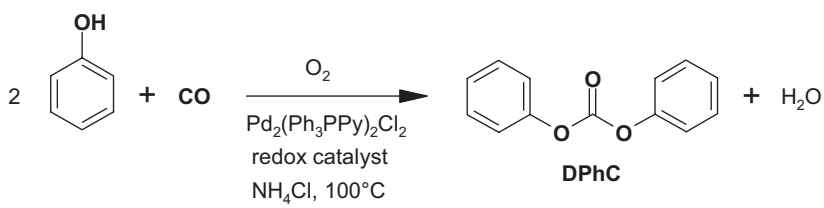
An investigation of eight classes of catalysts (exchange resins, zirconium, titanium, and tin homogeneous catalysts, Group VB and VIB compounds, alkali metal silicates, zeolites, acidic resins, tertiary phosphine polymer catalysts) for **DMC** production from **EC** is given in [700]. The relative performance advantages and mechanistic pathways of these different classes of catalysts are compared and discussed.

The above presented process with CoYO as catalyst is employed in the production of **DPhC** in 95% yield from **EC** [701]. It is a continuous process using a fixed bed reactor at 130 °C, a pressure of 9 kg cm^{-2}, and an LHSV of 3 h^{-1}.



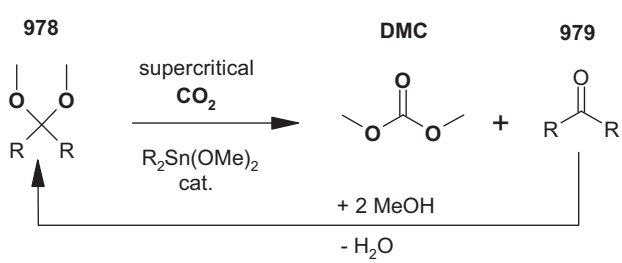
4.3.3.8 Carbon Oxides, CO, CO_2, and MCO_3

Another route to **DPhC**, besides transesterification of **DMC** or **EC** with phenol as in Section 4.3.3.7, is the oxidative carbonylation of phenol with **carbon monoxide** (**CO**) and aerial oxygen, as catalyzed by a Pd dinuclear complex and a redox catalyst [702, 703].



The reaction proceeds smoothly on Pd dinuclear complexes bridged by the pyridylphosphine ligand, i.e. $[Pd_2(Ph_2Ppy)_2X_2]$, in the presence of a redox catalyst, ammonium halide, **CO**, and air at 100 °C; the TOF reaches 19.21 (mol-DPhC/mol-Pd h).

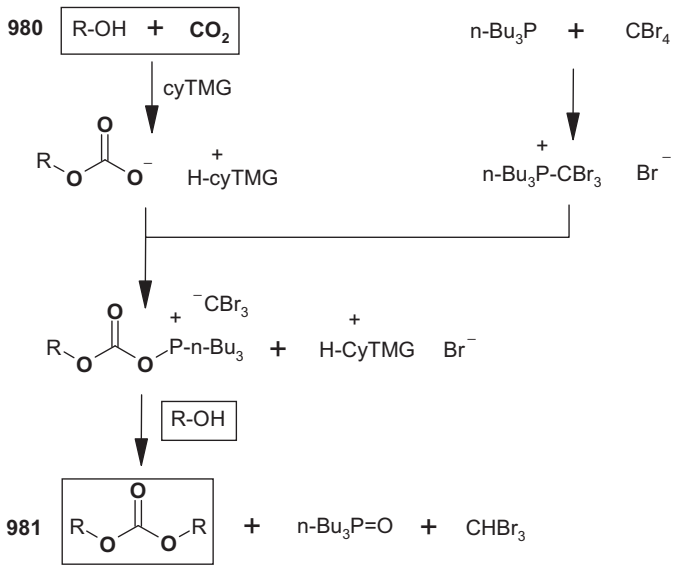
Carbon dioxide (**CO_2**) can be reacted with alcohols under various conditions to form dialkyl carbonates. One of the most attractive synthetic goals starting from CO_2 is DMC. An approach is the reaction of dehydrated derivatives of methanol (ortho ester and acetals **978**) with supercritical **CO_2** [704–706].



The reaction of acetals is especially attractive because the starting material is much less expensive compared with ortho esters, and the co-produced carbonyl compounds **979** can be recycled. Hence, the reaction can be regarded as a synthesis of **DMC** from **CO_2** and methanol. In these reactions, carbonate complexes generated by CO_2 insertion into the tin–oxygen bond of $R_2Sn(OMe)_2$ are proposed as key intermediates [704, 706].

Another route to the synthesis of dialkyl carbonates from **CO_2** is the reaction with alcohols and tertiary amines mediated by acetylene. As alcohols, ethanol, isopropanol, and allyl alcohol have been employed. The resulting dialkyl carbonates are obtained in yields of 12–30% [707].

A direct condensation reaction of **CO_2** with alcohols, using a trisubstituted phosphine/tetrabromomethane/base system to prepare dialkyl carbonates, has been developed. Optimal conditions require CyTMG as a strong, hindered, nonnucleophilic, and highly polarizable base, which is more effective than other bases such as DBU. The solvent of choice is DMF [708]. Yields of dialkyl carbonates **981** derived from various primary alcohols **980** are 54–91%; from secondary alcohols **980** they are 14–22%.



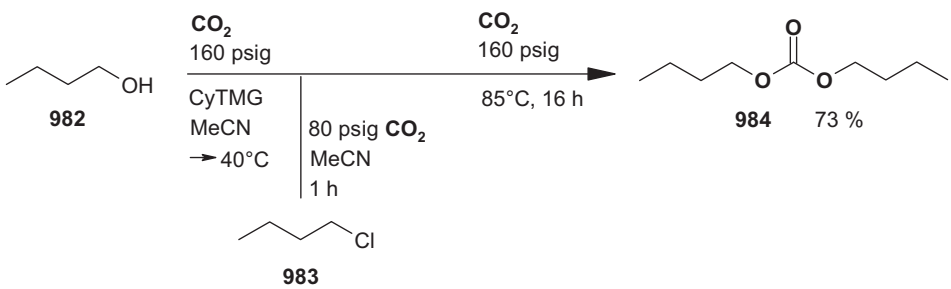
Typical procedure. *Dibenzyl carbonate* **981** [708]: To a stirred solution of benzyl alcohol (0.216 g, 2.00 mol), tributylphosphine (0.303 g, 1.50 mmol), and CyTMG (0.394 g, 2.00 mmol) in DMF (2.00 mL), **CO_2** was added at room temperature. After 15 min, tetrabromomethane (0.663 g, 2.00 mmol) was added, the reaction vessel was sealed, and the contents were stirred for 2 h. Thereafter, the reaction mixture was diluted with ethyl acetate, washed successively with 0.5 M aqueous HCl and saturated aq. $NaHCO_3$ solution, and dried over Na_2SO_4. Diphenylmetha-

nol was added to the organic solution as an internal standard and the yield of dibenzyl carbonate was determined from the relative integrals of a methylene peak of the carbonate and a methine peak of diphenylmethanol in the ^{1}H NMR spectrum of the ethyl acetate solution. Dibenzyl carbonate, prepared by a larger scale reaction of **CO_2** with benzyl alcohol (1.08 g, 10.0 mmol), was isolated by column chromatography (cyclohexane/ethyl acetate, 50:1) in 67.3% yield (0.816 g); IR (NaCl): $\nu_{max} = 1747\ cm^{-1}$.

A series of methods has been published for the preparation of dialkyl carbonates from **CO_2** and **carbonate salts** using alkyl halides. Carbonic esters can be prepared in a phase-transfer catalytic reaction from primary alkyl halides and a mixture of dry potassium hydrogen carbonate and dry **potassium carbonate** in non-polar solvents. Yields of dialkyl carbonates obtained are 67–83%. The conversion is ineffective in the absence of the hydrogen carbonate and or a phase-transfer catalyst (PTC) [709].

General procedure. *Dialkyl carbonates* [709]: Dry potassium hydrogen carbonate (10.0 g, 0.01 mol) is mixed with dry **potassium carbonate** (14.0 g, 0.1 mol). To this mixture is added a solution of aliquat 336 (400 mg, 1 mmol) and alkyl halide (0.1 mol) in toluene or petroleum ether (10 mL). The reaction mixture is stirred at 100 °C for 8–15 h, then filtered and concentrated, and the residue is fractionated. Dialkyl carbonates are purified by distillation in a kugelrohr apparatus or by recrystallization.

Dialkyl carbonates can also be prepared in a three-component coupling system of aliphatic alcohol/**CO_2**/alkyl halide under a pressure of CO_2 (160 psig) and in the presence of a peralkylated guanidine. In this way, di-*n*-butyl carbonate **984** is obtained in 73% yield (by GC) [710].



982 **983** **984** 73 %

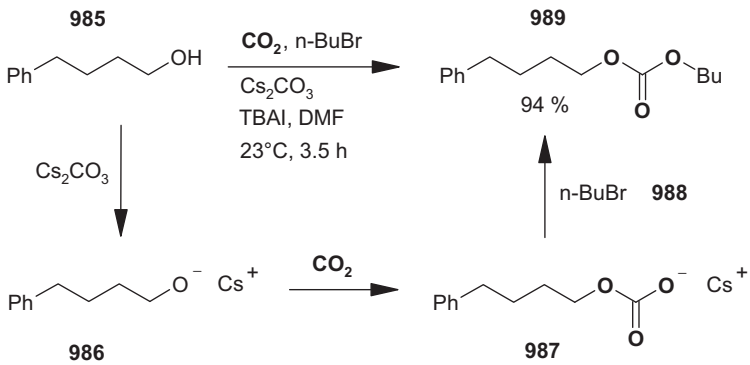
Typical procedure. *Di-n-butyl carbonate* **984** [710]: A 160 mL Parr autoclave was charged with butanol **982** (2.22 g, 0.03 mol), *N*-cyclohexyl-*N*′,*N*′,*N*″,*N*″-tetramethylguanidine (CyTMG; 6.9 g, 0.035 mol), and acetonitrile (30 mL). The autoclave was attached to a pressure head, and 160 psig **CO_2** was introduced with stirring at room temperature. An exothermic reaction ensued, leading to an increase in temperature to ca. 40 °C. In a Fischer–Porter bottle was placed a solution of 1-chlorobutane **983** (8.33 g, 0.09 mol) in acetonitrile (10 mL). This bottle was attached to

Tab. 4.27. Carbonate formation using alcohols, halides, and CO_2 in the presence of Cs_2CO_3 [711].

Alcohol (R-OH) 985	*Halide (R′-X) 988*	*Time (h)*	*Yield (%)*
4-phenylbutanol	*tert*-butyl 2-bromoacetate	5	95
	benzyl chloride	2.5	94
	allyl bromide	4	91
	sec-butyl bromide	23	98
	n-butylbromide	4.5	92
2-phenyl-propan-1-ol	*tert*-butyl 2-bromoacetate	5	96
	benzyl chloride	3	98
	n-butyl bromide	5	96
	MPMCl	3	92

a pressure head, and 80 psig CO_2 was introduced above the solution. After 1 h, the solution of 1-chlorobutane was added in one portion under 80 psig CO_2 to the pre-formed carbonate anion solution generated in the autoclave. After the addition, the pressure was increased to 160 psig with CO_2, and the reaction mixture was warmed to 85 °C for 16 h. Thereafter, the reaction mixture was allowed to cool to room temperature, and then the pressure was released. An aliquot was removed, diluted with diethyl ether, and $CyTMGH^+Cl^-$ was filtered off; by GC analysis using biphenyl as an internal standard, the yield of dibutyl carbonate **984** was calculated as 73%; oil; IR (film): $\nu_{max} = 1746\ cm^{-1}$; MS (FAB): $m/z = 175\ [MH^+]$.

An approach for the synthesis of *mixed* dialkyl carbonates **989** employs the above three-component coupling system of aliphatic alcohol/CO_2/alkyl halide in the presence of Cs_2CO_3, but without CO_2 pressure. This method shows great versatility in terms of the alcohols **985** and alkyl halides **988** that can be used (see Table 4.27), reaction times are 2.5–23 h, and the yields of the resulting mixed dialkyl carbonates **989** are 91–98% [711].

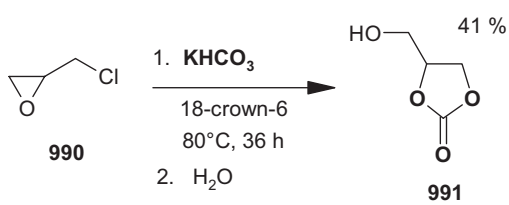


In summary, a three-way coupling is performed using alcohols **985**, **carbon dioxide**, and halides **988**, leading to the exclusive synthesis of mixed alkyl carbonates **989**.

Here, the use of cesium bases is crucial due to the inherently enhanced nucleophilicities of the corresponding cesium alkoxides generated in situ from various aliphatic alcohols. Primary and secondary alcohols are easily incorporated into **CO_2**, and then the products, in turn, react with diverse halides, including secondary bromides, which are usually resistant to alkylations due to eliminations. The stereochemical sense is lost to a negligible extent, if at all. Using chiral templates, carbonates are formed efficiently without any elimination or hydrolysis, and little or no racemization is observed [711].

Typical procedure. *O-4-Phenylbutyl-O′-butyl carbonate* **989** [711]: To 4-phenyl-1-butanol **985** (100 mg, 0.67 mmol) in anhydrous DMF (1.6 mL, 0.4 M) were added cesium carbonate (625 mg, 2.10 mmol, 3 equiv.) and tetrabutylammonium iodide (208 mg, 0.67 mmol, 1 equiv.). **CO_2** gas (flow rate 25–30 mL min^{-1}) was bubbled into the reaction mixture for 2–3 min, and then 1-bromobutane **988** (274 mg, 0.22 mL, 2.0 mmol) was added to the suspension. The reaction proceeded at ambient temperature with **CO_2** gas bubbling for 3.5 h, after which time the starting material (4-phenyl-1-butanol) had been consumed. The reaction mixture was then poured into water (30 mL) and extracted with hexanes/EtOAc (3:1 *v*/*v*, 60 mL). The organic layer was washed with water (2 × 30 mL) and brine (30 mL), and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by flash column chromatography (hexanes/EtOAc, 9:1 *v*/*v*) afforded *O*-4-phenylbutyl-*O′*-butyl carbonate **989** (157 mg, 94%) as a colorless oil.

Cyclic carbonates can be obtained by reactions of alkali metal carbonates with *epi*-halohydrins. 1-Chloro-2,3-epoxypropane **990** reacts with **potassium hydrogen carbonate** to form 4-hydroxymethyl-1,3-dioxolan-2-one **991** in 41% yield [712].



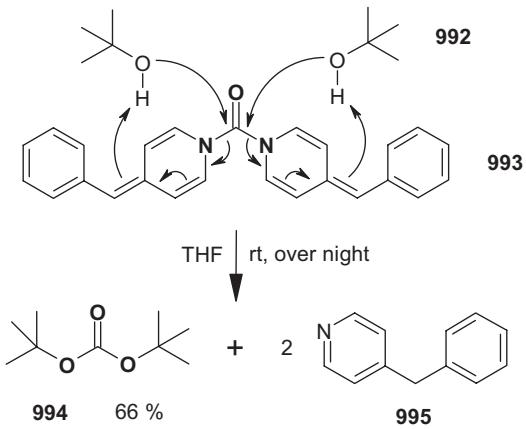
Typical procedure. *4-Hydroxymethyl 1,3-dioxolan-2-one* **991** [712]: A stirred mixture of **potassium hydrogen carbonate** (10.0 g, 0.1 mol), 18-crown-6 (0.2 g, 0.76 mmol), and 1-chloro-2,3-epoxypropane **990** (27.6 g, 0.3 mol) was heated at 80 °C for 36 h. After cooling and removal of the potassium salt by filtration, the organic layer was washed with water and **991** was distilled at 152–160 °C/0.6–0.8 mmHg; yield 4.83 g (41%); IR: ν_{max} = 3500, 1800 cm^{-1}.

The stereoselective conversion of 1,2-diols into alkane-1,2-diyl carbonates at room temperature by adding them to acetonitrile solutions containing CO_3^{2-} or HCO_3^- anions in the presence of tetraalkylammonium cations has been described. These solutions can be prepared by electrochemical or chemical routes [713]. The

O_2^-/CO_2 system, originating from electrochemical single-electron reduction of dioxygen in dipolar aprotic solvents and in the presence of CO_2, converts primary and secondary alcohols bearing a leaving group at the α or β position into the corresponding cyclic carbonates in high yields [714].

4.3.3.9 Ureas

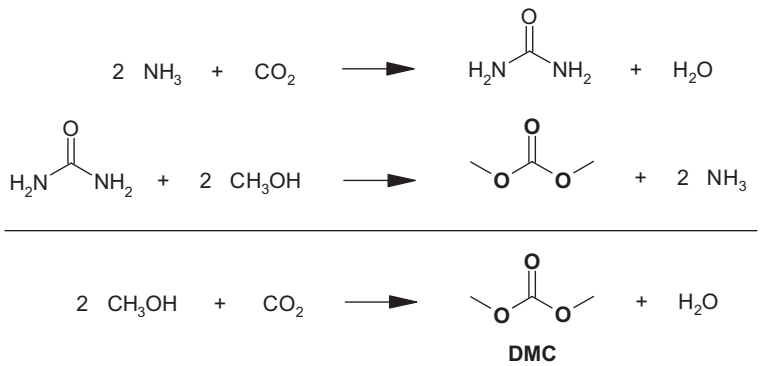
A method for the synthesis of dialkyl carbonates makes use of **1,1′-carbonyl-bis(4-benzylidene-1,4-dihydropyridine)** **993** as a reagent. The required activation energy for this reaction is provided by the aromatization energy of the 1,4-dihydropyridine system forming the 4-substituted pyridine **995**. Di-*tert*-butyl carbonate **994** can be obtained in 66% yield [715].



General procedure. *Di-tert-butyl carbonate* **994** [715]: To a solution of the tertiary alcohol **992** (45 mmol) in absolute THF (25 mL) was added sodium (120 mg) and the mixture was stirred for 4 h. Then, under nitrogen, a solution of **1,1′-carbonyl-bis(4-benzylidene-1,4-dihydropyridine)** **993** (7.29 g, 20 mmol) in THF (50 mL) was added dropwise and the mixture was stirred overnight. After evaporation of the solvent, the residue was redissolved in diethyl ether (50 mL). This ethereal solution was washed with aq. sodium hydrogen carbonate solution and dried over magnesium chloride. The solvent was evaporated and the residue was treated with iodomethane (5 mL) to react with 4-benzylpyridine **995** overnight. Diethyl ether (50 mL) was then added and the 4-benzyl-1-methylpyridinium iodide deposited was filtered off. The filtrate was concentrated and the residue was distilled in vacuo or recrystallized from ethanol or ethanol/water (**994**). For **994**: yield 66%; mp 36–38 °C; IR (Nujol): $\nu_{max} = 1730\ cm^{-1}$.

Recent patent literature deals with processes for producing dimethyl carbonate (**DMC**) in high yield from **urea** and methanol [716, 717]. There is a need for low-cost **DMC**, since it is becoming more and more important in fuel applications as a

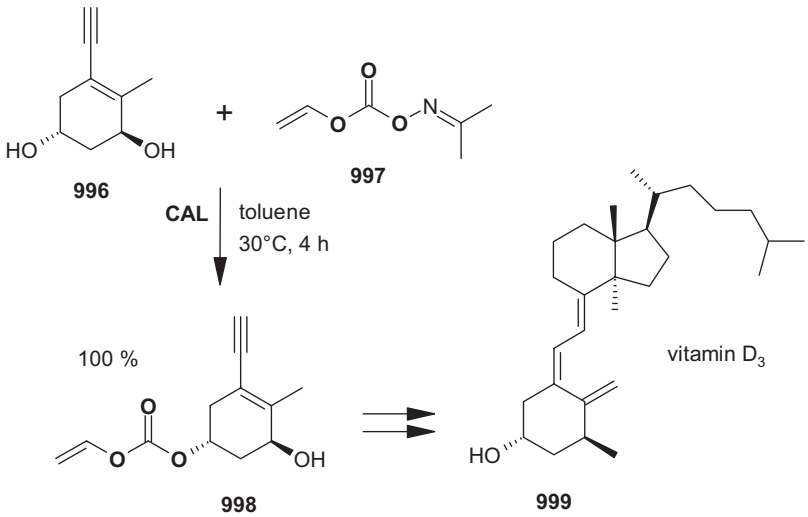
gasoline additive, especially since the recent banning by California of methyl *tert*-butyl ether (MTBE). **DMC** has many desirable properties: almost three times the oxygen content of MTBE, a good octane number for blending (RON of 130), lower volatility than MTBE, and biodegradability [718].



The tin-catalyzed reaction of methanol with urea to give **DMC** is a well-known synthesis; however, the yields are low because intermediate methyl carbamate is prone to decomposition into isocyanic acid or isocyanuric acid. Ryu has found that by using high-boiling, organic electron-donor solvents, such as triethylene glycol dimethyl ether (triglyme), in conjunction with tin catalysts, and continually distilling off product **DMC** as it is made, high yields of **DMC** can be realized. In an example given in the patent, the reactor (which is also the distillation still) was charged with methyl carbamate (125 g), methanol (120 g), triglyme (80 g), and dibutyltin dimethoxide (25 g). The still temperature was maintained at 349–357 °F (176–181 °C) by controlling the overhead temperature. The flow rate of overhead liquid product was maintained at 2 mL min^{-1}. A feedstock made up of urea (106 g) dissolved in methanol (2200 g) was continually fed to the still to maintain a constant liquid level. After 12 h, urea/methyl carbamate conversion was 98.3%, and **DMC** selectivity was 98.2%. The inventor notes that by integrating such a **DMC** plant with a urea facility, costs could be optimized further – the ammonia by-product could be recycled to the urea process. In effect, this process would allow the production of **DMC** from methanol and carbon dioxide [716].

4.3.3.10 Enzyme Catalysis

The A-ring precursor **999** of vitamin D has been prepared by selective alkoxycarbonylation using **enzymes** in organic solvents. *Candida antarctica* lipase (**CAL**) is found to be the best catalyst in toluene solution. Other suitable enzymes are **PSL** and **CVL**, and alternative solvents are THF and 1,4-dioxane; the yields of alkoxycarbonylation products depend strongly on the conditions and amount to 17–100%. Regioselective alkoxycarbonylation occurs only at the C-5-(*R*) hydroxy group [719, 720].



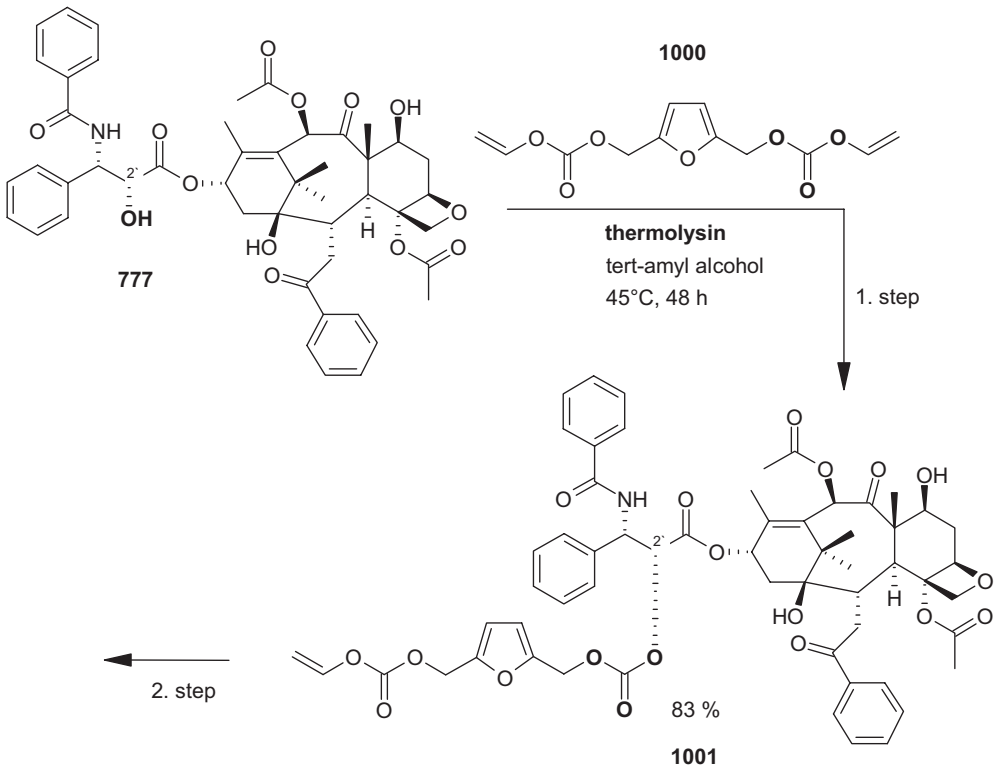
Typical procedure. *(3S,5R)-1-Ethynyl-3-hydroxy-2-methyl-5-vinyloxycarbonyl-1-cyclohexene* **998** [720]: To a solution of **996** (10 mg, 0.066 mmol) in toluene (2.5 mL) was added **CAL** (45 mg) and *acetone O-vinyloxycarbonyloxime* **997** (94.5 mg, 0.66 mmol). The suspension was shaken at 30 °C for 4 h (the progress of the reaction was followed by TLC and GC analysis until no further reaction was apparent). After removal of the enzyme by filtration, evaporation of the solvent, and ^{1}H NMR analysis, the residual mixture was purified by HPLC (Spherisorb W, 1 × 25 cm, 5 μm silica gel 60 column, 15% ethyl acetate/hexanes, 4 mL min^{-1}) to give 100% of the monovinyloxycarbonylation product **998**.

Enzymatic acylation in organic solvents has also been employed to synthesize water-soluble *Paclitaxel* derivatives. Thus, potential new *prodrugs* can be generated possessing high solubility in water. The approach involves a two-step enzymatic acylation. In the first step, paclitaxel **777** is reacted with a bifunctional acylating reagent **1000**, catalyzed by **thermolysin** (from *Bacillus thermoproteolyticus rokko*) to give an activated acyl derivative **1001** (83% conversion), which is then used as a complex acyl donor in the second step [721].

4.3.4 Ureas

Ureas have found use in a wide variety of areas ranging from applications as active pharma ingredients [722] and dyes for cellulose fibre to their use as antioxidants in gasoline, corrosion inhibitors, and intermediates for the production of carbamates, which represent raw materials for agrochemicals. Their biological activities as plant growth regulators, agroprotectives, as well as tranquillizing and anticonvulsant agents are also important [723]. Potent HIV-1 protease inhibitors

having the structure of substituted ureas with amino acid groups have been reported [724, 725].



Ureas have hitherto been synthesized mainly by methodologies based on the use of traditional reagents such as **phosgene** and **isocyanates**. In the last few years, however, these reagents have been increasingly substituted by alternative cleaner and inherently safer compounds, since the goal of modern environmentally friendly synthetic chemistry is the development and optimization of reaction conditions to reduce or eliminate the use and production of hazardous materials while maximizing energy usage [726].

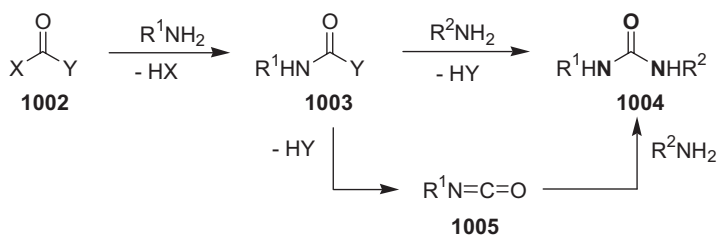
The majority of the most important of the wide variety of methods for preparing mono-, di-, and trisubstituted ureas [723, 727] fall into three main groups [728].

In the first group, primary amines are reacted with carbonyl insertion compounds such as **phosgene** [727, 729], and sometimes phosgene substitutes such as **triphosgene** [507], various **carbonates** [503, 730, 731], **bis(4-nitrophenyl)carbonate** [503], **di-*tert*-butyl dicarbonate** [664], ***S,S*-dimethyl thiocarbonate** [577], and ***N,N′*-carbonyldiimidazole** [732], **1,1-carbonylbis(benzotriazole)** [728], and **trihaloacetyl chlorides**. Most of these compounds have been utilized as safer reagents that can be stored and handled without special precautions.

The second class comprises the reactions of primary amines with **NCO equivalent compounds** such as **carbamates** [733–735], **formamides** (in the presence of ruthenium catalysts) [736], and, most importantly, **isocyanates** [727, 737].

Thirdly, ureas have been prepared by the catalyzed carbonylation of amines using **carbon monoxide** [738–741] or **carbon dioxide** [742, 743] in the presence of metal complexes, selenium [738], phosphorus compounds [744, 745], and ***N,N′*-dicyclohexylcarbodiimide** [746]. Moreover, the large scale production of urea derivatives by using these simpler and less expensive raw materials (CO and CO_2) in catalytic processes avoids production of large amounts of saline by-products, which represent the main constituent of chemical waste.

The simplest and most direct synthesis of substituted ureas is generalized in the scheme below. The process essentially involves two steps: (1) reaction of the reagent **1002** containing the carbonyl group with the selected amine to form the intermediate **1003**, still possessing a leaving group linked to the carbonyl; (2) further reaction of the intermediate **1003** with the same amine ($R^1 = R^2$) or with a different amine ($R^1 \neq R^2$) to form the symmetrical or the unsymmetrical substituted urea **1004**, either directly or through the more reactive isocyanate **1005**. The scheme below also illustrates the general reactivity of tricoordinated carbonic acid derivatives in nucleophilic substitutions, which readily eliminate a protonated leaving group, e.g. hydrogen halides, to form dicoordinated derivatives (isocyanates or carbon dioxide).



Since the addition of amines to isocyanates **1005** can be regarded as the main route for the synthesis of the more challenging *N,N′*-unsymmetrical substituted ureas **1004**, isocyanates **1005** are starting reagents in many urea formation reactions. However, it is important to underline, as described in the Section 4.3.1, that isocyanates themselves are toxic and are usually prepared from **phosgene** [311, 747].

Apart from the preparation of the parent urea, commercially produced by dehydration of ammonium carbamate obtained by direct reaction of ammonia with **carbon dioxide** [727, 748], the earliest classical method for the preparation of *N,N′*-symmetrically substituted ureas involved the reaction of amines with **phosgene** (**1002**; X, Y = Cl).

The procedures described below can be applied to the small- or medium-scale preparation of those ureas which are difficult to synthesize efficiently by other and safer methods, mainly compounds incorporating different functionalities and chiral carbons in the side chains.

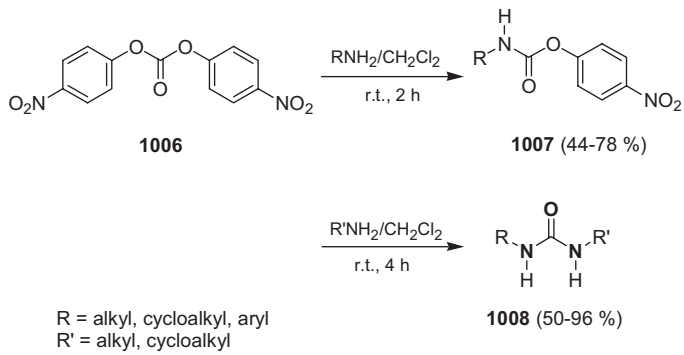
The following section illustrates the use of phosgene equivalents for the synthesis of ureas, with particular emphasis on the advantages of completely phosgene-free synthetic methods based on the use of **alkyl carbonates**, **CO**, **CO_2**, and other miscellaneous carbonylating reagents.

4.3.4.1 Phosgene and Symmetrical Phosgene Equivalents

The two identical leaving groups (X = Y) in phosgene substitutes **1002** can be consecutively replaced to prepare both symmetrical and unsymmetrical ureas. The selectivity toward the unsymmetrical *N*,*N*′-disubstituted ureas is critically dependent on the relative reaction rates of the two consecutive nucleophilic substitutions. If the second step is much slower than the first one, the formation of the symmetrical urea is minimized [726].

Bis(4-nitrophenyl)carbonate

Bis(4-nitrophenyl)carbonate 1006, a very stable reagent, can be converted into carbamates **1007** (44–78% yield) by reaction with equimolecular amounts of primary aliphatic or aromatic amines within 2 h in dichloromethane [503]. Intermediates **1007** react further with different primary amines to give the unsymmetrical ureas **1008** in good yields (50–96%).



1006 **1007** (44-78 %) **1008** (50-96 %)

The second step is considerably slower that the first and requires a longer reaction time of ca. 4 h. By reacting **1006** with an excess of amine (1:2 ratio), symmetrical ureas are formed directly in high yield (50–95%).

General procedure. *Unsymmetrical N,N′-disubstituted ureas* **1008** [503]: To a solution of 4-nitrophenyl *N*-alkyl- or *N*-aryl carbamate **1007** (for the synthesis, see Section 4.3.2 ''Carbamates'') (2 mmol) in dichloromethane (20 mL), amine (2 mmol) was added and the mixture was allowed to stand for 4 h. The solvent was then evaporated in a rotary evaporator. The residue was dissolved in methanol (2 mL) and the solution was filtered through a 1.2 × 20 cm column filled with Dowex-1 (OH^- form, 3.5 mequiv/g). The product was eluted with methanol (100 mL). The methanolic solution was concentrated to dryness, and the residue was recrystallized from methanol or triturated with diethyl ether (5 mL). In the case of amines that formed an insoluble precipitate with 4-nitrophenol, an additional portion of amine

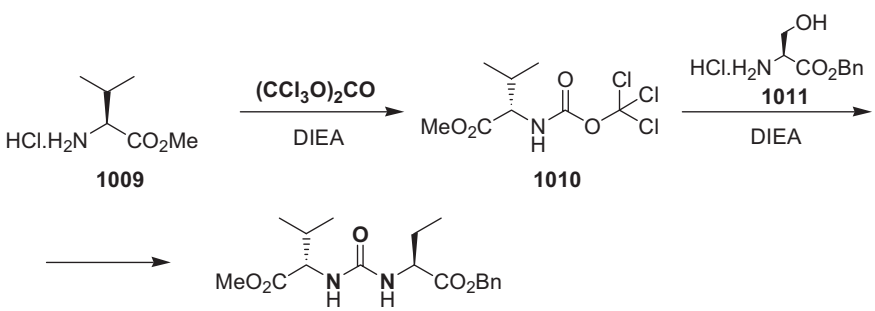
(2 mmol) was added, and the precipitate was filtered off before evaporation of the solvent.

General procedure. *Symmetrical N,N′-disubstituted ureas* **1008** [503]: A solution of **bis(4-nitrophenyl) carbonate** (1.52 g, 5 mmol) and amine (10.5 mmol) in dichloromethane, or DMF, or pyridine (40 mL) was allowed to stand for 4 h. The solvent was then evaporated, and the residue was purified on a Dowex-1 (OH^-) column as described above. The products were crystallized from methanol or triturated with diethyl ether (5 mL).

Bis(trichloromethyl)carbonate (Triphosgene)

Triphosgene, a safe and stable crystalline solid substitute for phosgene [53, 148], is successfully utilized in the sequential synthesis of unsymmetrical ureas also bearing chiral amino acid derivatives, without any need to purify the intermediates [507].

Thus, in a model reaction, valine methyl ester hydrochloride **1009** was reacted with **triphosgene** in the presence of diisopropylethylamine (DIEA) in dichloromethane at room temperature for 30 min to give the intermediate **1010**. Serine benzyl ester hydrochloride **1011** and DIEA in dichloromethane were then added over a period of 10 min. Product **1012** was obtained in 89% yield through a typical sequential, three-component reaction. The reaction can be successfully applied to various amines bearing multiple functionalities and exhibits high selectivity for N-nucleophiles; amines (primary and/or secondary) bearing an unprotected primary or secondary hydroxy group can be used directly (85–88% yield). The methyl, benzyl, and even acid-sensitive *tert*-butyl ester are unaffected. The less sensitive amino component is always used for the first step of the synthesis. Products resulting from racemization of the α-center are not detected.



1012 (89 %)

Typical procedure. *Unsymmetrical urea* **1012** [507]: **Triphosgene** (110 mg, 0.37 mmol) was dissolved in dichloromethane (2 mL). A mixture of valine methyl ester hydrochloride **1009** (167.5 mg, 1 mmol) and diisopropylethylamine (DIEA, 378 μL, 2.2 mmol) in dichloromethane (3.5 mL) was slowly added to the stirred solution of **triphosgene** over a period of 30 min using a syringe pump. After a further 5 min of

stirring, a solution of serine benzyl ester hydrochloride **1011** (231.5 mg, 1 mmol) and DIEA (378 μL, 2.2 mmol) in dichloromethane (2 mL) was added in a single portion. The reaction mixture was stirred for 10 min at room temperature, concentrated to dryness, and the residue was diluted with ethyl acetate. The resulting solution was washed with 10% aqueous $KHSO_4$, 5% aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated to give pure unsymmetrical urea **1012** (314 mg, 89%), which was crystallized from petroleum ether/ethyl acetate.

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 yields of 45–49%) as starting materials for a variety of pharmacologically active compounds [322]. Addition of the selected *O*-trimethylsilyl-protected amino acid hydrogen chloride to a solution of **triphosgene** in chloroform in the presence of DIEA results in the formation of the isocyanate intermediate, which is converted *in situ* into the urea dipeptide upon reaction of a second amino acid methyl ester in methanol.

An important application of **triphosgene** is the preparation of peptide analogues and other bioactive compounds. Under mild conditions, **triphosgene** can be used to convert the four amino groups of 4.0-tetrakis(*o*-aminophenyl)porphyrin (4.0-TAPP) to isocyanato groups. This generates the useful new intermediate, α,α,α,α-tetrakis(*o*-isocyanatophenyl)porphyrin (4.0-TIPP) (see Section 4.3.1 ''Isocyanates''), which can be derivatized with an almost unlimited range of functionalized groups, giving the freedom to prepare sophisticated superstructures, such as urea-functionalized porphyrins and urea-linked superstructured porphyrins, that may more accurately mimic natural hemeprotein structures [195].

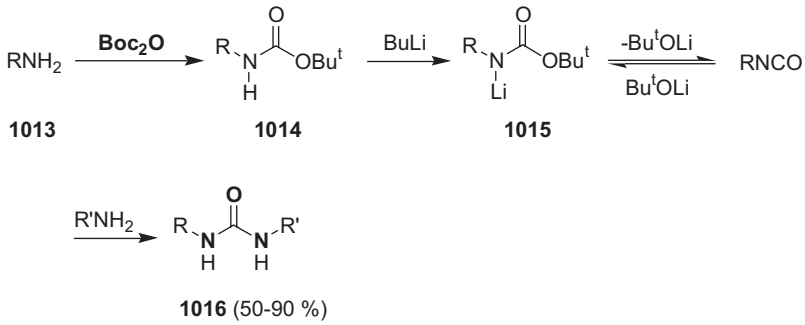
The crystal structures of a series of ureylene-dicarboxylic acids, predicted to form a two-dimensional hydrogen-bonded network, have been determined as part of a project directed towards the design of molecular solids [749]. The ureylene-dicarboxylic acids were prepared, for example, from glycyl-glycine and **triphosgene**.

Polymers containing phenyleneiminocarbonyl iminophenylene groups for use as hydrophilic membranes for ultrafiltration have been prepared with **triphosgene** [750]. An aromatic or heteroaromatic diamine (for example, bis(4-aminophenyl)-sulfone) is polymerized with **triphosgene** or **phosgene** in a dipolar solvent (*N*,*N*-dimethylacetamide, DMA) in the presence of complexing metal ions, and a membrane is produced by further casting and coagulation in water.

Di-*tert*-butyl dicarbonate

Similar applications have been reported for **di-*tert*-butyl dicarbonate** (**Boc_2O**) [664], a well known reagent utilized for protecting the amino group as an *N*-Boc primary amine **1014** with high yield and selectivity. Reagents **1014** can be converted into unsymmetrical substituted ureas **1016** by reaction with a strong base such as an alkyllithium, which converts **1015** into the corresponding isocyanate. Subsequent fast addition of a second amine affords the final unsymmetrical urea **1016** [751].

Softer and more *safely handled* organic bases, such as 4-dimethylaminopyridine (DMAP), can be utilized and eventually recovered at the end of the reaction, giving symmetrical as well as unsymmetrical ureas in 80–99% yield by stirring the reaction mixture for 14 h at 40 °C [734].

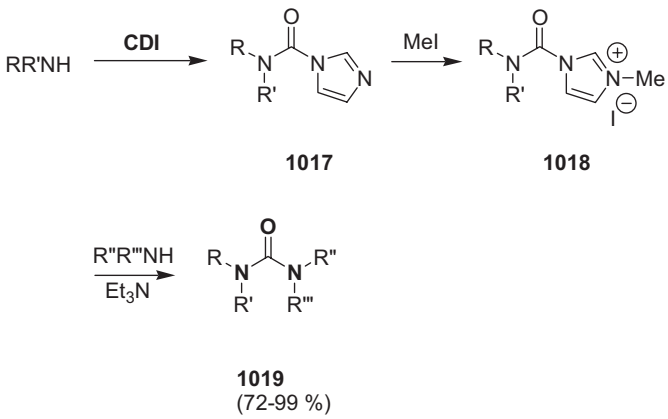


R = aryl, phenylalanyl-*tert*-butyl ester
R' = alkyl, cycloalkyl

The crucial role of isocyanates as intermediates in this approach has been confirmed by a detailed mechanistic study, which demonstrated that carbamates are by-products that cannot be converted into ureas [221].

N,N′-Carbonyldiimidazole (CDI)

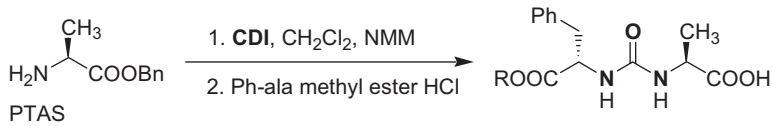
The commercially available and easily handled crystalline solid ***N,N′*-carbonyldiimidazole** (**CDI**) is utilized as a starting reagent for the general synthesis of unsymmetrical tetrasubstituted ureas. The intermediate carbamoyl imidazole **1017** is first obtained by reaction of **CDI** with a secondary amine. Compound **1017** is then converted into the more reactive and resonance-stabilized imidazolinium salt **1018** by *N*-alkylation of the imidazole moiety. Addition of a different secondary amine to **1018** furnishes *N,N,N′,N′*-unsymmetrical tetrasubstituted ureas **1019** in high yield (72–99%).



Imidazolinium salts **1018** are produced quantitatively and do not require additional purification for the final conversion to the ureas **1019**. Although the salts **1018** are

hygroscopic, they can be stored for several weeks without detectable decomposition [752].

The carbonyldiimidazole-based approach has been successfully applied to the synthesis of some more sophisticated urea dipeptides, which represent building blocks for the preparation of inhibitors of HIV-protease. These compounds are simply obtained by sequential addition of **CDI** and the requisite amino acid ester hydrochloride to the selected amino acid *p*-toluenesulfonic acid salt **1020** in the presence of triethylamine, DIEA, or *N*-methylmorpholine (NMM) and avoiding the use of strong bases such as BuLi or lithium diisopropylamide (LDA), which can racemize the stereogenic centers [753].



1020 **1021**

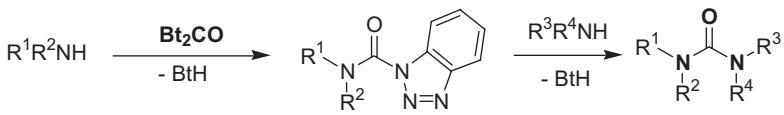
R = Me (80 %)
R = tBu (79 %)

Typical procedure. *Urea ester* **1021** (R = Me) [753]: A solution of **CDI** (1.25 g, 7.70 mmol, 1.10 equiv.) in dichloromethane was stirred at room temperature, and then a solution of alanine benzyl ester *p*-toluenesulfonate **1020** (2.45 g, 7.00 mmol) and *N*-methylmorpholine (NMM) (3.0 mL, 2.50 mmol) in dichloromethane was added via a cannula. The reaction mixture was stirred for 5 min, and then a second solution of phenylalanine methyl ester hydrochloride (1.50 g, 7.00 mmol) and NMM (3.0 mL, 2.50 mmol) in dichloromethane was added. The entire sequence of events was performed under a positive pressure of N_2. The resultant reaction mixture was poured into a separatory funnel containing dilute aqueous $NaHCO_3$ solution. The organic layer was washed several times with water and dried over Na_2SO_4. Filtration and evaporation of the solvent in vacuo left a viscous oil, which was kept under vacuum for 2 h to remove all traces of NMM. The residue was further purified by column chromatography (EtOAc/hexane, 3:1) to give 2 g of the urea ester **1021** as a viscous oil.

N,N′-Carbonyldibenzotriazole

Although numerous methods are available for the preparation of symmetrical and unsymmetrical di- or trisubstituted ureas in good to excellent yields, the only hitherto reported synthesis of unsymmetrical tetrasubstituted ureas involves reaction of a carbamoyl chloride (prepared from a secondary amine and phosgene) with a secondary amine [754]. Moreover, this method, as used more recently [755, 756], suffers from several drawbacks. An excess of amine and/or the use of an acid scavenger (such as pyridine or triethylamine) is required, and the carbamoyl chloride intermediate can be both unstable and difficult to isolate when needed. Moreover, the production of hydrochloric acid prevents the application of this method when acid-sensitive functionalities are present. ***N,N′*-Carbonyldibenzotriazole** can be utilized to synthesize *N,N,N′,N′*-unsymmetrical tetrasubstituted ureas **1023** by a

one-pot reaction with the first amine to produce the carbamoylbenzotriazole intermediate **1022**, which, under more forceful conditions, can react with a second amine to give the final urea in satisfactory to good yields (24–85%) [728].



1022 **1023** (25-85 %)

The reaction conditions and the yields of intermediate **1022** are significantly affected by the steric hindrance of the substituents of the amines utilized. With cyclic, aliphatic, and aromatic amines, the reaction occurs within 2 days in THF at room temperature in 40–71% yield, whereas with congested secondary amines harsher conditions are required and lower yields are obtained. In laboratory-scale preparations, ***N,N′*-carbonyldibenzotriazole** is synthesized directly from benzotriazole and **phosgene**.

Typical procedure. *N-Phenyl-N′-n-octyl-urea* [728]: **1,1′-Carbonyldibenzotriazole** (1.06 g, 4 mmol) was dissolved in dry THF (40 mL) under an atmosphere of dry nitrogen, and aniline (0.37 mL, 4 mmol) was added. The reaction mixture was stirred at room temperature for 27 h, octylamine (0.65 mL, 4 mmol) was then added, and the resulting mixture was stirred at room temperature for 27 h. It was then extracted

Tab. 4.28. Preparation of ureas by successive treatments of ***N,N′*-carbonyldibenzotriazole** with R^1R^2NH and R^3R^4NH.

Product 1023	R^1	R^2	R^3	R^4	*Yield (%)*
a	Ph	H	*n*-octyl	H	85[a]
b	Ph	H	-$(CH_2)O(CH_2)_2$-		16[a]
b	Ph	H	-$(CH_2)O(CH_2)_2$-		70[b]
c	*n*-Bu	Me	-$(CH_2)_4$-		82[c,d]
d	*n*-Bu	Me	Ph	Me	80[c,d]
e	*n*-Bu	Me	Ph	Me	71[c,d]
f	-$(CH_2)O(CH_2)_2$-		-$(CH_2)_3$-		71[c,d]
g	-$(CH_2)O(CH_2)_2$-		*n*-Bu	Me	80[c,d]
h	-$(CH_2)O(CH_2)_2$-		Benzyl	Me	25[c,d]
i	-$(CH_2)O(CH_2)_2$-		Ph	Ph	51[c,d]
j	-$(CH_2)O(CH_2)_2$-		Ph	Me	57[c,d]
k	-$(CH_2)_2N(CH_3)(CH_2)_2$-		Ph	Ph	47[c,d]
l	-$(CH_2)_2N(CH_3)(CH_2)_2$-		Ph	Me	51[c,d]

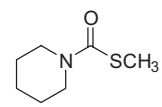
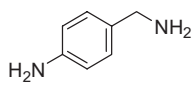
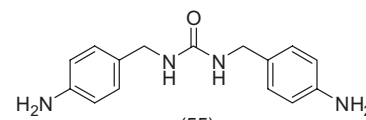
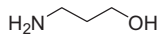
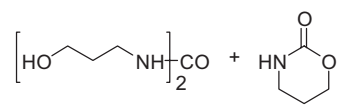
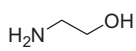
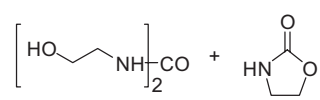
[a] One-pot procedure carried out at room temperature; [b] One-pot procedure carried out at room temperature after addition of the primary amine and with heating under reflux after addition of the secondary amine; [c] Two-pot procedure; [d] Heating under reflux and use of the sodium salt of the amine.

with diethyl ether (3 × 40 mL). The ethereal extracts were successively washed with 2 N HCl (2 × 20 mL), 2 N NaOH (2 × 20 mL), and saturated NaCl (30 mL), dried with $MgSO_4$, and filtered. Removal of the solvent under reduced pressure gave *N*-phenyl-*N′*-*n*-octyl-urea as a white powder (0.84 g, 85%).

S,S-Dimethyldithiocarbonate (DMDTC)

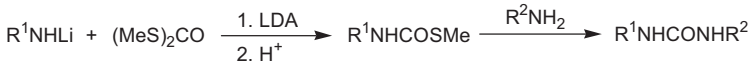
***S,S*-Dimethyldithiocarbonate** (**DMDTC**) **786** represents a mild and safely handled reagent, structurally similar to phosgene, which is useful in the synthesis of ureas (see also Section 4.3.2 "Carbamates"). Tables 4.29, 4.30, and 4.31 illustrate various symmetrical and unsymmetrical ureas prepared with DMDTC.

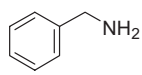
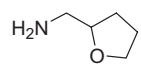
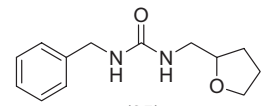
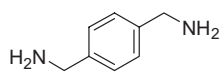
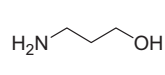
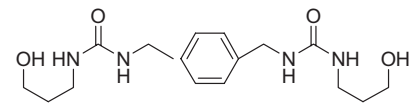
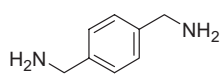
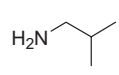
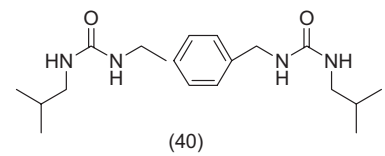
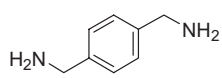
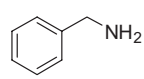
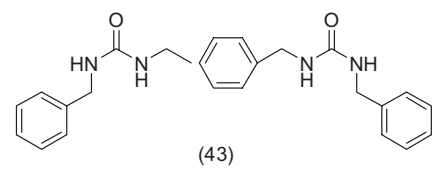
Tab. 4.29. Preparation of symmetrical ureas by condensation of various amines with **DMDTC** [577].

Entry	*Starting amine*	*Solvent (conc.)*[a]	*Product (yield, %)*[b]
1	isobutylamine	MeOH (1 M)	*N,N′*-diisobutylurea (92)
2	allylamine	MeOH (1 M)	*N,N′*-diallylurea (80)
3	benzylamine	MeOH (1 M)	*N,N′*-dibenzylurea (85)
4	1-methylpropylamine	no solvent	*N,N′*-bis(1-methylpropyl)urea (70)
5	cyclohexylamine	no solvent	*N,N′*-dicyclohexylurea (65)
6		MeOH (1 M)	 (75)
7		MeOH (1 M)	 (55)
8			
		MeOH (1 M)	70 30
		MeOH (4.5 M)	90 10
		no solvent	(70)
9			
		MeOH (1 M)	5 95
		no solvent	75(55) 25

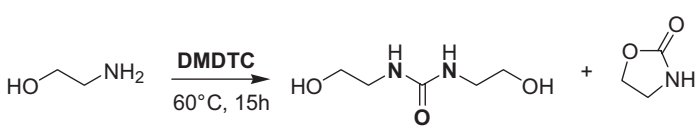
[a] Initial concentration of the starting amine. [b] Isolated yield.

Tab. 4.30. Condensation of various diamines and amino alcohols with **DMDTC** [577].



Entry	R^1NH_2	R^2NH_2	*Product (yield, %)*[a]
1			 (65)
2			 (40)
3			 (40)
4			 (43)

[a] Overall isolated yield.

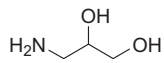
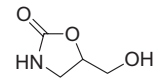
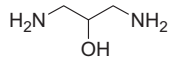
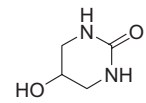
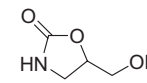
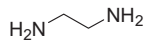
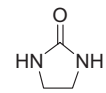
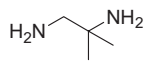
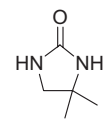
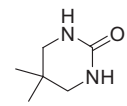
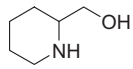
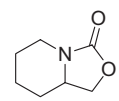
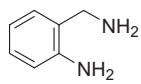
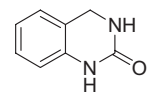


1024 **1025**

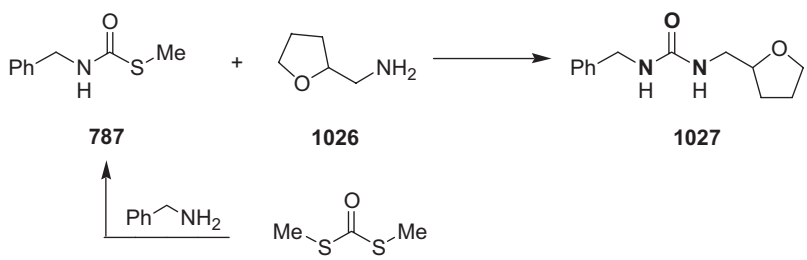
Typical procedure. *N,N′-Bis(2-hydroxyethyl)urea* **1024** [577]: Excess ethanolamine and **DMDTC** were mixed and heated at 60 °C for 15 h. The released malodorous methyl sulfide by-product was absorbed and oxidized by NaOCl solution. When the reaction was complete, the unreacted ethanolamine was removed under reduced pressure by simple distillation, leaving a crude mixture of oxazolidinone **1025** and bis(2-hydroxyethyl)urea **1024**, which was further purified by recrystallization from methanol/ethyl acetate (1:4.5) to give *N,N′*-bis(2-hydroxyethyl)urea as colorless crystals.

Tab. 4.31. Preparation of unsymmetrical ureas from **DMDTC** [577].

$$2\ RNH_2 + (MeS)_2CO \longrightarrow RNHCONHR$$

Entry	*Starting amine*	*Solvent (conc.)*[a]	*Product (yield, %)*[b]
1		MeOH (1 M)	 (68)
2		MeOH (0.7 M)	 (70)  (<5)
3		MeOH (0.5 M)	 (80)
4		MeOH (1 M)	 (81)
5		MeOH (1 M)	 (74)
6		no solvent	 (55)
7		MeOH (1 M)	 (40)

[a] Initial concentration of the starting amine. [b] Isolated yield.

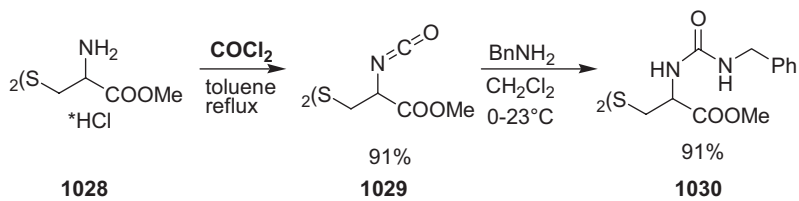


Typical procedure. *N-Benzyl-N′-tetrahydrofurfurylurea* **1027** [577]: To a stirred solution of *S*-methyl *N*-benzylthiocarbamate (for the synthesis, see Section 4.3.2 ''Carbamates'') (0.11 g, 0.63 mmol) in methanol (2 mL) was added tetrahydrofurfurylamine (0.12 g, 1.1 mmol). After heating at 60 °C for 24 h, the reaction mixture was concentrated under reduced pressure to leave a crude solid. Recrystallization of this solid from $CHCl_3$/hexane gave *N*-benzyl-*N′*-tetrahydrofurfurylurea as colorless crystals (0.14 g, 88%).

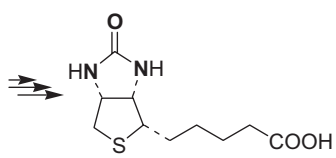
Phosgene

An enantioselective and stereospecific synthesis of the important vitamin (+)-Biotin **1031**, in 12 steps from L-cystine dimethyl ester, required the preparation of bis(urea) **1030** [729].

The preparation was achieved in two steps by a sequence of: (1) treatment of L-cystine dimethyl ester dihydrochloride **1028** suspended in refluxing toluene with a slow stream of **phosgene** for 5 h (for the phosgene source, see Chapter 7) to afford, after concentration, the corresponding diisocyanate **1029** in high yield; and (2) reaction of this diisocyanate **1029** with a 10% excess of benzylamine in dichloromethane (0 °C initially and then 23 °C for 1 h) to give, after addition of methanol (just enough to give a clear solution), dilution with petroleum ether, and cooling at 4 °C, the bis(urea) **1030**; mp 166–167 °C (91%).



1028 91% **1029** 91% **1030**

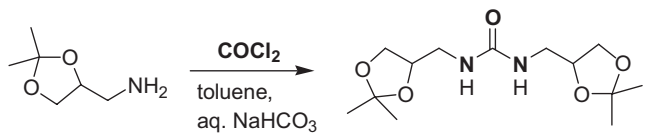


1031
(+)-Biotin

Bis-4-(2,2-dimethyl-1,3-dioxolyl)methyl carbodiimide (**BDDC**) **1034**, a useful reagent for racemization-free esterifications, peptide couplings, and dehydration, has been prepared via the symmetrical urea **1033** by a reaction sequence involving an amine *phosgenation* [758].

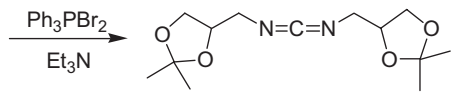
Typical procedure. *N,N′-Bis-4-(2,2-dimethyl-1,3-dioxolyl)methyl urea* **1033** [758]: A solution of amine **1032** (149 g, 1.14 mol) in toluene (680 mL) was added to a solution of $NaHCO_3$ (192 g, 200 mol%) in H_2O (680 mL). This two-phase mixture was

cooled to 0 °C and vigorously stirred as a **freshly prepared** solution of **phosgene** (for a *safe source*, see Chapter 7) in toluene (231 mL, 2.46 M solution, 50 mol%) was added dropwise over a period of 2 h. The reaction mixture was stirred at room temperature for an additional 16 h, the layers were separated, and the toluene phase was dried, filtered, and concentrated to leave a white solid residue. The aqueous phase was extracted with EtOAc (3 × 300 mL), and the combined organic extracts were dried and concentrated. The combined residual white solids were recrystallized from toluene/hexane to afford 142 g (87%) of *N,N′*-bis-4-(2,2-dimethyl-1,3-dioxolyl)methyl urea **1033**.



87%

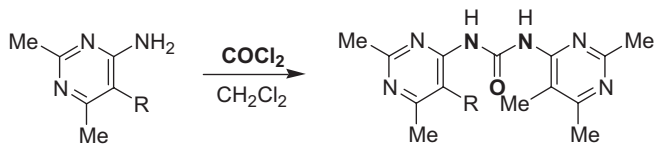
1032 **1033**



89%

1034

The synthesis of ureas **1036** from 4-amino-2,6-dimethylpyrimidines **1035** and **phosgene** has also been described [759].



80-82%

1035 **1036**

R = H, Cl

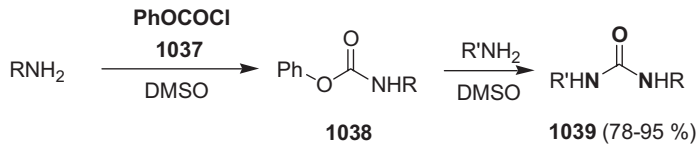
Typical procedure. *N,N′-Bis(4-amino-2,6-dimethylpyrimidine) urea* **1036** [759]: A solution of **phosgene** (for a *safe source*, see Chapter 7) (9.9 g, 0.1 mol) in tetrachloromethane (50 mL) was added dropwise to a stirred suspension of **1035** (0.04 mol) in dichloromethane (300 mL; dried over 4 Å molecular sieves). The reaction temperature was kept at 25–30 °C by cooling with ice/NaCl. Stirring was maintained at room temperature for 3–5 h, and then the precipitate was isolated, thoroughly stirred with H_2O (200 mL), collected by filtration once more, washed with a little H_2O, and dried at 60–70 °C. In the case of compound **1036** (R = Cl), the precipitate obtained was successively stirred with ethanol (60 mL) and H_2O (100 mL); yield 80–82%.

4.3.4.2 Unsymmetrical Phosgene Equivalents

Unsymmetrical equivalents of phosgene are less reactive and the rate and selectivity of carbonylation can be conveniently controlled by selecting the nature of the leaving groups and the conditions of consecutive displacements.

Phenyl carbamates

Various *N*,*N*′-disubstituted ureas **1039**, including some chiral compounds, are efficiently synthesized by the reaction of amines with carbamates **1038**, which, in turn, are prepared from phenyl chloroformate **1037** [760].



R, R' = aryl, alkyl, cycloalkyl

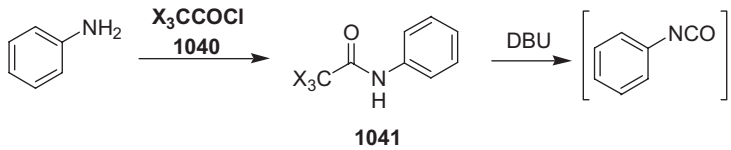
The reaction occurs at room temperature in 78–95% yield simply by mixing the reagents in DMSO, the only by-product being phenol, which is easily removable by an aqueous NaOH wash. The method can also be successfully applied to secondary amines to generate *N*,*N*,*N*′-trisubstituted ureas in 78–89% yield, irrespective of the steric hindrance of the reagents. The reaction conditions are compatible with a number of functional groups, such as chiral amines, amino acids, and amino alcohols. The rate and yield of the reaction are highly dependent on the solvent used. The use of DMSO is critical to the mildness of the conditions. Compared to DMSO, the reaction was found to be much slower in methanol, dioxane, DME, or dichloromethane, in which carbamate **1038** is not readily soluble. A possible drawback of this approach is associated with the use of DMSO as solvent, which is toxic, a possible carcinogen, and potentially explosive when mixed with some organic and inorganic reagents [761].

Typical procedure. *N-(4-Acetylphenyl)-N′,N′-dibutylurea* [760]: In a dry 100-mL flask equipped with an N_2 inlet adapter, a rubber septum, and a magnetic stirring bar, was placed a solution of phenyl *N*-(4-acetylphenyl)carbamate **1038** (R = 4-AcPh) (6.38 g, 25 mmol) in DMSO (50 mL). Dibutylamine (4.42 mL, 26.25 mmol) was then slowly added. The resulting solution was stirred at room temperature for 15 min, and then diluted with EtOAc (250 mL). The resulting mixture was washed successively with H_2O (2 × 50 mL), 1 M HCl (100 mL), H_2O (100 mL), 1 M NaOH (100 mL), and brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a crude solid, which was triturated with Et_2O/hexane to furnish *N*-(4-acetylphenyl)-*N*′,*N*′-dibutylurea as a white solid; yield 6.98 g (96%).

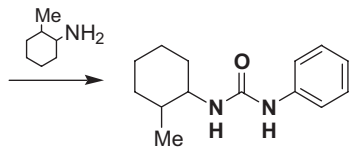
Trihaloacetyl chlorides and trihaloacetamides

Trihaloacetyl chlorides 1040 represent a second class of unsymmetrical reagents **1002** which are commercially available at reasonable prices. They can be quantita-

tively converted into the corresponding trihaloacetamides **1041** (80–90%), which are easily handled crystalline solids with long shelf-lives, by reaction with convenient aromatic or aliphatic amines. These compounds react with various aliphatic amines in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give unsymmetrical ureas **1042** such as *Neburon* and *Siduron*, which exhibit biological activity [762].



1041



1042 **SIDURON**

X = F, Cl, Br

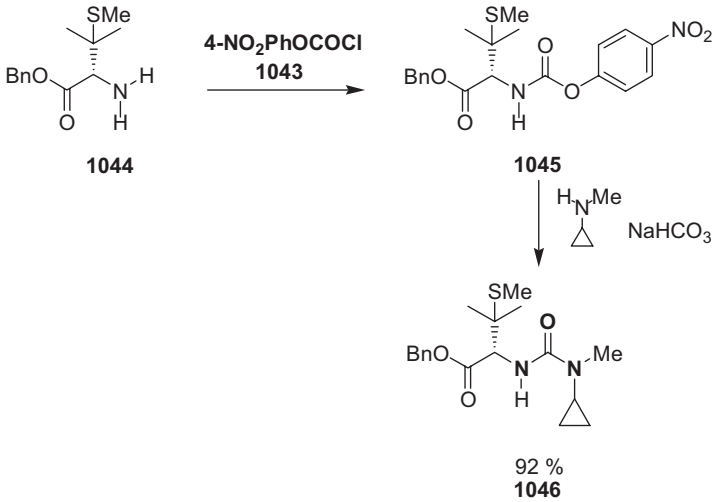
β-Elimination of haloform from stable and readily available trihaloacetamides **1041** in the presence of strong bases exhibits a strong dependence on the nature of the trihalomethyl group in the order $RCOCF_3 < RCOCCl_3 < RCOCBr_3$. As for some other reported methodologies, this ''one-pot'' synthesis of ureas from readily available **trihaloacetanilides** has the clear advantage that it avoids the need to isolate the highly toxic isocyanates. The crucial role of the **isocyanates** in the present reaction is confirmed by the unreactivity of trichloroacetamides derived from *N,N*-disubstituted amines, which cannot afford isocyanates. Formation of haloforms is the main drawback of the method.

General procedure. *Ureas from* **trihaloacetamide** [762]: To a solution of the **trihaloacetamide** $RNHCOCCl_3$ or $RNHCOCBr_3$ (0.5 mmol) and the appropriate amine (0.5 mmol) in dry DMSO (3 mL), DBU (0.5 mmol) was added and the reaction mixture was heated at 80 °C for 4 h for reaction with $RNHCOCCl_3$ or 0.5 h for reaction with $RNHCOCBr_3$. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (10 mL) and washed with 3% aq. HCl, aq. $NaHCO_3$ solution, and saturated brine. After drying over $MgSO_4$ and removal of the solvent, the product was recrystallized from a suitable solvent. The products were obtained in yields of 80–92%.

4-Nitrophenyl chloroformate

Ureas containing structurally complex frameworks, including amino acid derivatives, are efficiently prepared from **4-nitrophenylchloroformate 1043**. To give an

example, *S*-methyl-*O*-benzyl-L-penicillamine **1044** reacts with **1043** in acetonitrile at 0 °C within 30 min to give carbamate **1045**. Further addition of cyclopropylmethylamine in the same solvent and in the presence of $NaHCO_3$ gives the amino acid urea **1046** in 92% yield.



The reaction occurs under very mild conditions owing to the good leaving group ability of the 4-nitrophenyl group, and hence is not applicable to tetrasubstituted ureas [417].

4.3.4.3 Carbon Monoxide

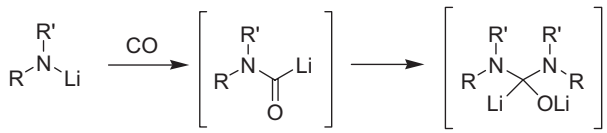
Although carbon monoxide is a toxic gas, it is utilized in a wide variety of industrial carbonylation processes owing to its low cost, ready availability, and easily controlled reactivity [238].

Direct carbonylation of primary amines to give *N*,*N*′-symmetrical ureas can be achieved in good yield (56–67%) using a nitrido tungsten(IV) carbonyl complex. The reaction is carried out at room temperature under nitrogen, and is 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 amines afford formamides [763].

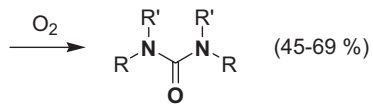
N,*N*,*N*′,*N*′-Tetrasubstituted ureas **1049** have been obtained in variable yields (45–69%) by reaction of lithium aliphatic amides **1047** in THF solution with **carbon monoxide** under mild conditions (atmospheric pressure, 0 °C) followed by *in situ* oxidation with oxygen of the intermediate **1048** prior to work-up. The advantages of this method are the short reaction time and the use of molecular oxygen as oxidant [764].

Selenium reacts with **carbon monoxide** and amines under mild conditions (15 °C, 1 atm) to give ammonium carbamoselenoates **1050**, which are then converted to the corresponding ureas **1051** by aminolysis upon oxidation with molecular oxy-

gen; this converts the unwanted hydrogen selenide into selenium, thereby regenerating the catalyst [765].

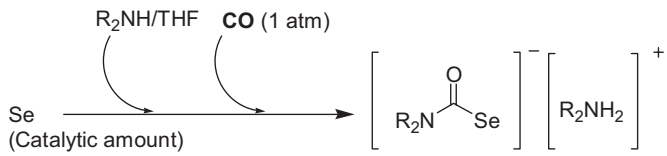


1047 **1048**

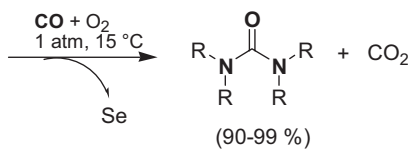


1049

R, R' = Bu, *i*-Pr, *c*-C_6H_{11}



1050



1051

R_2NH = NH_3, $BuNH_2$, $PhNH_2$, cyclohexylamine, piperidine

Under controlled conditions, the reaction proceeds in the presence of a catalytic amount of selenium and its turnover number reaches ca. 1×10^4. The reaction is strongly accelerated at elevated temperatures and pressures, e.g. 120 °C, O_2 (4 atm).

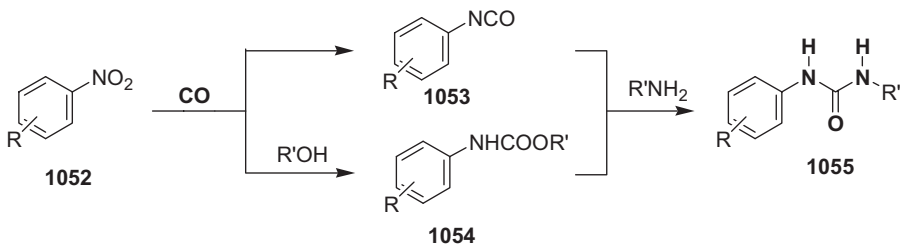
The above approach is applicable to the synthesis of unsymmetrical phenylureas through selenium-catalyzed reductive carbonylation of nitrobenzene in the presence of aliphatic secondary amines as co-reagents. The reaction is characterized by good yields (40–80%) and selectivities. In contrast, when primary amines are used as co-reagents, a mixture of all three possible ureas is obtained [766].

There is a need to develop salt-free technologies that not only involve simpler raw materials, but also permit the replacement of stoichiometric reactions with catalytic processes [767]. Ureas are mainly synthesized through carbonylation of

amines, with the generation of large amounts of inorganic salts, and these represent the main components of industrial waste.

Catalytic carbonylation of nitro compounds, with particular emphasis on nitroaromatic compounds, has been extensively studied, with the main focus being on the production of isocyanates that have achieved great commercial importance in the preparation of important industrial targets including ureas [768].

Various catalysts have been used to promote the process, including metal complexes of groups 8–10 (mainly Pd, Ru, and Rh) combined with a Lewis acid co-catalyst (mainly $FeCl_3$, $MoCl_5$, V_2O_5, or Fe_2O_3) or a Brønsted acid (e.g. trimethylbenzoic acid). The methodology was particularly studied and developed with the aim of producing methylenediphenyl isocyanates and phenyl diisocyanate, which are of commercial importance in the manufacture of polyurethanes. Due to the instability of monoisocyanates under the reaction conditions, the process was better utilized in the production of *N*-phenylcarbamates **1054** by trapping isocyanates with alcohols.



Furthermore, isocyanates can be converted *in situ* into symmetrical diphenyl ureas by reaction with amines either added to the reaction mixture or produced *in situ* by reduction of the nitro compound [238].

Diphenylurea (DPU) **1058** is synthesized in almost quantitative yield from nitrobenzene, aniline, and **CO**, in the presence of a Pd(π) complex with triphenylphosphine (0.2 mol% with respect to aniline), dissolved in a non-polar solvent such as toluene or xylene at 120 °C.

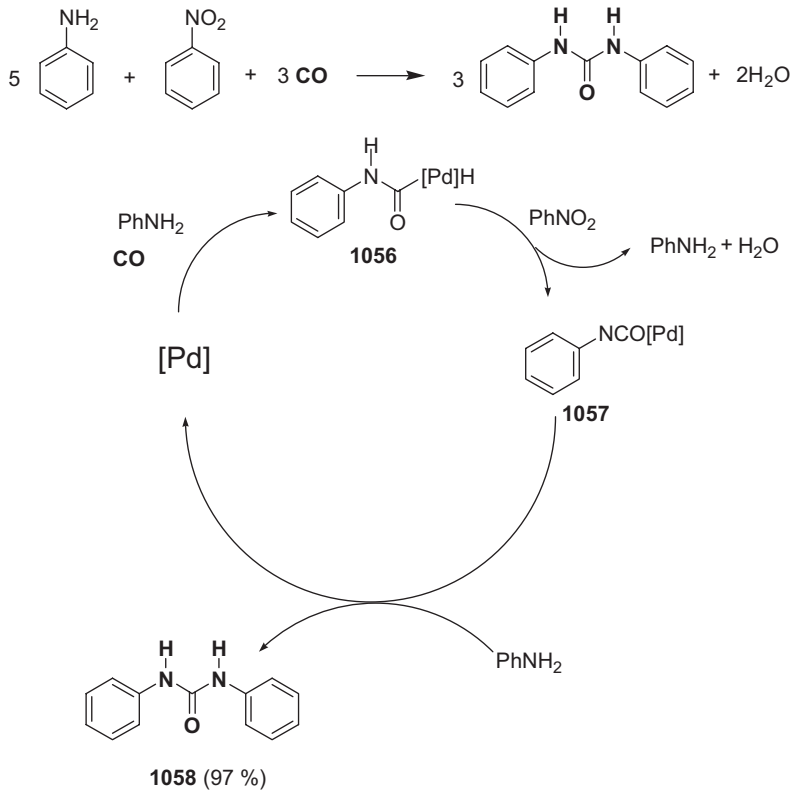
Mechanistic studies with deuterated nitrobenzene suggest that the reaction involves the carbamoyl complex [PhNCO(Pd)] **1057**, although it is not clear as to how important this pathway is [769–771].

Symmetrical *para*-substituted diaryl ureas can be obtained in satisfactory yields (27–88%) by the reaction of accessible aromatic nitro compounds in the presence of $Ru_3(CO)_{12}$ in *cis*-cyclooctene as the solvent (substrate/catalyst ratio 25:1) [772].

Unsymmetrical substituted ureas are likewise synthesized by reductive carbonylation of 4-substituted nitrobenzenes with **CO** in the presence of an excess of an aliphatic secondary amine using palladium acetate, bipyridyl, and copper tosylate as co-catalyst; the best selectivity is obtained by continuously adding the aliphatic amine during the course of the reaction (ca. 10 h) [773].

N,*N*′-Disubstituted ureas are obtained in fairly low yields (45–55%) using less expensive catalysts by dioxygen-induced carbonylation of amines in the presence

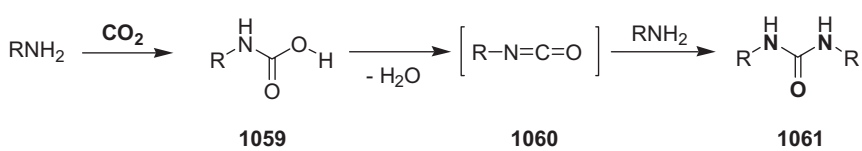
of nickel carbonyl complexes (substrate/catalyst ratio 100:1) [774] or (η-methylcyclopentadienyl)manganese tricarbonyl under irradiation with UV light [775].



4.3.4.4 Carbon Dioxide

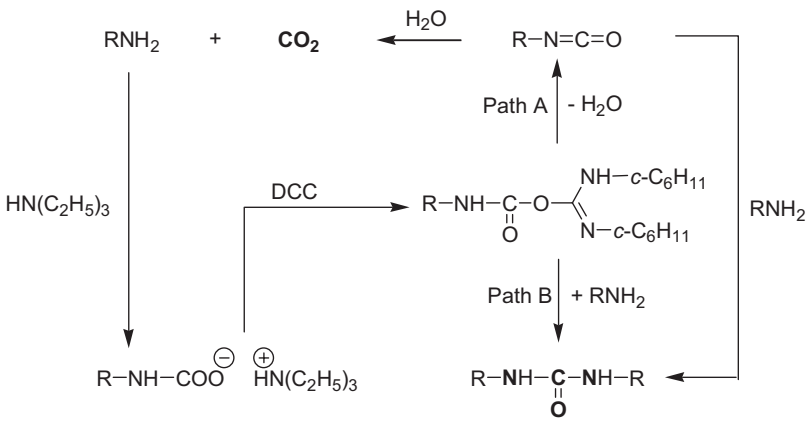
Direct fixation of carbon dioxide into the target compound represents an important strategy for the minimization of carbon dioxide emission [599]. Despite the fact that the activation and use of carbon dioxide in chemical reactions is not an easy process, several important applications have been developed, such as the production of carbamates; these are utilized *per se* and as intermediates for fine chemicals, including unsymmetrical ureas.

The formation of ureas **1061** from carbamic acids, however, involves transformation of carbamic acids **1059** to isocyanates **1060**, the active intermediates, and requires high reaction temperatures (near 200 °C) and a CO_2 pressure in excess of 10 MPa [727].



Moreover, the synthesis of ureas from amines and CO_2 involves the elimination of water. The use of some dehydrating agents, such as **carbodiimides** [746] and **diorganophosphites** [744], converts this method into a direct condensation, thus offering a new synthetic process that proceeds under mild conditions.

A synthetic method has been reported for preparing large amounts of disubstituted ureas directly from **carbon dioxide** and amines using dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide as a condensing reagent in the presence of a tertiary amine [746]. The tertiary amine plays an important role, and no urea was obtained in its absence.



Typical procedure. *N,N′-Dicyclohexylurea (preparation under atmospheric pressure)* [746]: An excess of **dry ice** (200 g) was added gradually to a solution of dicyclohexylcarbodiimide (2.06 g, 0.01 mol), cyclohexylamine (1.98 g, 0.02 mol), and triethylamine (2.2 g, 0.02 mol) in THF at −75 °C over a period of 8 h. After stirring for 8 h, the reaction mixture was concentrated under reduced pressure and the resultant precipitate was collected. Fractional recrystallization of the precipitate from

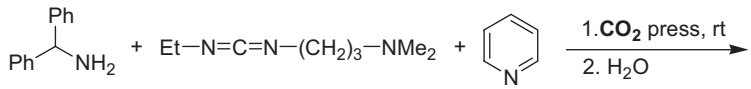
Tab. 4.32. Preparation of ureas using CO_2 and dicyclohexylcarbodiimide.

R	*Yield (%) using amine*[a]			
	A	*B*	*C*	*D*
Ph_2CH	91	81	85	91
c-C_6H_{11}	98	75	89	91
Ph	–	31	–	–
$PhCH_2$	–	–	80	–
i-Pr	48	–	–	–
n-Pr	–	–	–	58

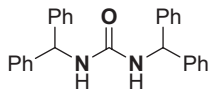
[a] Amines: A: triethylamine; B: *N*-methylmorpholine; C: 2,6-lutidine; D: pyridine.

acetone/methanol gave *N,N′-dicyclohexylurea*; yield 2.2 g (98% based on dicyclohexylcarbodiimide and cyclohexylamine).

When 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide **1063** was used as a condensing reagent, low yields of ureas (30–40%) were obtained after 1–2 days. However, the reactions proceeded smoothly in an autoclave under a pressure of **carbon dioxide** at room temperature within 1 h, to yield 95–100% of ureas of type **1064**.



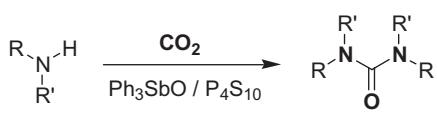
1062 **1063**



1064

Typical procedure. *N,N′-Diphenylmethylurea* (preparation under pressure) [746]: To a mixture of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.55 g, 0.01 mol), 1,1-diphenylmethylamine **1062** (1.84 g, 0.01 mol), and pyridine (1.58 g, 0.02 mol) in dichloromethane (50 mL) in an autoclave, **carbon dioxide** (60 atm) was charged at room temperature. After 1 h, water (100 mL) was added to deposit a crystalline precipitate. Recrystallization of this precipitate from diethyl ether gave *N,N′*-diphenylmethylurea **1064**; yield 3.92 g (100%). Similarly, by using triethylamine, *N*-methylmorpholine, or 2,6-lutidine instead of pyridine, yields of 100%, 95%, and 100%, respectively, were obtained.

Triphenylstibine oxide (Ph_3SbO) with the assistance of tetraphosphorus decasulfide (P_4S_{10}) is a highly effective catalyst for the carbonylation of both amines and diamines with **CO_2** in the presence of 3 Å molecular sieves, giving the corresponding linear and cyclic ureas in yields of 83–98% [777, 778].



1065 **1066**

R, R´= Bu, H; *i*-Bu, H; *s*-Bu, H; *t*-Bu, H; allyl, H; Ph, H; Me, Me

The carbonylation of primary amines by **CO_2** in the presence of Ph_3SbO/P_4S_{10} proceeds smoothly, and the corresponding 1,3-disubstituted ureas **1066** are obtained in good yields even at 80 °C (Table 4.33). Furthermore, the carbonylation of secondary amines is also feasible by increasing the amount of catalyst and short-

Tab. 4.33. Synthesis of 1,3-dialkylureas **1066** from amines and **carbon dioxide**[a] [778].

Starting amine RR′NH		*Temperature* °C	*Yield of ureas*[b] %
R	*R′*		
Bu	H	80	88 (100)
i-Bu	H	80	89
s-Bu	H	80	73
t-Bu	H	80	30[c]
allyl	H	80	62[d]
Ph	H	120	48[d]
Me	Me	120	33[d–f]

[a] General reaction conditions: amine/Ph_3SbO/P_4S_{10} = 40/1.0/2.0 mmol, benzene (20 mL), CO_2 at 4.9 MPa, time 12 h; [b] Isolated yield (HPLC yield); [c] Resinous by-product was obtained; [d] Ph_3SbO (2.0 mmol) and P_4S_{10} (4.0 mmol) were employed; [e] Reaction time 3 h; [f] Prolonged reaction time and higher reaction temperatures, e.g. 24 h and 160 °C, caused thionation of the ureas.

ening the reaction time in order to prevent undesirable thiolation. For example, tetramethylurea is obtained in 33% yield at 120 °C, while the formation of thiolation products such as thiourea becomes predominant at reaction temperatures higher than 130 °C.

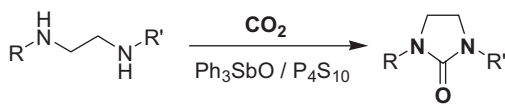
Typical procedure. *1,3-Dibutylurea* **1066** [778]: The reactions under **CO_2** pressured conditions were carried out in a stainless steel reactor (SUS 304, 30 mL, TVS-5 type). Thus, butylamine (2.9 g, 40 mmol), Ph_3SbO (370 mg, 1.0 mmol), P_4S_{10} (890 mg, 2.0 mmol), and benzene (20 mL) were charged into the reactor, and then **CO_2** was introduced at a pressure of 4.9 MPa (50 kg cm^{-2}, ca. 65 mmol) at room temperature. The reactor was heated at 80 °C in a temperature-regulated incubator for 12 h. When a reaction temperature higher than 100 °C was necessary, an oil bath was used. After the heating, the reactor was cooled and carefully decompressed. The contents were treated with hot benzene (3 × 20 mL) and filtered to remove an insoluble residue containing the catalyst and phosphoric acid derivatives. The collected benzene solution was then concentrated to dryness in vacuo with cooling. Pure 1,3-dibutylurea was isolated by recrystallization from ligroin (yield 2.99 g, 88%).

Cyclic ureas **1068** were readily prepared from *N*-methylethylenediamine or hydroxylated ethylenediamine in the presence of Ph_3SbO as a catalyst [777], but it was found that ethylenediamine, *N*-phenylethylenediamine, and *N*,*N*′-dimethylethylenediamine would not react with **CO_2**. The modified catalyst Ph_3SbO/P_4S_{10} is highly active in the carbonylation of these diamines, and the corresponding 2-imidazolidinones were obtained at 80–150 °C (Table 4.34). It is interesting to note that tri- and tetrasubstituted ureas were readily obtained without thionation, even at 150 °C.

Tab. 4.34. Synthesis of cyclic ureas **1068** from diamines and **carbon dioxide**[a] [778].

Starting amine RR′NH		*Temp.*	*Time*	*Yield of ureas*[b]
R	*R′*	*°C*	*h*	*%*
H	H	150	12	85
		150	24	0[c]
		80	24	17
Me	H	80	12	60
Ph	H	80	24	40
$HOCH_2CH_2$-	H	150	24	95
$HOCH(CH_2)CH_2$-	H	150	24	54
Me	Me	150	24	75

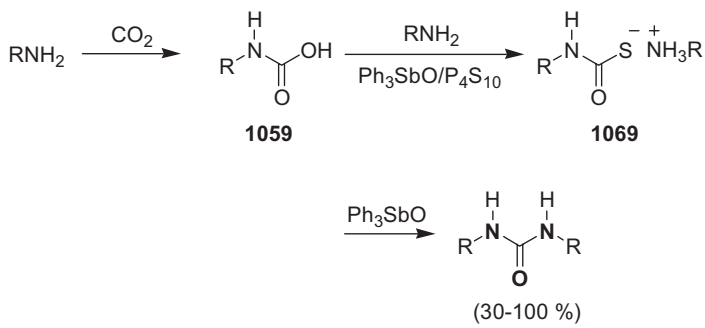
[a] General reaction conditions: diamine/Ph_3SbO/P_4S_{10} = 20/1.0/2.0 mmol, benzene (20 mL), CO_2 at 4.9 MPa, time 12 h; [b] Isolated yield; [c] In the absence of the catalytic system.



1067 **1068**

Typical procedure. *Imidazolidinone* **1068** [778]: A mixture of ethylenediamine (1.2 g, 20 mmol), Ph_3SbO (1.0 mmol), and P_4S_{10} (2.0 mmol) was autoclaved under a pressure of $\mathbf{CO_2}$ (4.9 MPa). Imidazolidinone was isolated by column chromatography (silica gel; eluent: ethyl acetate/hexane, 1:1, *v*/*v*); yield 1.5 g (85%).

Monitoring the reaction of primary amines with $\mathbf{CO_2}$ by ^{13}C NMR spectroscopy revealed that the reaction course involves thiolation of the carbamic acid **1059** to give an intermediate antimony carbamate species **1069**, followed by aminolysis of the carbamothioic acid thus formed.



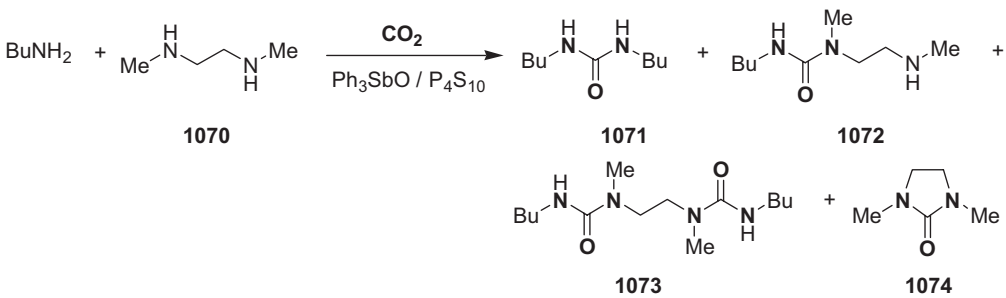
1059 **1069**

The approach described above exploits the aminolysis of thiol carbamic acids under mild conditions, thereby by-passing the difficulties encountered in the un-

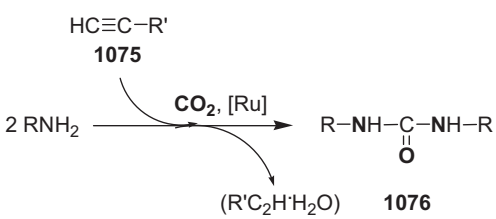
catalyzed carbonylation of amines by **CO_2**, where the generation of free isocyanate by degradation of carbamate salts under severe conditions is thought to give rise to the high temperature requirement.

Although all attempts to prepare tetraethylurea from diethylamine and **carbon dioxide** failed (the main product at 160 °C was tetraethylthiourea), the co-carbonylation of butylamine and diethylamine gave trisubstituted urea in 42% yield at 80 °C [778].

Co-carbonylation of butylamine with *N*,*N*′-dimethylethylenediamine **1070** gave *N*,*N*-dimethyl-2-imidazolidinone **1074** in good yield under mild conditions. This cyclic urea could not be obtained at reaction temperatures lower than 150 °C in the direct carbonylation of *N*,*N*-dimethylethylenediamine **1070**, but it could even be obtained at 80 °C in this co-carbonylation system. These results suggest that a transcarbonylation from the butyl carbamate to the diamine plays an important role, accelerating carbonylation of the diamine through thiolation.



Aliphatic and benzylic primary amines react with **carbon dioxide** in the presence of ruthenium complexes and stoichiometric amounts of terminal alkynes **1075**, especially propargyl alcohols, which act as water scavengers, to directly afford *N*,*N*′-disubstituted symmetrical ureas **1076**.



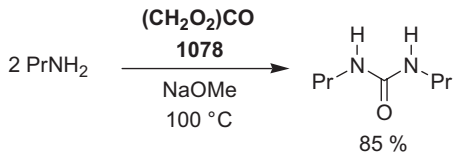
The reaction is usually performed at 120–140 °C in the presence of a mixture of $RuCl_3 \cdot H_2O$ and Bu_3P (amine/Ru molar ratio 100:1) and an excess of the propargyl alcohol derivative (generally 2-methylbut-3-yn-2-ol) affording *N*,*N*′-disubstituted symmetrical ureas **1076** in 41–68% yield [779, 780].

More conveniently, ureas **812** can be synthesized by reaction of amines with carbamate esters **811** prepared from alkyl halides and **carbon dioxide** in the presence of bases, as described in Section 4.3.2.10 [286].

4.3.4.5 Organic Carbonates

Carbonic acid diesters are very attractive reagents and of great economic interest because they represent safe, non-corrosive, and environmentally acceptable alternatives to phosgene for carbonylation and carboxylation reactions. For example, methoxycarboxylation with **dimethyl carbonate** offers an eco-friendly alternative route for the production of carbamates and isocyanates, which are valuable precursors of ureas (see Sections 4.3.1 and 4.3.2) [781, 782]. The method is comparable, from an environmental point of view, with the transition metal catalyzed carbonylation of nitro compounds and amines with CO.

Ethylene carbonate 1078, which is prepared in large amounts by reacting ethylene oxide with CO_2 [288], represents an effective carbonylating reagent for the conversion of *n*-propylamine **1077** into *N*,*N*′-di-*n*-propylurea **1079**.



Reaction of **1078** with an excess of *n*-propylamine **1077** in 28% methanolic NaOMe in an autoclave at 100 °C for several hours affords the product **1079** in 85% yield [783]. The procedure can be efficiently applied to the large-scale synthesis of both symmetrical and unsymmetrical *N*,*N*′-disubstituted ureas in high yield.

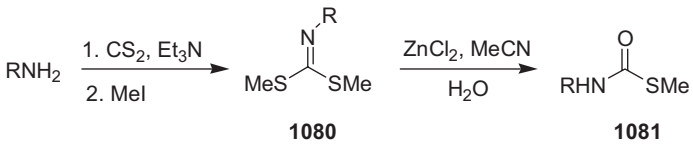
4.3.4.6 Aminolysis of *S*-Methylthiocarbamates Prepared from Carbonimidodithioates

Carbonimidodithioates 1080, which can be regarded as thioketals of isocyanates, are easily prepared by reaction of primary amines or amino acid esters with CS_2, followed by methylation with MeI. These compounds are converted into ***S*-methylthiocarbamates 1081** in good yields upon treatment with $ZnCl_2$ in $MeCN/H_2O$ (3:1) at 60 °C for 6–10 h. *S*-Methylthiocarbamates **1081** can also be conveniently prepared from ***S,S*-dimethyldithiocarbonate** (**DMDTC**) **786**, as described in Section 4.3.2 ''Carbamates''.

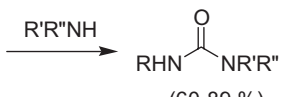
Further treatment of **1081** with 2 equivalents of another primary or secondary amine in MeCN at 30–80 °C leads to unsymmetrical ureas **1082** in 60–89% yield. The second amine molecule can also be an amino acid ester, leading in such cases to the urea dipeptides [784].

4.3.4.7 Diiodosilane Method

Isocyanates are formed under very mild, low temperature reaction conditions from a wide variety of carbamates by treatment with commercially available diiodosilane (SiI_2H_2) and diisopropylethylamine (iPr_2EtN, *Hunig's base*). *In situ* trapping of the isocyanate with primary or secondary amines efficiently leads to ureas [206]. Since isocyanates are both products and key intermediates, the diiodosilane method has been extensively described in Section 4.3.1 ''Isocyanates''.

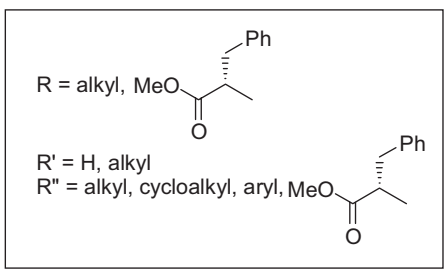


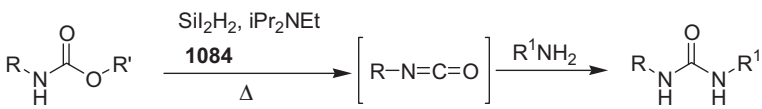
1080 **1081**



(60-89 %)

1082



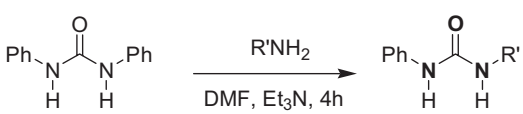


1083 **1085**

4.3.4.8 *N*-Alkylation of Simple Ureas

Urea itself and ***N,N′*-disubstituted ureas** can be conveniently utilized as versatile and environmentally safe building blocks for the synthesis of more complex targets containing the ureido moiety, through various reactions, including displacement of one or both amino groups, *N*-alkylation, and imine/enamine formation. Some recent applications are summarized below.

N,N′-Diphenylurea **1086** (R = Ph) is converted into *N*-phenyl-*N*-alkylurea **1087** in 77–92% yield by treatment with a large excess of a primary amine and a small amount of triethylamine in DMF at reflux for 4 h [785].

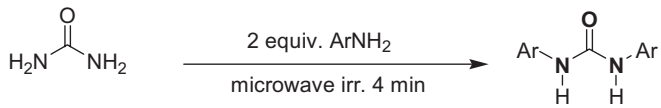


77-92 %

1086 **1087**

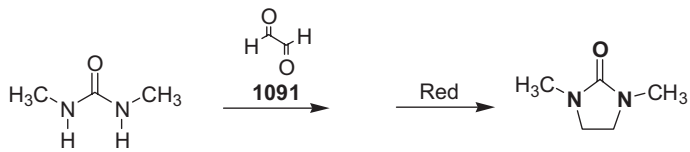
The method does not proceed with hindered secondary amines, gaseous amines, or aromatic amines bearing electron-withdrawing substituents. The latter, however,

are converted into symmetrical *N*,*N*′-diarylureas **1089** in 40–85% yield upon microwave irradiation of a 2:1 molar mixture of the selected amine and urea **1088** for 4 min [786].

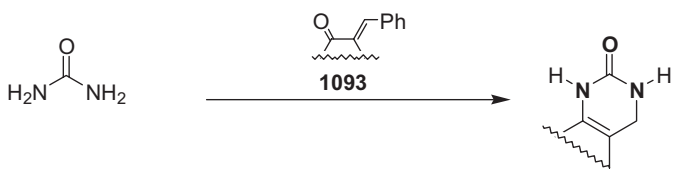


1088 **1089**

Cyclic ureas **1092** and **1094** can be prepared in satisfactory yields (54 and 77%, respectively) by condensation of *N*,*N*′-dialkylureas of type **1090** with glyoxal **1091** or of urea **1088** with α-functionalized carbonyl compounds **1093**, followed by hydrogenolysis or removal of water [787–789].

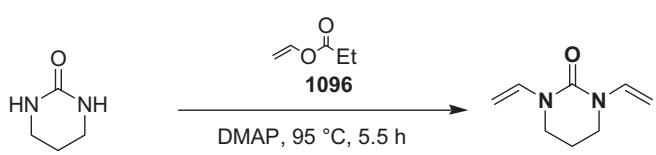


1090 **1092**



1088 **1094**

N-Alkylation of ureas represents a further useful method for the selective synthesis of *N*,*N*,*N*′,*N*′-tetrasubstituted ureas, including cyclic ones. Thus, *N*,*N*′-divinylpropyleneurea **1097** is prepared in 89% yield by the addition of vinyl propionate **1096** over a period of 15 min to a mixture of propyleneurea and dimethylaminopyridine (DMAP) at 95 °C and refluxing for 5.5 h [790].

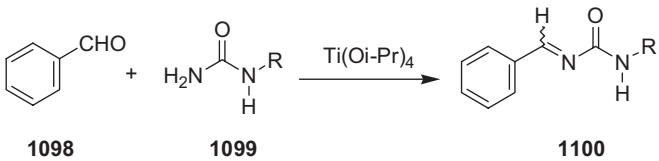


1095 **1097**

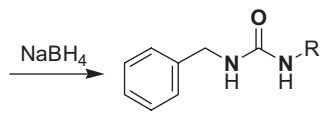
4.3.4.9 The Reductive Amination of Aldehydes with Monoalkylureas

Two similar methods for the synthesis of unsymmetrical *N*,*N*′-disubstituted ureas by the reductive amination of aldehydes with monoalkylureas or urea have recently been reported.

Reductive amination of aldehydes with monoalkylureas in the presence of **titanium(IV) isopropoxide** and **sodium borohydride** in THF represents a viable, laboratory-scale route to unsymmetrical *N*,*N*′-disubstituted ureas in 39–94% yield.



1098 **1099** **1100**

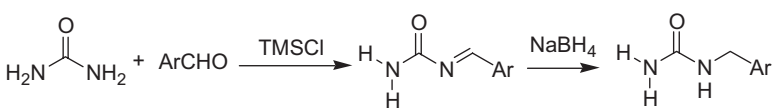


39-94 %

1101

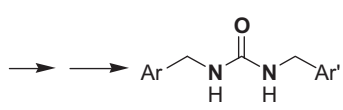
Titanium(IV) isopropoxide behaves as the Lewis acid as well as as an efficient acid scavenger, and is compatible with a variety of functional groups, such as lactams, acetamides, acetals, and *tert*-butyldimethylsilyl ethers. Unfortunately, aldehydes with an α-hydrogen do not undergo selective reactions [791].

A rather similar method based on reductive alkylation of urea involves the use of **trimethylsilyl chloride** (**TMSCl**) as the catalyst in the condensation step and again utilizes **sodium borohydride** as the reducing agent [792]. Under these conditions, the parent urea can be converted into monosubstituted as well as disubstituted ureas in yields of 60–92%.



60-92 %

1088 **1102** **1103**



65-89 %

1104

Ar, Ar' = Ph, 2-$CF_3C_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-$Et_2NC_6H_4$, 4-$MeOC_6H_4$, 4-$Bu^tC_6H_4$, 2-$MeOC_6H_4$, 4-BrC_6H_4, 3-$MeOC_6H_4$, 4-HOC_6H_4

Although both of these methods offer some advantages over the previous ones and are able to produce a variety of unsymmetrical substituted ureas without the use of gas-phase or highly toxic reagents, they share a major drawback in that they generate large amounts of waste salts.

4.3.4.10 Catalytic [$Ru(PPh_3)_3$] Aminolysis of Formamides

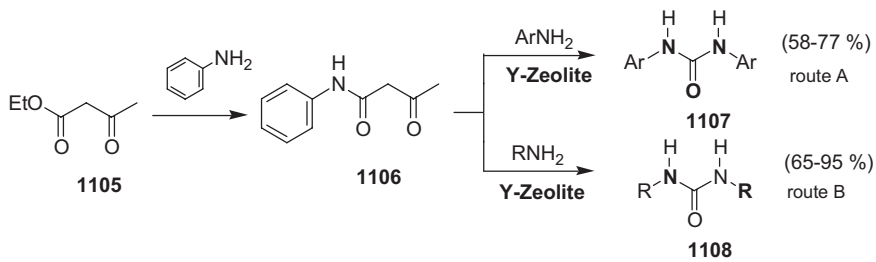
In a more convenient and more environmentally friendly protocol, unsymmetrical *N,N′*-disubstituted ureas, including sterically hindered ones, can be synthesized (76–93% yield) from *N*-aryl-substituted formamides and amines in the presence of catalytic amounts of $Ru(PPh_3)_3$ (substrate/catalyst ratio 20:1) [736]. A catalytic cycle involving the formation of an isocyanate-coordinated ruthenium dihydride intermediate is postulated.

4.3.4.11 HY Zeolite HSZ-360 Catalyzed Aminolysis of Acetoacetanilides

A commercially available acid zeolite has also been reported to be an efficient catalyst in the completely salt-free production of ureas. Reaction of aromatic amines with ethyl acetoacetate **1105** in the presence of **HY zeolite HSZ-360** (1 g of zeolite/20 mmol of amine) under solvent-free conditions gives symmetrical diarylureas **1107** in good yields (58–77%) and with excellent selectivity (93–96%) through a straightforward procedure (route A). Acetone, ethanol, and traces of acetoacetanilides are the sole by-products [793].

This type of synthesis cannot be applied to aliphatic amines because these compounds undergo nucleophilic attack at the keto group to produce *β*-alkylaminocrotonic acid ethyl esters as the main products.

However, symmetrical aliphatic ureas **1108** can be successfully prepared (65–95% yield) by reacting primary aliphatic amines with acetoacetanilide **1106** over the same zeolite catalyst (route B) (Table 4.35) [794].

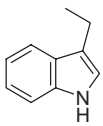
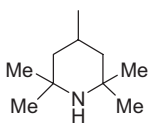


Ar = 4-$MeOC_6H_4$, C_6H_5, 3-MeC_6H_4, 4-MeC_6H_4, 4-ClC_6H_4
R = alkyl, cycloalkyl

In both cases, the zeolite catalyst can be recovered and reused for at least five runs without a discernible decrease in its activity.

General procedure. *N,N′-Dialkylureas* **1108** [794]: To a solution of the selected aliphatic amine (20 mmol) and **zeolite HSZ-360** (0.5 g) at 180 °C, the acetoacetanilide (0.9 g, 5 mmol) was added portionwise. After 3 h, the reaction mixture was cooled to room temperature, hot methanol (50 mL) was added, and the catalyst was removed by filtration and washed with hot methanol (50 mL). After cooling the combined methanol solutions to room temperature, the *N,N′*-dialkylurea **1108** was

Tab. 4.35. Synthesis of various *N,N′*-dialkylureas **1108** [794].

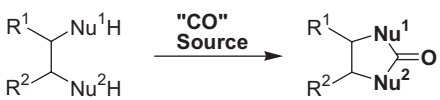
Alkyl group, R	*N,N′-dialkylureas Yield (%)*	*Selectivity (%)*
$PhCH_2$	95	97
C_6H_{11}	85	95
C_8H_{17}	82	93
C_9H_{19}	80	94
$C_{10}H_{21}$	85	95
(*R*)-$Ph(CH_3)CH$	75	97
$PhCH_2CH_2$	78	93
	65	96
	70	97

precipitated by adding distilled water (150 mL). The product was isolated by Buchner filtration and recrystallized from methanol.

4.3.5

Reactions with Binucleophiles

Phosgene and several of its equivalents react with 1,2-binucleophiles **1109** forming 2-oxo-five-membered heterocycles. Oxazolidin-2-ones (**1110**, $Nu^1 = NH$, $Nu^2 = O$), thiazolidin-2-ones (**1110**, $Nu^1 = NH$, $Nu^2 = S$), imidazolidin-2-ones (**1110**, Nu^1, $Nu^2 = NH$), and 1*H*-benzo[*d*][1,3]oxazine-2,4-diones (**1110**, $Nu^1 = COO$, $Nu^2 = NH$) are the most important classes of reaction products.



1109 **1110**

Nu^1 = O, S, NH, COO
Nu^2 = O, S, NH

Several synthetic methods were presented in Sections 4.3.2, 4.3.3, and 4.3.4, in which five-membered cyclic carbamates (oxazolidin-2-ones), cyclic carbonates (1,3-dioxolan-2-ones), and cyclic ureas (imidazolidin-2-ones), respectively, were constructed. General reviews of the synthesis and chemistry of 2-oxazolidinones and thiazolidin-2-ones [363, 364], reporting the reactions of *N,O*- and *N,S*-1,2-binucleophilic substrates with various carbonylating agents, are available.

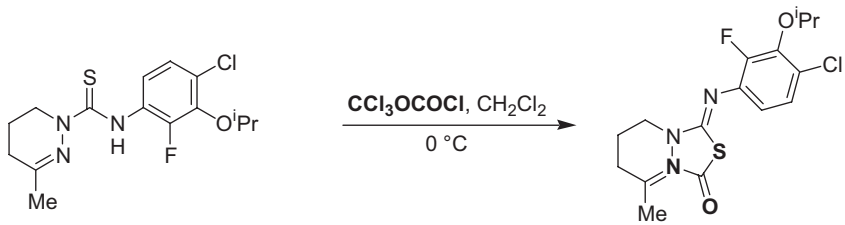
When the substrates **1109** are α-amino acids (1,1-binucleophiles having $Nu^1H = COOH$ and $Nu^2 = NH$), a special class of mixed anhydrides, 2,5-dioxo-

1,3-oxazolidines, more commonly referred to as *N*-carboxy-α-amino acid anhydrides (NCAs), is formed.

4.3.5.1 *N,O*- and *N,S*-Binucleophiles. Formation of Oxazolidin-2-ones and Thiazolidin-2-ones

Aryl and **alkyl chloroformates**, **alkyl and aryl carbonates**, **diphosgene**, and **oxalyl dichloride** are the most commonly employed reagents. For many reasons, as discussed in Section 4.3.2, reactions of vicinal amino alcohols with **triphosgene** [522–524, 526, 528] or **1,1′-carbonyldiimidazole** [461–463, 467–483] have recently emerged as the preferred and most cited methods for preparing 2-oxazolidinones.

An interesting cyclocarbonylation with **diphosgene** involving a thiourea-type sulfur atom has been reported in relation to a synthesis of condensed pyridazine derivatives, which are used as herbicides [795].

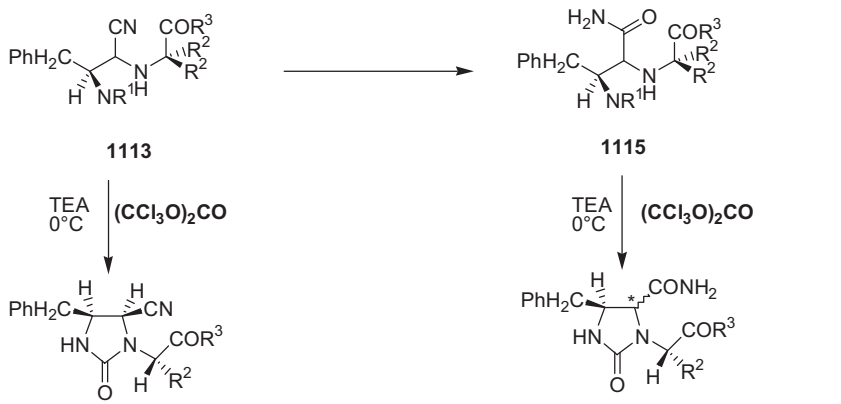


1111 **1112**

4.3.5.2 *N,N*-Binucleophiles. Formation of 2-Oxoimidazolidines

The formation of several cyclic ureas by methods employing phosgene equivalents has been discussed in part in Section 4.3.4. In this Section, additional interesting cyclization examples and methods are described.

The *N*-deprotected pseudopeptides **1113** and **1115** were cyclized to the corresponding 2-oxoimidazolidines with **triphosgene** and triethylamine in dry dichloromethane at 0 °C [796–798].

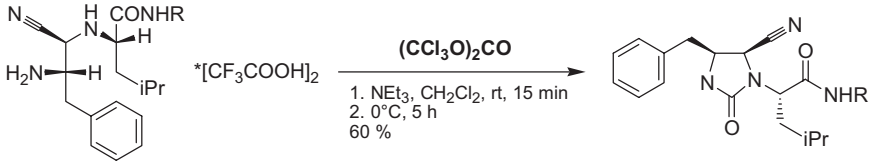


1113 **1115**

1114 **1116**

R^1 = H, R^2 = $CH_2CH(CH_3)_2$, R^3 = NH_2
R^1 = H, R^2 = $CH_2CH(CH_3)_2$, R^3 = Ala-NH_2
R^1 = H, R^2 = $CH_2CH(CH_3)_2$, R^3 = OMe
R^1 = H, R^2 = $CH_2CH(CH_3)_2$, R^3 = Ala-OMe

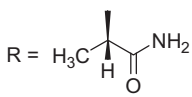
Other interesting similar examples are presented below [796, 799]:

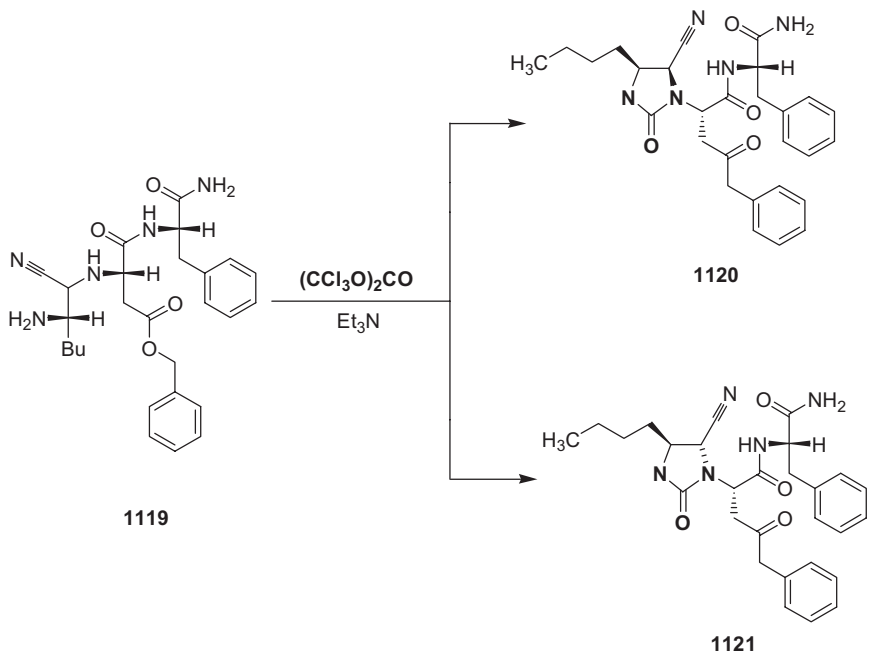


1117 **1118**

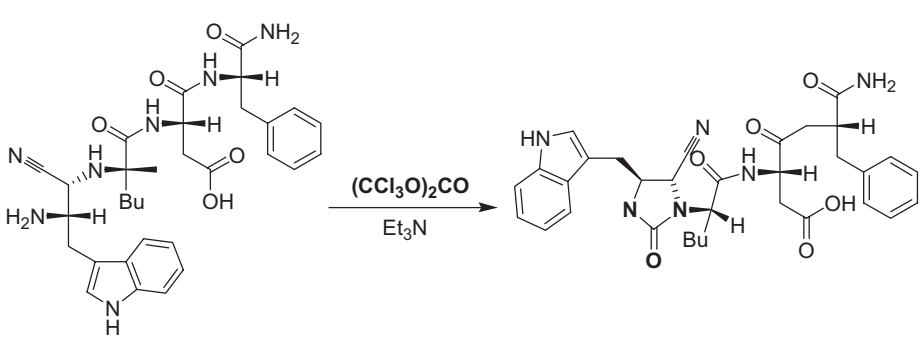
R = H, Yield 60 %

R = Yield 50 %



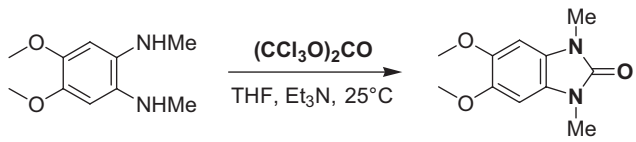


1119 **1120** **1121**



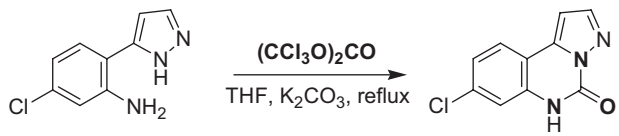
1122 **1123**

Cyclic urea **1125** has been obtained with **triphosgene** and Et_3N in THF at 25 °C [800].



1124 **1125**

Triphosgene has proved to be of general utility in closing anilino heterocycles **1126** to the corresponding quinazolinone ring systems **1127** [801].



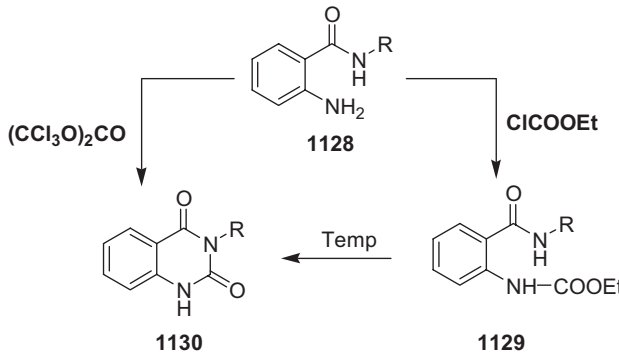
1126 **1127**

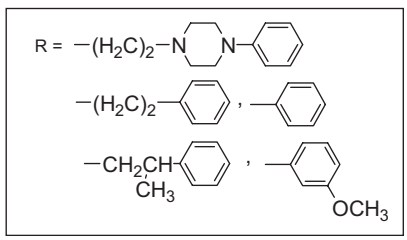
Typical procedure. *8-Chloropyrazolo[5,1-c]quinazolin-5(6H)-one* **1125** [801]: **Triphosgene** (1.83 g, 6.17 mmol) was added to a solution of pyrazole **1126** (1.0 g, 5.16 mmol) in THF (30 mL). Solid K_2CO_3 was added and the suspension was heated under reflux for 22 h. After cooling, water was added and the precipitate formed was collected by filtration to yield 1.07 g of 8-chloropyrazolo[5,1-*c*]quinazolin-5(6*H*)-one **1127**. Recrystallization from DMF afforded 0.638 g of crystalline material.

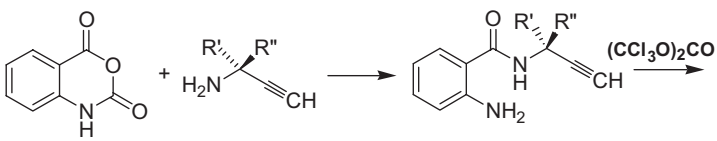
o-Aminobenzamides **1128** are easily ring-closed to quinazolinediones **1130**, which possess excellent antihypertensive properties [802, 803]. Two ring-closure methods have been evaluated [804].

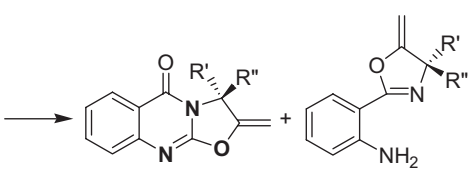
General procedure. *Quinazolinediones* **1130** [804]: A solution of *o*-aminobenzamide (5 mmol) in dichloromethane (50 mL) was stirred at room temperature, and then a solution of **triphosgene** (0.5 g, 1.7 mmol) in the same solvent (10 mL) was added. The mixture was refluxed for 2 h. Thereafter, the organic phase was washed with water and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave quinazolinedione **1130** in 78–88% yield.

Oxazoloquinazolines **1134** and oxazoles **1135** have been prepared from *o*-amino-*N*-(1,1-disubstituted-propynyl)benzamides **1133** with **triphosgene** by angular cyclization, promoted by either the initial exothermic reaction on the addition of **triphosgene** and/or by refluxing in pyridine [805].









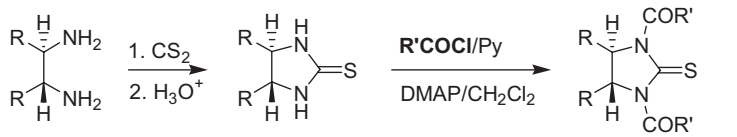
R' = R" = Me
R' = R" = Et
R' = R" = -$(CH_2)_5$-

General procedure. *2-Methylene-3,3-disubstituted-oxazolo[2,3-b]quin-5(3H)-ones* **1134** [805]: To a well-stirred and ice-cooled solution of an *o*-amino-*N*-(1,1-disubstituted-propynyl)benzamide **1133** (5 mmol) in pyridine (15 mL) was added **triphosgene** (5 mmol). The reaction mixture was allowed to warm to room temperature, then slowly heated to reflux, and maintained under reflux for 6–8 h. After cooling to room temperature, the excess pyridine was neutralized with 5% hydrochloric

acid and the mixture was extracted with dichloromethane. The organic layer was washed with 5% aq. sodium hydroxide at pH 8, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a viscous brown oil in each case. Column chromatography (CH_2Cl_2) gave oxazoles **1135** as the first-eluting components. The oxazoloquinazolines **1134** were eluted subsequently; yields 31–50%.

It has been reported that reaction of *trans*-1,2-diaminocyclohexane **1136a** with either **phosgene** or *phosgene equivalents* such as **1,1′-carbonyldiimidazole**, **urea**, **dimethyl carbonate**, or **methyl chloroformate** does not give the desired imidazolidin-2-one **1139a**, but rather an oligomeric product [806]. This indicates that the intermolecular reaction competes effectively with the intramolecular cyclization, a result that has some precedent in the reaction of 1,2-diaminoethane (ethylenediamine) with **urea** [807].

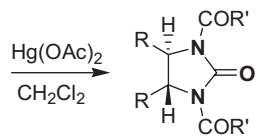
A particularly attractive alternative approach is the introduction of a thiocarbonyl group, to give the imidazolidine-2-thione **1137**, followed by acylation to give **1138**, and finally dethionation to the 1,3-diacylimidazolidin-2-one **1139** [806]. The overall yield is 70–80%, depending on the particular substituents.



1136a R = -$(CH_2)_4$-
1136b R = Ph

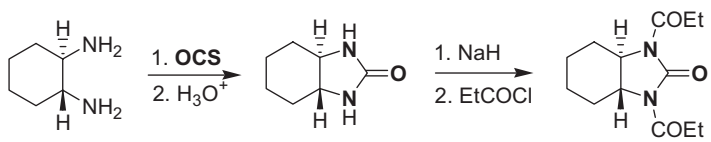
1137a R = -$(CH_2)_4$-, yield 94 %
1137b R = Ph, yield 90 %

1138a R = -$(CH_2)_4$-
1138b R = Ph



1139a R = -$(CH_2)_4$-
1139b R = Ph

A shorter route, in which **carbon disulfide** is replaced by **carbonyl sulfide**, has also been proposed [806].



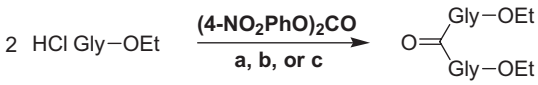
70 %

91 %

1140 **1141** **1142**

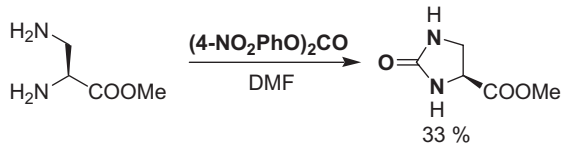
Bis(4-nitrophenyl)carbonate 717 (for a preparation, see Section 4.3.3.2) may be recommended as a convenient reagent for the introduction of a carbonyl bridge

between two amino groups. Its application enables syntheses of different types of urea derivatives: *N*,*N*-dialkyl or aryl ureas, *N*,*N*′-carbonyl-bis(amino acid ester)s, *N*-alkyl or arylaminocarbonylamino acid esters, and peptides containing the urea residue.



1143 **1144**

a: Py, 60-67%
b: TEA/DMF, 48%
c: 4-NO_2PhONa/DMF, 77%



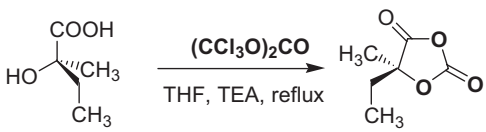
1145 **1146**

An interesting method for the preparation of *N*,*N*′-carbonyl-bis(amino acid ester)s by reaction of **bis(4-nitrophenyl)carbonate** (see also Section 4.3.4 ''Ureas'') with amino acid esters has been reported [808, 809]. When the carbonate is reacted with two equivalents of a peptide ester **1143**, *N*,*N*′-carbonyl-bis(peptide ester) **1144** is obtained, but a hydantoin derivative is formed as a side product. The hydantoin derivative is a major product when equimolar amounts are allowed to react. This method has found application in the preparation of larger *N*,*N*-carbonyl-bis-peptides.

4.3.5.3 *O*,*O*-Binucleophiles. Formation of Cyclic Carbonates

The formation of several cyclic carbonates by methods employing **phosgene equivalents** has been discussed in part in Section 4.3.3 ''Carbonates''. In this Section, additional reported cyclization procedures with **triphosgene** are illustrated.

(*S*)-(−)-5-Ethyl-5-methyl-1,3-dioxolane-2,4-dione **1148** has been obtained in 68% isolated yield by treatment of enantiomerically pure **1147** with **triphosgene** (0.67 equiv.) in THF containing triethylamine (1.0 equiv.) for 5 h under reflux [810].

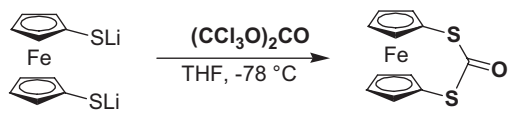


1147 **1148**

Typical procedure. *(S)-(−)-5-Ethyl-5-methyl-1,3-dioxolane-2,4-dione* **1148** [810]: To a solution of (*S*)-(+)-2-hydroxy-2-methylbutyric acid **1147** (1.06 g, 8.97 mmol) in THF

(20.5 mL) containing triethylamine (1.25 mL, 8.97 mmol) at room temperature, a solution of **triphosgene** (1.78 g, 5.98 mmol) in THF (4.5 mL) was added dropwise via a cannula over a period of 10 min. The resulting heterogeneous reaction mixture was refluxed for 5 h and then concentrated in vacuo. The residue was triturated with diethyl ether and filtered through a plug of glass wool. The combined filtrate and washings were concentrated in vacuo to give a yellow oil, which was distilled under reduced pressure to afford 872 mg (69%) of (*S*)-(−)-5-ethyl-5-methyl-1,3-dioxolane-2,4-dione **1148** as a colorless liquid.

Starting from **triphosgene** and 1,1′-ferrocenediols, 1,3-dioxa-[3]ferrocenophan-2-ones ''ferrocenylenecarbonates'' $Fe(C_5H_4O)_2CO$, and the corresponding thio derivative 1,3-dithia-[3]ferrocenophan-2-one, ''ferrocenylenedithiocarbonate'' $Fe(C_5H_4S)_2CO$ **1150**, were obtained [811].



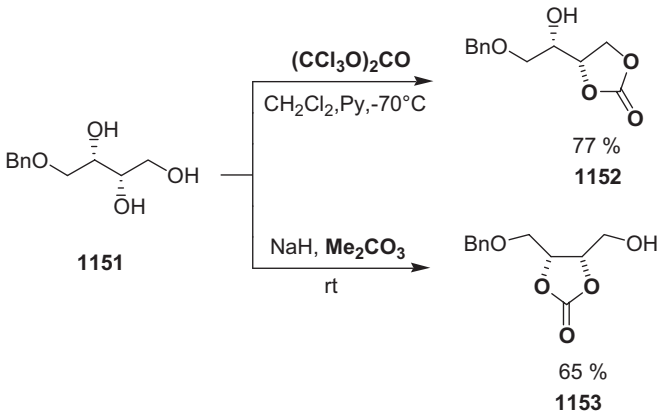
1149 **1150**

Typical procedure. *1,3-Dithia-[3]ferrocenophan-2-one $Fe(C_5H_4S)_2CO$* **1150** [811]: To a solution of $Fe(C_6H_4SLi)_2 \cdot 2THF$ **1149** (406 mg, 1 mmol) in THF (20 mL) at −78 °C, a solution of **triphosgene** (0.33 mmol, 98 mg) in THF (5 mL) was added dropwise. After warming to ambient temperature, the solution was decanted off from the precipitated LiCl, filtered through Celite, and concentrated in vacuo. Recrystallization of the residue from CH_2Cl_2 afforded colored crystals, which decomposed at 194 °C; yield 224 mg (82%).

The regioselective preparation of five-membered cyclic carbonates by treatment of 1,2,3-, 1,2,4-, or 1,2,5-triols with **triphosgene**, **dimethyl carbonate**, or **1,1′-carbonyldiimidazole** has been reported [812].

The substituted 1,2,3-triol **1151** reacts with **triphosgene** in the presence of pyridine (Method A) to afford five-membered 1,2-cyclic carbonate **1152** as the sole product. However, reaction of 1,2,3-triol **1151** with **dimethyl carbonate** (Method B) affords the more stable internal cyclic carbonate **1153**.

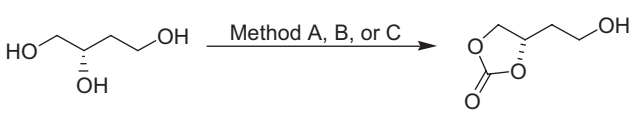
Typical procedure. *(2S,3S)-4-Benzyloxy-1,2,3-butanetriol 1,2-cyclic carbonate* **1152** (*Method A*) [812]: To a stirred solution of **triphosgene** (104 mg, 0.35 mmol) in dichloromethane (1 mL) at −70 °C were added pyridine (0.29 mL, 3.59 mmol) and a solution of triol **1151** (125 mg, 0.59 mmol) in dichloromethane (1 mL). Once the addition was complete, the reaction mixture was allowed to warm to room temperature. The resultant homogeneous solution was quenched with saturated aq. ammonium chloride solution, washed with 1 N aq. HCl, saturated aq. $NaHCO_3$, and brine, and dried over anhydrous $MgSO_4$. The organic layer was filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using EtOAc/hexanes (1:1) as eluent to afford (2*S*,3*S*)-4-benzyloxy-1,2,3-butanetriol 1,2-cyclic carbonate **1152** (108 mg, 77%).



Typical procedure. *(2S,3S)-4-Benzyloxy-1,2,3-butanetriol 2,3-cyclic carbonate* **1153** (*Method B*) [812]: To a stirred solution of triol **1151** (130 mg, 0.61 mmol) in **dimethyl carbonate** (1 mL) at room temperature was added NaH (60% dispersion in mineral oil, 34 mg, 1.42 mmol) and the mixture was stirred for 30 min. The reaction was then quenched with brine and the mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using ethyl acetate as eluent to afford (2*S*,3*S*)-4-benzyloxy-1,2,3-butanetriol 2,3-cyclic carbonate **1153** (95 mg, 65%).

Treatment of (*S*)-1,2,4-butanetriol **1154** with **triphosgene** (Method A), **dimethyl carbonate** (Method B), or **1,1′-carbonyldiimidazole** (**CDI**, Method C) provided the five-membered 1,2-cyclic carbonate **1155** as the only isolated product, without formation of the six-membered cyclic carbonate [812].

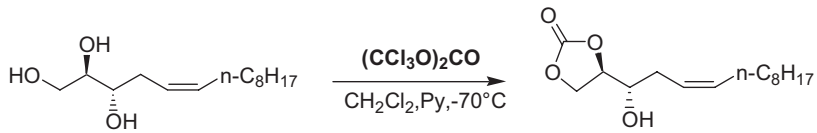
Typical procedure. *(S)-1,2,4-Butanetriol 1,2-cyclic carbonate* **1155** (*Method C*) [812]: To a stirred solution of triol **1154** (150 mg, 1.41 mmol) in dichloromethane (2 mL) at room temperature under nitrogen atmosphere was added **CDI** (340 mg, 1.55 mmol). After stirring for about 30 min, the reaction mixture was filtered through silica gel and the dichloromethane was evaporated in vacuo. The crude product was purified by column chromatography on silica gel using EtOAc/hexanes (2:1) as eluent to afford (*S*)-1,2,4-butanetriol-1,2-cyclic carbonate **1155** (147 mg, 79%).



1154 **1155**

Method A: **$(CCl_3O)_2CO$**, CH_2Cl_2, Py, -70°C, 66%
Method B: **$(CH_3O)_2CO$**, NaH, rt, 76 %
Method C: **CDI**, CH_2Cl_2, rt, 79 %

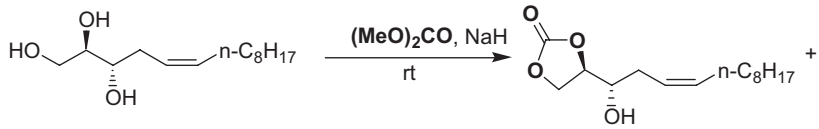
Reaction of *cis*-substituted 1,2,3-triol **1156** with **triphosgene** yielded (2*R*,3*S*)-(*Z*)-5-tetradecene-1,2,3-triol 1,2-cyclic carbonate **1157** in 60% yield [812].



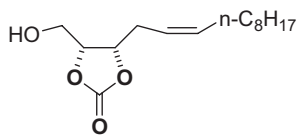
60 %

1156 **1157**

However, cyclocarbonylation of *cis*-substituted 1,2,3-triol **1156** with **dimethyl carbonate** gave a mixture of cyclic carbonates **1157** and **1158** in a 1:1 ratio [812].



1156 **1157** 1 : 1

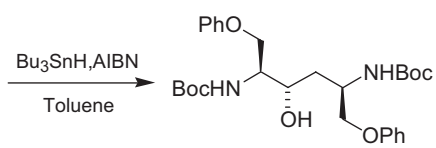


1158

Monodeoxygenation of the aminodiol **1159**, previously protected as thiocarbonate **1160**, thereby affording **1161** has been reported [411]. Compound **1159** was reacted with thiocarbonyldiimidazole **SCDI** to give the cyclic thiocarbonate **1160** in 70% yield.

70 %

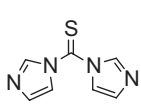
1159 **1160**



68 %

1161

SCDI =



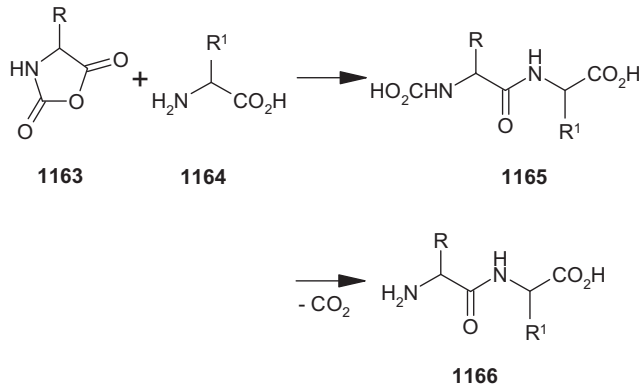
The stereoselective conversion of 1,2-diols into alkane-1,2-diyl carbonates has been carried out at room temperature, without employing catalysts or toxic and/or polluting reactants, by adding the 1,2-diol and then the alkylating agent to a solutions of $C_2O_6^-$, CO_3^-, or HCO_3^- anions and tetraalkylammonium cations in acetonitrile. Such solutions can be easily prepared by simple electrochemical or chemical routes [713].

Oxalyl chloride has been reported as a *phosgene equivalent* in the formation of cyclic carbonates [814, 815].

4.3.5.4 N,COOH Binucleophiles. Formation of *N*-Carboxyanhydrides of α-Amino Acids

2,5-Dioxo-1,3-oxazolidines 1165, more commonly referred to as ***N*-carboxy-α-amino acid anhydrides (NCAs)** or Leuchs' anhydrides [816, 817], constitute a special class of mixed anhydrides featuring simultaneous amino group protection and carboxylate activation of α-amino acids.

NCAs have proven to be very effective as activated intermediates for the stepwise synthesis of peptides, particularly for the manufacture of dipeptides.



1163 **1164** **1165**

1166

Since **NCAs** are used as monomers for high molecular weight polypeptide preparation, a clean synthesis is required to ensure production of polymerization grade material.

The apparent advantage of the concurrent amine protection and carboxylate activation in NCAs is, however, counterbalanced by their high reactivity. These reagents are sensitive to moisture and are prone to polymerization [818–820]; therefore, difficulties are encountered in controlling amide bond formation.

Dipeptide formation, by condensation of one amino acid with the **NCA** of a second, is a facile process, but there are difficulties in controlling the amide bond-forming reaction when the NCA technology is applied to heteropolymers. An additional problem is the fact that **NCAs** themselves are only accessible by less-than-straightforward routes. These often involve harsh reaction conditions, long reaction times with poor yields, and, not inconsequentially, the use of toxic reagents [821]. Comprehensive reviews on the preparation and reactions of NCAs have appeared in the literature [822, 823].

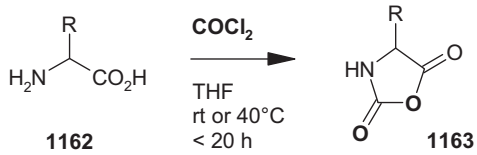
Tab. 4.36. NCAs **1163** from amino acids **1162** with **phosgene** [827–835].

Amino acid 1162		*Yield (%) of NCA 1163*	*References*
a	Val	100	827, 828
b	Leu	69–85	829, 830
c	Phe	65	831
d	Trp	46–84	832, 826
e	Glu	60–70	833, 835
f	Asp	80–85	834
g	Pro	100	835

Phosgene

Direct addition of **phosgene** (used in large excess at elevated temperatures) to the α-amino acid has been the preferred route, principally because facile, rapid reaction *prevents racemization* of the resulting NCA.

NCAs are often formed by the reaction of unprotected amino acids with an excess of **phosgene** [824–835]. Work-up of most such reaction mixtures is very simple. On removal of the excess phosgene and the solvent by evaporation, the corresponding NCAs are obtained in good yields and in pure form. In most cases, further purification is not necessary, although several preparations add a recrystallization step (Table 4.36).



Typical procedure. *L-Valine-N-carboxyanhydride [(S)-4-Isopropyl-2,5(3H,4H)-oxazolidinone]* **1163a** [827]: To a stirred suspension of L-valine **1162a** (46.8 g, 0.4 mol) in dry THF (400 mL) was slowly added a solution of **phosgene** (0.8 mol) (for a *safe source*, see Chapter 7) in toluene (stock solution ca. 5 M). In the closed vessel (Author's remark: It is better to use a reflux condenser cooled to at least −15 °C or a dry-ice reflux condenser under ambient pressure), the mixture was stirred at 45 °C for 7 h in order to obtain a clear solution. The solvent was then evaporated in vacuo at room temperature. The residue was redissolved in dry THF and this solution was concentrated to dryness. The crystalline residue was dried over $CaCl_2$ in vacuo; yield 57.0 g (quantitative), mp 62 °C, $[\alpha]^{22}_D = -42.9$ ($c = 1.0$, THF). IR (KBr): $\nu_{max} = 1760\ cm^{-1}$ (C=O).

Typical procedure. *4-(2-Methylpropyl)oxazolidine-2,5-dione [L-Leu-NCA]* **1163b** [829]: A solution of **phosgene** (for a *safe source*, see Chapter 7) (12.5% in toluene, 25 mL, 31.6 mmol) was added to a suspension of L-leucine **1162b** (1.31 g, 10 mmol) in

dioxane (30 mL) and ethyl acetate (25 mL) at 40 °C under a static atmosphere of nitrogen. After 4 h, the leucine had dissolved and then the excess phosgene was removed in a stream of nitrogen. The solvent was removed at 40 °C in vacuo and the residue was recrystallized from diethyl ether/light petroleum (bp 40–60 °C) to yield colorless needles of 4-(2-methylpropyl)oxazolidine-2,5-dione **1163b** (1.01 g, 69%); mp 76–77 °C; IR: ν_{CO} ($CHCl_3$) = 1855, 1780 cm^{-1}.

Typical procedure. *α,N-Carboxytryptophan anhydride [DL-Trp-NCA]* **1163d** [826]: The DL-anhydride was prepared by passing **phosgene** (for *safe phosgenation*, see Chapter 7) for 45 min through a suspension of DL-tryptophan **1162d** in dry dioxane maintained at 40 °C, from which oxygen had been removed by a stream of nitrogen; yield 84%; mp 142 °C (from ethyl acetate/petroleum ether; dec. with CO_2 evolution).

Typical procedure. *(S)-4-(2-Methoxycarbonylethyl)oxazolidine-2,5-dione [L-Glu(OMe)-NCA]* **1163e** [835]: **Phosgene** (for *safe phosgenation*, see Chapter 7) was bubbled through a suspension of L-Glu(OMe)·HCl **1162e** (24.3 g, 150 mmol) in THF (600 mL) over a period of 8 h at 40 °C. The THF was then evaporated in vacuo at 40 °C. The residue was redissolved in dichloromethane (100 mL) and an insoluble solid was filtered off. Removal of the solvent from the filtrate gave a solid in 60% yield; $[\alpha]^{30}_D = -25.24$ ($c = 1.034$, DMSO).

Indiscriminate addition of **phosgene** can lead to side reactions, the products of which can inhibit subsequent polymerization of the **NCAs** [837]. The problem of metering the **phosgene** gas and of maintaining the proper stoichiometric balance has now been solved by the *safe phosgenation* method with special equipment (see Chapter 7).

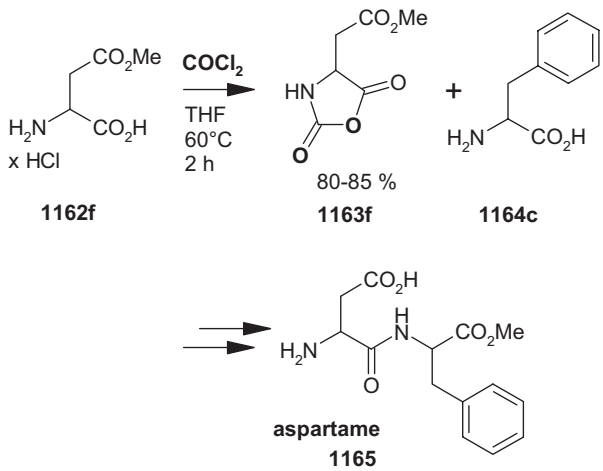
A **phosgene**-based method [838] involves monitoring NCA formation by infrared spectroscopy and employs a standardized *solution of* **phosgene** in benzene, which circumvents the need for large excesses of the gas.

The use of NCAs in biphasic carbonate buffer, as described by Japanese workers, also largely overcomes the above limitation [839–842]. In addition, the application of urethane-protected **NCAs** allows for their facile use in the stepwise synthesis of peptides on solid supports [843].

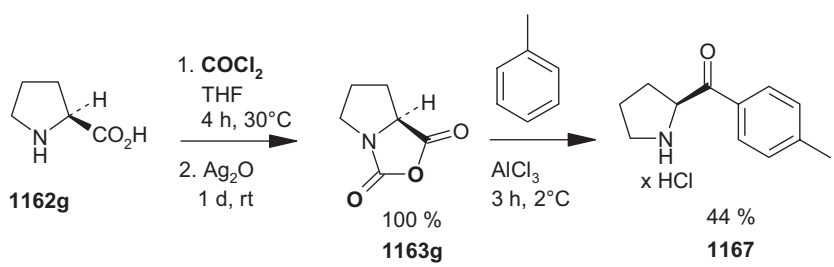
Aspartame is a nutritive sweetener approximately 200 times as sweet as sucrose, which was discovered in 1969. Its chemical constitution is α-L-aspartyl-L-phenylalanine methyl ester **1165**, which can be advantageously and regioselectively produced from L-Asp(OMe)-NCA **1162f** and H-Phe-OMe **1163f**. This protocol is shorter by several preparative and separatory steps compared with other syntheses [834].

Typical procedure. *β-Methyl L-aspartate-N-carboxyanhydride [L-Asp(OMe)-NCA]* **1163f** [834]: Gaseous **phosgene** (for *safety phosgenation*, see Chapter 7) (95 g, 0.96 mol) was bubbled into a slurry of β-methyl L-aspartate hydrochloride **1162f** (80 g, 0.44 mol) in THF (800 mL). The mixture was then heated at 60 °C for 2 h. Thereafter, a rapid stream of nitrogen was passed through the solution to remove excess phos-

gene. The solvent was evaporated, and the colorless residue was placed in an ice bath. It was treated with ethyl acetate (40 mL) followed by petroleum ether (90 mL). The product precipitated to give an isolated yield of 64 g (80–85%); mp 59–61 °C; $[\alpha]^{22}_D = -71.7$ ($c = 3.0$, chloroform).



Friedel–Crafts α-aminoacylation of aromatic compounds with several chiral *N*-carboxy-α-amino acid anhydrides (NCAs) prepared with **phosgene**, **triphosgene**, and **PBr_3** has recently been reported [835, 836]. L-Proline-NCA **1163g** was prepared from proline **1162g** with **phosgene** in ca. 100% yield. Pro-NCA **1163g** reacts with toluene to afford (*S*)-2-*p*-toluoylpyrrolidine hydrochloride **1167** [835].

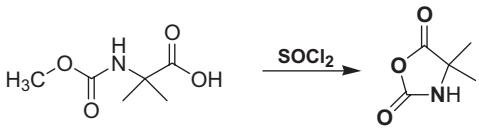


Typical procedure. *L-Pro-NCA* **1163g** [835]: Gaseous **phosgene** (for *safe phosgenation*, see Chapter 7) was bubbled into a suspension of L-Pro **1162g** (17.25 g, 150 mmol) in THF (400 mL) for 4 h at ca. 30 °C. The THF was then evaporated from the homogeneous solution to leave *N*-chlorocarbonyl-L-proline (*N*-COCl-L-Pro) as a yellow oil. To a solution of *N*-COCl-L-Pro (35.7 g, 150 mmol) in acetone (400 mL) were added Ag_2O (20.4 g, 88 mmol) and Norit A (4.5 g) and the mixture was stirred for at room temperature for 1 d. The mixture was then filtered from the black Norit A and the THF (*could be acetone, see above*; the author) was evaporated to afford

L-Pro-NCA **1163g**; yield: 21.1 g (ca. 100%); mp 44.2–48.0 °C; $[\alpha]^{25}_{D} = -99.66$ ($c = 1.002$, $CHCl_3$).

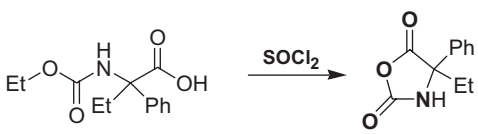
Thionyl chloride, phosphorus tribromide, phosphorus trichloride, and phosphorus pentachloride

α-Methoxycarbonylamino isobutyric acid **1168** reacts with **thionyl chloride** to give 4,4-dimethyl-oxazolidine-2,5-dione **1169** [844].



1168 **1169**

By heating 2-ethoxycarbonylamino-2-phenyl butyric acid **1170** with **thionyl chloride**, 4-ethyl-4-phenyl-oxazolidine-2,5-dione **1171** was formed [845].



1170 **1171**

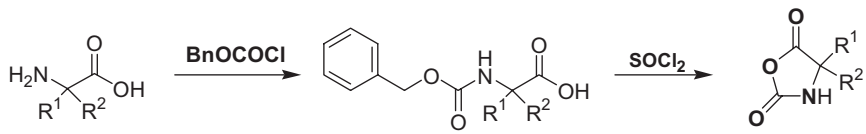
Various L-α-amino acids (glycine, L-alanine, L-valine, L-aspartic acid, L-isoleucine, histidine) have been converted into the corresponding *N*-carboxyanhydrides by N-protection with **benzyl chloroformate** and further reaction with **$SOCl_2$** [846–853].

2-Amino-2-phenyl-propionic acid and 2-amino-2-ethylbutyric acid, **1172**, react with **benzyl chloroformate** in aqueous alkali and then with **thionyl chloride** to give 4-methyl-4-phenyl-oxazolidin-2,5-dione [854] and 4,4-diethyl-oxazolidine-2,5-dione **1174** [855].

The preparation of N^{ω}-*p*-nitrobenzyloxycarbonyl-L-arginine-NCA hydrochloride **1177** with **thionyl chloride** has also been reported [856].

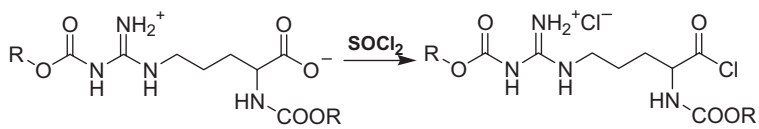
Typical procedure. *N^{ω}-p-Nitrobenzyloxycarbonyl-L-arginine-NCA hydrochloride* **1177** [856]: Di-*p*-nitrobenzyloxycarbonyl-L-arginine (3.4 g, 6.4 mmol) was dissolved in **thionyl chloride** (15 mL), and the solution was warmed to about 40 °C in a flask fitted with a reflux condenser with a calcium chloride guard tube attached. After about 30 min, the solution became cloudy and an oil began to rise to the surface. Crystallization soon began. After a further 30 min, the reaction appeared to be complete (the lower thionyl chloride layer became clear) and the reaction flask was transferred to an ice-bath for 1.5 h to complete the crystallization. The excess thionyl chloride was then removed with the aid of a filter stick. The product was treated several times with 5 mL portions of cold thionyl chloride and was then

collected on a sintered glass filter. The anhydride was rapidly washed with four portions of absolute diethyl ether and dried for 2 h over phosphorus pentoxide and sodium hydroxide pellets. The yield was 2.13 g (80%).

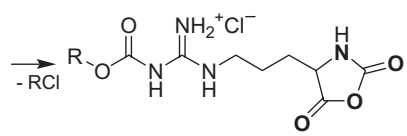


1172 **1173** **1174**

R^1 = Me, R^2 = Ph
$R^1 = R^2$ = Et

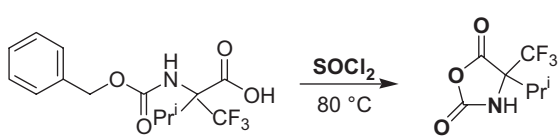


1175 **1176**



R = 4-NO_2-C_6H_5 **1177**

Treatment of 2-Cbz-amino-4-methyl-2-trifluoromethyl-pentanoic acid with **$SOCl_2$** at 80 °C gave 4-isobutyl-4-trifluoromethyl-oxazolidine-2,5-dione **1179** in 82% yield [857].

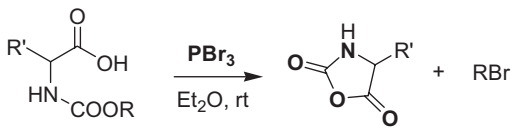


1178 **1179**

Alternative procedures for the preparation of *N*-carboxyanhydrides include reaction of the N^{α}-protected amino acids with **PBr_3**. Generally, methods involving the use of phosphoro halides are hampered by the need for very long reaction times and extensive product purification, and often give only very poor yields.

Treatment of *N*-carbalkoxy-α-amino acids (*N*-Cbetho-DL-phenylalanine, *N*-Cbzo-DL-phenylalanine, *N*-Cbetho-DL-alanine, *N*-Cbzo-DL-alanine, *N*-Cbetho-DL-valine, *N*-

Cbzo-DL-valine, *N*,*N*′-dicbzo-L-lysine, *N*-Cbzo-sarcosine, *N*-Cbetho-anthranilic acid, and *N*-Cbzo-anthranilic acid) with phosphorus tribromide at room temperature resulted in their conversion to the corresponding *N*-carboxy-α-amino acid anhydrides in high yields (60–88%) [858].



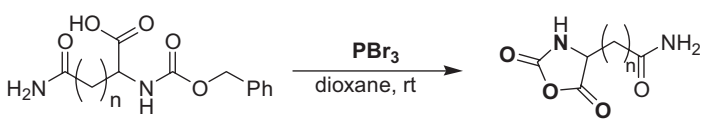
1180 **1181**

General procedure. *N-Carboxy-α-amino acid anhydrides (with* ***PBr₃****)* [858]: **Phosphorus tribromide** (0.02 mol) was slowly added to the *N*-carbalkoxy-α-amino acid (0.05 mol) dissolved or suspended in anhydrous diethyl ether (50 mL). The reaction mixture was kept at room temperature for 12 h. Dry petroleum ether (100 mL) was then added, and crystallization of the anhydride was induced by keeping the reaction mixture at 4 °C for several hours. The anhydride, which separated out as a crystalline mass, was collected by filtration, washed thoroughly with dry petroleum ether, and recrystallized from a dry mixture of EtOAc and petroleum ether.

Improved methods using **PBr_3** have also been reported [835, 836, 859].

N-Cbz-protected histidine, L-glutamine, L-arginine, and L-asparagine react with **PBr_3** in THF or dioxane at ambient temperature to give the corresponding **NCAs**. The isolated yield after chromatography on silica gel is 33% [859].

Because **phosgene** reacts with primary amide groups to yield nitriles, especially in the presence of bases, the **NCAs** of glutamine (**1183a**) and asparagine (**1183b**) cannot be prepared by the phosgenation of these amino acids.



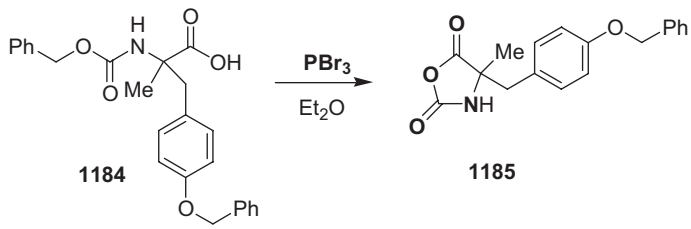
1182 a, n = 2
1182 b, n = 1

1183 a
1183 b

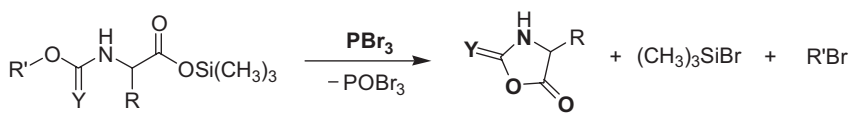
Typical procedure. *L-4-Oxazolidine-2,5-dione propionamide (NCA of L-glutamine)* **1183a** [859]: A suspension of benzyloxycarbonyl-L-glutamine **1182a** (30 g) in dioxane (300 mL) was stirred for 5 min under nitrogen atmosphere. To the resulting solution, a solution of **PBr_3** (4.0 mL) in dioxane (5 mL) was added from a dropping funnel over a period of 1 min. All of the starting material dissolved during the addition of PBr_3. The mixture was stirred for an additional 2 h, during which a solid separated. A silica gel column was prepared using dichloromethane. The solvent was then displaced with dioxane. An exothermic reaction resulted. The column was then washed with dichloromethane to resettle the silica gel. The crude reaction mixture was applied to the column, which had been allowed to stand overnight,

and the flask was rinsed with dioxane (60 mL). The column was developed with 6 L of acetone/dichloromethane (1:1) followed by 6 L of acetone/dichloromethane (3:1). The next 2–3 L of eluent contained the lachrymator benzyl bromide. Thereafter, 250 mL fractions were collected. It was convenient to follow the chromatography by concentrating 5 mL aliquots to dryness and triturating the residue with a few drops of dioxane. Fractions containing crystallizable product were combined, and concentrated in vacuo to a volume of 200 mL. To the resulting solution, *n*-hexane was slowly added at room temperature. After the addition of 50 mL of hexane, the product was collected by filtration under a dry atmosphere and dried to constant weight at room temperature to give a total of 6.1 g (33% yield). This material was about 95% pure as indicated by CO_2 analysis.

Similarly, 4-(4-benzyloxybenzyl)-4-methyl-oxazolidine-2,5-dione **1185** was formed by reacting the corresponding protected amino acid **1184** with **PBr_3** in diethyl ether [860].



High yields of pure oxazolidine-2,5-diones (**1187a**) and thiazolidine-2,5-diones (**1187b**) may be obtained by the reaction of *N*-(alkoxycarbonyl)- and *N*-(alkoxythiocarbonyl)amino acid trimethylsilyl esters (**1186a**,**b**) with **phosphorus tribromide**. Alkoxythiocarbonyl derivatives cyclize more readily than the corresponding alkoxycarbonyl derivatives. The thiazolidine-2,5-diones are also more thermally and chemically stable than the corresponding oxazolidine-2,5-diones. In contrast to *N*-silylated oxazolidine-2,5-diones, *N*-silylated thiazolidine-2,5-diones do not rearrange to the isomeric α-isocyanatothiocarboxylic acid trimethylsilyl esters at 0 °C [861].

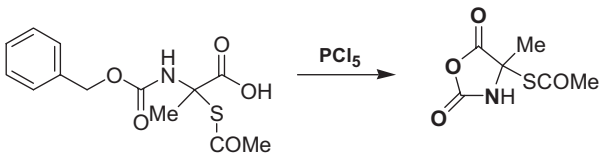


1186 a : Y = O
1186 b : Y = S
R = H, Alkyl
R' = Alkyl

1187 a,b

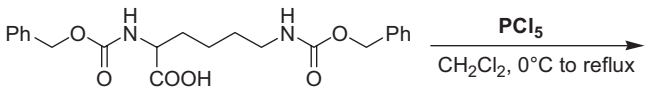
Phosphorus trichloride, **PCl_3**, in dichloromethane at 0 °C has been employed to prepare (*S*)-4-benzyl-oxazolidine-2,5-dione in yields of 95% and 98% from *N*-Boc-L-tryptophan and *N*-Boc-L-phenylalanine, respectively [862].

4-Acetylsulfanyl-4-methyl-oxazolidine-2,5-dione **1189** was prepared with **PCl_5** in diethyl ether [863].

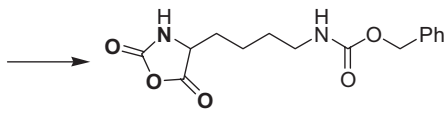


1188 **1189**

N^2,N^6-Bis-benzyloxycarbonyl-L-lysine **1190** reacts with **PCl_5** in dichloromethane on heating from 0 °C to reflux to give L-Lys(Z)-*N*-carboxy anhydride **1191** in 64–88% yield [864–866].



1190



1191

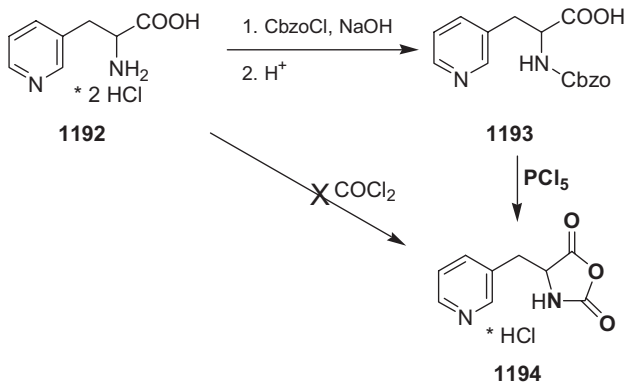
Similarly, (*R*)-4-benzylsulfanylmethyl-oxazolidine-2,5-dione was prepared from *S*-benzyl-*N*-Cbz-L-cysteine and PCl_5 in diethyl ether [867], while (*S*)-3-(oxazolidine-2,5-dion-4-yl)propionic acid esters were prepared from *N*-Bbzo-L-glutamic acid 5-alkyl esters and PCl_5 [868].

NCAs of L-aspartic acid 4-benzyl ester, L-cysteine [869, 870], L-cystine [871, 872], L-tyrosine [873], 4-nitrophenylalanine [874], 1-benzyl-histidine [875], 2,6-diamino-heptanedioic monobenzyl ester [876], L-ornithine, and L-alanine [865] have been prepared from the protected amino acids and **PCl_5**.

A quantitative yield of **L-alanine NCA** was reported starting from the *N*-Boc-protected amino acid and **PCl_3** at 0 °C in dichloromethane [862].

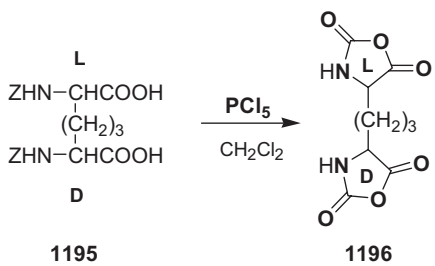
The preparation of 4-(3-pyridylmethyl)oxazolidine-2,5-dione **1194**, the **NCA** of *β*-pyridylalanine, is made difficult by the presence of a pyridyl group in the amino acid. The pyridyl group complicated attempts to phosgenate the amino acid, since hydrogen chloride generated in the phosgenation reaction formed insoluble salts with the amino acid and with any anhydride that may have formed [877].

The preparation of 4-(3-pyridylmethyl)oxazolidine-2,5-dione hydrochloride **1194** from the carbobenzoxy derivative **1193** was accomplished in 92% yield by treatment with a solution of **PCl_5** in dioxane [877].



Typical procedure. *4-(3-Pyridylmethyl)oxazolidine-2,5-dione hydrochloride* **1194** [877]: A suspension of triply recrystallized α,*N*-carbobenzoxy-β-(3-pyridyl)-DL-alanine **1193** (2.92 g, 9.7 mmol) in dry dioxane (50 mL) was treated, in a drybox and with rapid stirring, with a solution of **PCl_5** (3.06 g, 14.7 mmol) in dioxane (125 mL). After a few minutes, a clear solution was transiently formed, which then became cloudy once more. After about 2 h, precipitation began. After about 6 h, the precipitate was collected by filtration, stirred overnight with dry diethyl ether or chloroform to remove occluded PCl_5, filtered once more, and dried to yield 2.05 g (92.4%) of 4-(3-pyridylmethyl)oxazolidine-2,5-dione hydrochloride **1194**.

The synthetically available di-*Z*-*meso*-2,2′-diaminopimelic acid **1195** was treated with **PCl_5** (2.2 equiv.) in dichloromethane (0 °C → reflux, 1 h) to form the crystalline bis(*N*-carboxy anhydride) **1196** [878–880].



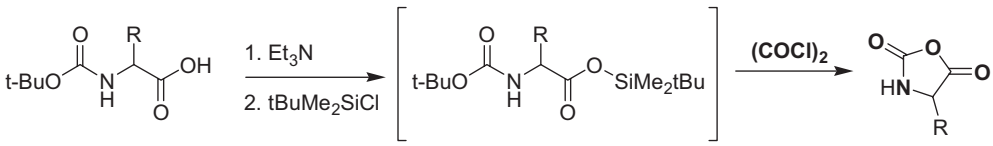
Chloroformates

Amino-diphenyl-acetic acid **1197** was cyclized to 4,4-diphenyl-oxazolidine-2,5-dione **1198** with ethyl chloroformate in aqueous sodium hydroxide solution [881].

DL-Phenylalanine was converted into 4-benzyl-oxazoline-2,5-dione with methyl chloroformate [882].

Oxalyl dichloride

N-Carboxy anhydrides **1201** of several α-amino acids, including β-chloro-L-alanine, can be formed by reaction of an N-*tert*-butoxycarbonyl (Boc) amino acid (**1199**) with *tert*-butyldimethylsilyl chloride and subsequent treatment of the resulting silyl ester **1200** with **oxalyl chloride** in the presence of dimethylformamide [821].



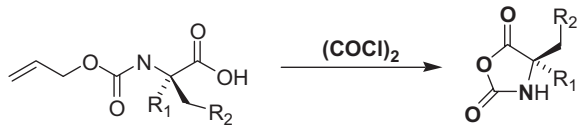
1199 **1200** **1201**

R = CH_3 (L-Ala)
R = CH_2Cl (β–Cl-L-Ala)
R = $CH(CH_3)_2$ (L-Val)
R = $CH_2C_6H_5$ (L-Phe)
R = $CH_2(COO)CH_2C_6H_5$ (β-benzyl-L-Asp)
R = $CH_2SCH_2C_6H_5$ (S-benzyl-L-Cys)
R = $(CH_2)_3NH(CO)$=-t-Bu (N^{α}-Boc-L-Orn)
R = $CH_2NH(CO)O$-t-Bu (N^{α}–Boc-D,L-diaminopropionate)

Typical procedure. *N-Carboxy-β-chloro-L-alanine anhydride* [821]: To a solution of *N*-Boc-β-chloro-L-alanine (400 mg, 1.8 mmol) and *tert*-butyldimethylsilyl chloride (283 mg, 1.9 mmol) in ethyl acetate (2 mL) at 0 °C was added triethylamine (244 µL, 1.8 mmol). Triethylamine hydrochloride was immediately precipitated, and after stirring for 30 min at 0 °C, it was filtered off (244 mg, 100%). The filtrate was then concentrated in vacuo to leave an oil, which was redissolved in dichloromethane (3.0 mL). After chilling to 0 °C, **oxalyl chloride** (195 µL, 2.25 mmol) was added, followed by 2–3 drops of DMF. Once gas evolution had subsided (approximately 2 min), additional DMF (2 drops) was added and the reaction mixture was allowed to warm to room temperature. Further DMF was added dropwise until no further gas was evolved (approximately 10 min). The solution was then diluted with THF (ca. 10 mL) and concentrated once more. This routine ensures removal of any unreacted oxalyl chloride. The flask containing the resulting oil was placed on a vacuum line, and evaporation of the DMF (over about 2 h) afforded white needles. Recrystallization from CH_2Cl_2/hexane gave the desired **NCA** in quantitative yield (270 mg).

By heating 2-allyloxycarbonylamino-2-methyl-3-phenylpropionic acid **1202** with **oxalyl dichloride**, the corresponding 4-benzyl-4-methyl-oxazolidine-2,5-dione **1203** was formed [883].

A similar transformation with **oxalyl chloride** as the reagent and *erythro- or threo*-2,3-bis-Cbz-diamino-succinic acid monomethyl- or di-4-nitro-benzyl ester as the substrate has been reported [884].



1202 **1203**

R_1 = H, R_2 = Ph
R_1 = iPr, R_2 = OBn

Diphosgene

An alternative method for the preparation of NCAs using **trichloromethyl chloroformate** (**diphosgene**) has been reported [885, 886]. Since the advantage of using a calculated amount of liquid **diphosgene** is offset by the very slow decomposition of **diphosgene** to phosgene (4–6 h at 60 °C), the method is not wholly satisfactory. The NCA of alanine, for example, is obtained only after extensive work-up and then only in about 60% yield [885, 887]. Without this decomposition of diphosgene prior to the reaction with the amino acids, the formation of the NCAs is usually unsuccessful [885].

Moderate to low yields of NCA have been obtained by using **diphosgene** as the sole reagent for cyclization [888].

In contrast, high yields of NCAs have been reported by employing **diphosgene** as an *in situ* **phosgene** source. **Diphosgene** decomposes instantly to give **phosgene** when catalyzed by activated charcoal. The amount of **diphosgene** needed for complete reaction with amino acids has been examined. Theoretically, half a mole of **diphosgene** should be enough to react with a mole of the amino acid, because one mole of **diphosgene** yields two moles of **phosgene**. Experimentally, however, even when a 10% excess of **diphosgene** was allowed to react with amino acids, 16% of the amino acid was left unreacted. The use of a 40% excess of **diphosgene** led to complete amino acid conversion to the NCA [887]. Table 4.37 illustrates the preparation of NCAs of some α-amino acids by the **diphosgene**/activated charcoal method.

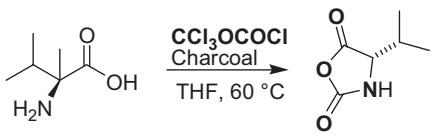
Tab. 4.37. Preparation of *N*-carboxy anhydrides of some α-amino acids by the **diphosgene**-activated charcoal method [887].

NCA	*Reaction time (min)*	*Yield (%)*
L-Ala	90	85
L-Val	40	93
L-Leu	30	89
L-Phe	30	86
L-Met	30	78
L-Glu(OBzl)	30	88
L-Glu(OMe)	30	91
L-Asp(OBzl)	25	93

Typical procedure for the preparation of NCAs [887]: L-Leucine (26.2 g, 0.2 mol) and activated charcoal (0.5 g) were suspended in THF (250 mL). **Diphosgene** (18 mL, 0.15 mol) was then added to the suspension with vigorous stirring. The temperature was gradually increased to 55 °C, and stirring was continued at this temperature until the amino acid had dissolved. The solution was then filtered through Celite placed on a glass filter. The filtrate was concentrated at 40 °C under reduced pressure to give a pale-yellow oil, which was crystallized by the addition of hexane. The product was twice recrystallized from diethyl ether/hexane to give colorless crystals of the NCA. Yield 89%.

The NCA of D-4-hydroxyphenylglycine was obtained in 95% yield from the corresponding amino acid and **diphosgene** in THF at 50 °C [889].

D/L-Valine **1204** gave the corresponding NCA **1205** in 93% yield when treated with **diphosgene** and charcoal in THF at 60 °C [890].



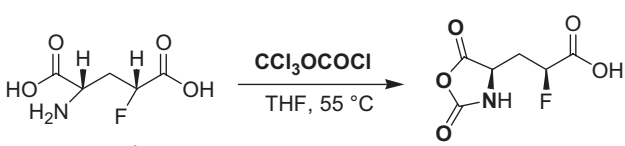
1204 **1205**

Typical procedure for the synthesis of L-valine *N*-carboxyanhydride, (2*S*)-4-isopropyloxazolidine-2,5-dione **1205** [887, 890]: L-Valine (12.9 g, 0.11 mol) and activated charcoal (0.5 g) were suspended in anhydrous THF (100 mL), and to the suspension was added **diphosgene** (10.0 mL, 0.083 mol). The temperature was gradually increased to 60 °C, and the mixture was maintained at this temperature for 1 h. Excess phosgene was then removed by purging with nitrogen and the suspension was filtered through Celite. The yellow filtrate was concentrated in vacuo (<40 °C). Addition of pentane (ca. 500 mL) gave crystals of L-valine NCA, which were recrystallized twice from diethyl ether/pentane (14.32 g, 91%).

4-D-Arabino-tetramethoxybutyl-1,3-oxazolidine-2,5-dione was obtained in 95% yield by treating 2-amino-2-deoxy-3,4,5,6-tetra-*O*-methyl-D-gluconic acid hydrochloride with **diphosgene** and active charcoal in THF at 55 °C [891].

Similarly, DL-*erythro*- and *threo*-4-fluoroglutamic acid have been transformed into the corresponding NCA **1207** by treatment with **diphosgene** and active charcoal in THF at 55 °C [892].

Triphosgene



erythro

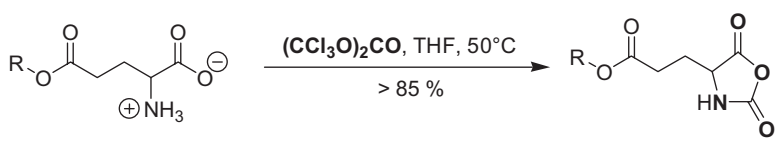
1206 **1207**

Tab. 4.38. Reaction of **triphosgene** with amino acids in THF [893].

Amino acid (AA)	*Triphosgene: AA*	*Yield[a] (%)*	*Scale (g)*	*Dissolution time (h)*
γ-stearyl-L-glutamate	1.04	89.5	10.0	<1
DL-2-aminostearic acid	1.07	81.8	0.3	1
γ-benzyl-L-glutamate	1.17	85.8	0.4	<3
O-benzyl-L-tyrosine	1.20	89.4	0.4	3[b]
L-phenylalanine	1.13	83.0	5.0	3
L-leucine	1.16	66.8	2.5	[c]
L-alanine	1.26	58.5	5.0	[c]
DL-valine	1.11	82.7	5.0	[c]

[a] Isolated yield; the low yields obtained from alanine, valine, and leucine can be attributed to their failure to dissolve completely; [b] slight suspension remained; [c] insoluble material removed by filtration after about 4 h.

Preparation of the *N*-carboxyanhydrides of several α-amino acids using **bis(trichloromethyl)carbonate** has also been reported [893]. **Triphosgene** is used to supply **phosgene** *in situ* in stoichiometric amounts and it is particularly effective for preparing NCAs of amino acids with long, aliphatic side chains (Table 4.38).



1208 **1209**

R = Alkyl or Benzyl

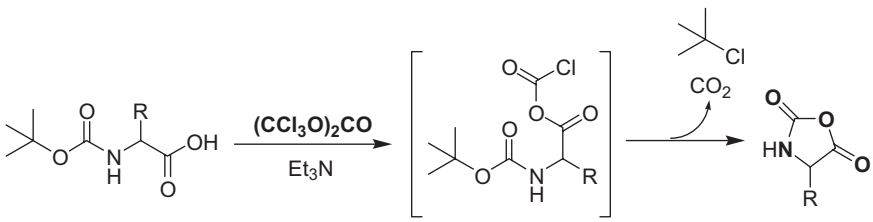
General procedure. *NCAs prepared with* ***triphosgene*** [893]: Treatment of a suspension of an amino acid in anhydrous THF with **triphosgene** (0.33 equiv.) at 40–50 °C usually leads to a completely homogeneous solution of the corresponding NCA within 1–3 h. Typically, the reaction is performed by suspending 10 g of the amino acid in 100 mL of THF, warming the mixture to 50 °C, and then adding an equivalent of triphosgene. If a clear solution has not formed within 1 h, 2–3 aliquots (0.05 equiv.) of further **triphosgene** may be added at 30 min intervals. As the reaction proceeds, the HCl by-product protonates the unreacted amino function of the residual amino acid, reducing its nucleophilicity and solubility. This problem is more acute with amino acids bearing short chain alkyl groups, as evidenced by a reduction in the isolated yields of the NCAs. Periodic purging with nitrogen improves product yields by driving the HCl evolved from the reaction medium. The addition of excess triphosgene fails to drive the reaction to completion. After 3 h, the reaction mixture was poured into hexane (300 mL), and the resulting suspension was stored overnight at −20 °C to ensure complete crystallization. Reaction

Tab. 4.39. *N*-Carboxy-α-amino acid anhydrides prepared with **triphosgene** [894].

NCA 1212	*Yield (%)*	*NCA 1212*	*Yield (%)*
L-valine	75	L-phenylalanine	75
O-benzyl-L-tyrosine	65	O^{γ}-benzyl-L-glutamic acid	72
O-benzyl-L-threonine	66	glycine	83
N-Boc-L-lysine	73		

times in excess of 5 h lead to discoloration, which complicates NCA purification. The NCA was recrystallized from THF/hexane until a constant melting point was reached.

A facile one-pot method for the formation of NCAs at room temperature employing **triphosgene** has been reported [894]. In a typical reaction, the *N*-Boc-amino acid **1210** and **triphosgene** are stirred in ethyl acetate at room temperature. Addition of triethylamine to the solution is accompanied by an instantaneous precipitation of triethylamine hydrochloride to give the intermediate **1211**. Thereafter, the progress of the reaction can be readily followed by measuring CO_2 evolution with a manometer connected to the flask. The requisite amount of CO_2 forms within 2–20 h depending on the nature of the amino acid. Ethyl acetate is used as solvent since triethylamine·HCl is marginally soluble in this solvent at room temperature. Triethylamine·HCl is recovered in >95% yield by filtration of the suspension obtained. The NCAs listed in Table 4.39 were each prepared by this procedure.

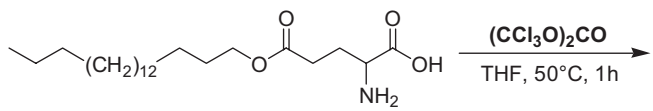


1210 **1211** **1212**

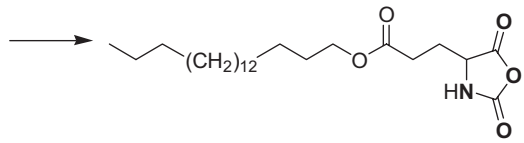
The chemical conversion of *N*-Boc-amino acids to NCAs is invariably quantitative, as judged by the degree of CO_2 evolution. The losses in the overall yields are a consequence of the low solubility of NCAs in most organic solvents, including ethyl acetate. At times, some NCAs contain a trace of triethylamine hydrochloride as an impurity (easily detected and quantified by ^{1}H NMR). The last traces of triethylamine hydrochloride can be precipitated from the solution by chilling the reaction mixture in ice/water for 5–10 min prior to filtration. However, this procedure results in somewhat lower yields of the desired NCA. If the potential contamination of the NCA by traces of triethylamine·HCl can be tolerated, the use of a larger volume of solvent in the reaction improves the recovery of NCAs.

Typical procedure. *N-Carboxy-L-valine anhydride* [894]: To a solution of *N*-Boc-L-valine (500 mg, 2.3 mmol) and **triphosgene** (273 mg, 0.92 mmol) in anhydrous ethyl acetate (55 mL), distilled triethylamine (353 mL, 2.5 mmol) was added over a period of 30 s at room temperature; $Et_3N{\cdot}HCl$ precipitated immediately. The vessel was connected to a manometer in order to monitor CO_2 evolution while maintaining vigorous stirring of the reaction mixture. The requisite amount of CO_2 was generated in 3 h, whereupon the suspension was filtered. The solid $Et_3N{\cdot}HCl$ was washed with a small portion of ethyl acetate (10 mL), and the filtrate was concentrated to dryness. The residue obtained was crystallized from dichloromethane and petroleum ether at −20 °C to give the title compound as white crystals (330 mg, 75%).

Poly(γ-stearyl L-glutamate) was prepared by polymerization of the corresponding amino acid *N*-carboxyanhydride monomer **1214** [895]. The cyclic *N*-carboxyanhydride monomer **1214** was synthesized using **triphosgene**.



1213

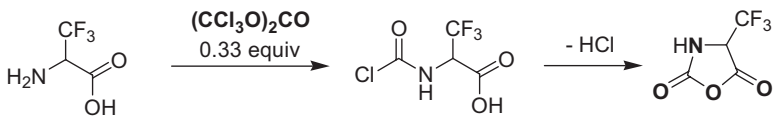


1214

Typical procedure. *γ-Stearyl α,L-glutamate N-carboxyanhydride* **1214** [895]: γ-Stearyl α,L-glutamate **1213** (10 g, 0.0251 mol) was suspended in THF (150 mL), and the reaction flask was fitted with a condenser which was vented into concentrated ammonium hydroxide solution to trap HCl or phosgene gas. After warming to 50 °C, **triphosgene** (2.52 g, 0.0085 mol; 0.33 equiv.) was added as a single aliquot. The slurry obtained usually became homogeneous within 1 h. After about 1 h, the reaction mixture was concentrated to about one-third to a half of its original volume in vacuo and poured into twice its volume of hexane. After overnight refrigeration, the crystals were recovered by suction filtration and then redissolved in chloroform or dichloromethane. After shaking with a small amount of sodium carbonate, this solution was filtered through a cake of Celite. The filtrate was concentrated, poured into hexane, and refrigerated. The recrystallization step was repeated twice. The yield was typically 85–90%.

D,L-Trifluoroalanine *N*-carboxy anhydride (D,L-TFANCA) **1217**, a reactive intermediate for the synthesis of low surface energy polypeptides, has been synthesized by phosgenation of 3,3,3-D,L-trifluoroalanine in THF [896]. Solid **triphosgene** was used as the phosgene source and the procedure of Daly and Poché [893] for natural

amino acids was followed. The higher reactivity of trifluoroalanine was not anticipated, since formation of the anhydride is believed to proceed via the following route [822].



1215 **1216** **1217**

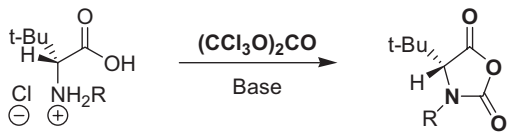
The suspension of trifluoroalanine became clear within 15 min after adding **triphosgene** at room temperature. It has been observed that heating of the reaction mixture to 50 °C is necessary to drive the reaction to completion.

Because the nucleophilicity of the amino group of trifluoroalanine is reduced by the strongly electron-withdrawing trifluoromethyl group in the α-position, the first step in anhydride formation is expected to be retarded. Three possible explanations for the observed high rate of phosgenation can be offered. The first possibility is that the ring-closure is the rate-determining step; if this were the case, the nucleophilicity of the amine would not affect the overall rate. The second is that the hydrogen chloride produced as by-product during the phosgenation reaction protonates the amino group of most natural amino acids, rendering them unreactive towards phosgene, while protonation of the less basic trifluoroalanine is reduced. Faster phosgenation would then result from the higher concentration of free amino groups in the case of trifluoroalanine. Lastly, Daly et al. [893] postulate that poor solubility accounts for the low yields characteristic of the phosgenation of alanine, valine, and leucine. The good solubility of fluorinated anhydrides in THF may also contribute to the faster phosgenation of trifluoroalanine.

Typical procedure. *D,L-TFANCA* **1217** [896]: D,L-Trifluoroalanine (0.715 g, 5 mmol) was suspended in dry THF (5 mL). A solution of **triphosgene** (0.495 g, 5 mequiv) in dry THF (1 mL) was then added dropwise. The mixture was periodically purged with nitrogen to remove excess HCl. The solution became clear after ca. 10 min, but a slight cloudiness developed during the course of the reaction. After 1 h, the solution was filtered and cold, dry petroleum ether was added to the filtrate. A small amount of precipitate was filtered off, the filtrate was purged with nitrogen, and most of the solvent was evaporated under reduced pressure. Twice more, dry THF was added and evaporated. The anhydride proved to be very soluble in THF, but partially crystallized in the form of white needles when most of the solvent had been evaporated. After standing in a freezer overnight, D,L-TFANCA **1217** (3.7 mmol, 75% yield) was obtained by filtration as a light-yellow solid.

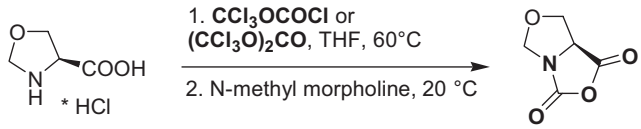
Typical procedure. *(R,S)-4-t-Butyl-2,3,4,5-tetrahydro-3-methyl-1,3-oxazole-2,5-dione* **1219** [897]: According to [887]: To a solution of (*R,S*)-α-alkylamino acid hydrochloride **1218** (100 mg, 0.55 mmol) in dichloromethane (30 mL) was added triethylamine

(56 mg, 0.55 mmol) followed by **triphosgene** (33 mg, 0.22 mmol). The mixture was stirred for 1 h at 20–25 °C and then filtered through silica gel. Removal of the solvent from the filtrate in vacuo afforded 60 mg (64%) of colorless crystals; mp 65–66 °C.



1218 **1219**

The *N*-carboxyanhydride of oxaproline is best prepared by treating oxaproline hydrochloride with **di-** or **triphosgene**, followed by *N*-methyl morpholine cyclization as illustrated below. The product, which is obtained as white crystals, shows no sign of racemization by chiral GC [898].



70 %

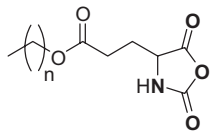
1220 **1221**

The NCA of formyltryptophan has been prepared with **triphosgene** in 85% yield [899]. Similarly, NCAs of 4-nitro-γ-benzyl-L-glutamate and γ-4-trifluoromethylbenzyl-L-glutamate have been prepared in yields of 84% and 75%, respectively, with **triphosgene** in dioxane [900].

Typical procedure. *γ-4-Nitrobenzyl-L-glutamate N-carboxyanhydride* [900]: A suspension of γ-4-nitrobenzyl-L-glutamate (0.5 g, 1.77 mmol) in dioxane (20 mL) was stirred for 10 min. Nitrogen was then passed into the suspension for 15 min. The suspension was slowly heated to 50 °C and **triphosgene** (0.53 g, 1.785 mmol) was added in a single portion. Elevation of the temperature to 50 °C should proceed slowly. After 2 h, the mixture became almost homogeneous. The solution was kept at 40 °C and nitrogen was passed through it for 2 h in order to remove any residual phosgene. It was then filtered, and the filtrate was concentrated to leave an oily residue. A small amount of ethyl acetate was added, with stirring, to dissolve the oil. When the solution became homogeneous, *n*-hexane was added dropwise until the cloud point, and the purged solution was stored at 5 °C overnight. Repetition of the precipitation step yielded γ-4-nitrobenzyl-L-glutamate *N*-carboxyanhydride, 0.46 g, 84% yield.

An unconventional and very interesting method for the synthesis and purification of *N*-carboxyanhydride derivatives of γ-alkyl-L-glutamates has recently been

Tab. 4.40. Yields of the NCA product after application of the purification method [901].



1222

n	*Scale*[a] *(g)*	*Typical yield (%)*
Benzyl	10	69
1	2	67
3	2	86
5	2	71
7	5	69
9	5	44
11	2	61
13	2	45
15	2	36
17	2	49

[a] amount of starting amino acid used

published [901]. The hydrochloride salt of the starting amino acid, and **triphosgene** itself, which are the main undesired impurities that severely limit the polymerization of the NCA, can be effectively removed by washing the reaction mixture with water and aqueous sodium hydrogen carbonate solution at 0 °C prior to isolation of the NCA, despite the well-known sensitivity of the NCA to water. The method is particularly useful for NCA derivatives that are isolated as oils, since purifying them by recrystallization or solvent washes is not feasible. Table 4.40 shows the yields of the NCA product after application of this purification method.

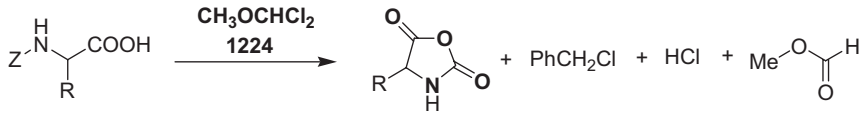
Typical procedure. *NCA of γ-benzyl-L-glutamate* [901]: γ-Benzyl-L-glutamate (10 g, 0.042 mol) was suspended in anhydrous EtOAc (300 mL) in a reaction flask fitted with a reflux condenser and nitrogen bubbler. After heating to reflux, triphosgene (4.2 g, 0.014 mol) was added in a single portion and the mixture was kept under reflux under nitrogen for 4–5 h. Generally, the reaction mixture became clear. In cases where it did not, a small quantity of triphosgene was added. For oily NCAs, no additional triphosgene was used. The reaction mixture was allowed to cool to room temperature, which in some cases led to the precipitation of a solid (presumably the HCl salt of the starting amino acid). The mixture was then cooled to −5 °C in the stoppered reaction vessel.

Isolation and purification procedure: (Note: Work attentively and quickly during this procedure.) The cold reaction mixture was transferred to a separatory funnel and washed with deionized water (100 mL) that had been chilled to 0 °C. As ex-

pected, the water wash was quite acidic, turning blue litmus paper red. The ethyl acetate layer was then washed with 0.5% aq. $NaHCO_3$ solution, also chilled to 0 °C. This wash was neutral or slightly basic and did not change the color of blue litmus (faint blue color change to red litmus). For NCAs with short hydrocarbon R groups (i.e. less than ten carbons), both layers were usually clear during the washing procedure. Any cloudiness due to unreacted starting material was eliminated during the washes. For NCAs with long side chains, the separatory funnel was allowed to stand for a few minutes in a cooler at below 5 °C. Vigorous shaking of the layers was generally avoided. The ethyl acetate layer was then treated with anhydrous $MgSO_4$ until no clumping was observed. The clear solution was gravity filtered and concentrated to about one-third of its original volume in a rotary evaporator. The temperature of the water bath of the evaporator was kept below 30 °C to minimize or eliminate deleterious reactions due to residual water. At this point, the usual care in minimizing exposure to moisture was observed. An equal volume of hexane or petroleum ether (30–60 °C cut) was then added to induce crystallization of the NCA. After chilling to −5 °C overnight, the NCA crystals were collected by suction filtration in a dry nitrogen atmosphere. For oily NCAs, the ethyl acetate was completely evaporated and the oil was immediately vacuum dried. See Table 4.39 for typical yields.

α,α-Dichloromethyl methyl ether (CHLOROMYL®)

α,α-Dichloromethyl methyl ether (**CHLOROMYL®**) **1224**, obtained by catalytic phosgenation of methyl formate in the presence of triphenylphosphine oxide, reacts, in excess, with Z- or Cbz-amino acids **1223** providing a practical and safe access to the *N*-carboxy anhydride **1225** [902–905] (Table 4.41). This method is superior to the thionyl chloride process by virtue of the facile removal of excess reagent and side products under mild conditions, as depicted in the scheme below.



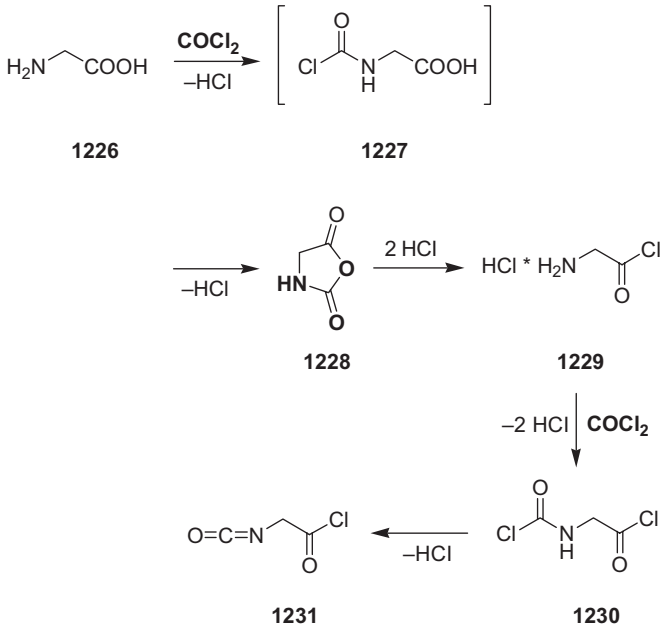
1223 **1225**

Tab. 4.41. *N*-Carboxy anhydrides prepared with **CHLOROMYL®** [905].

N-Carboxy anhydrides	*Yield (%)*	*N-Carboxy anhydrides*	*Yield (%)*
Glycine	84	*S*-Benzyl-L-cysteine	90
L-Alanine	80	*O*-Acetyl-L-tyrosine	69
D-L-Valine	72	*N*-δ-Z-D-L-ornithine	68
D-L-Phenylalanine	82	*N*-ε-Tos-L-lysine	44

Miscellaneous reagents

A series of *2-isocyanatoacyl chlorides* **1231** was prepared by treating glycine **1226**, DL-alanine, L-valine, L-leucine, and L-phenylalanine with **phosgene** in an inert solvent such as dioxane. The acid chloride group of the 2-isocyanatoacyl chloride is more reactive as an electrophile than the isocyanate group. In reactions with an equimolecular amount of ethanol or water, *2-isocyanatoacetyl chloride* **1231** gives ethyl 2-isocyanatoacetate and 2,5-oxazolidinedione, respectively. With a molar excess of *p*-phenetidine, it gives 3-(*p*-phenethyl)hydantoin, while with a 2 molar or greater excess of amine it gives the corresponding ureidoamide. Treatment with an equimolar amount of *N*-methylaniline in the presence of an equimolar amount of pyridine furnished *N*-methyl-2-isocyanatoacetanilide [447].



Typical procedure. *2,5-Oxazolidinedione* **1228** [447]: **Phosgene** (for a *safe source*, see Chapter 7) was passed in a fine stream into a suspension of finely ground glycine (15 g) in dry dioxane (750 mL) at 45–50 °C with efficient agitation. A clear solution was obtained after 5 h. This solution was filtered to remove unreacted glycine (1.7 g), and the dioxane was then removed under reduced pressure at a temperature below 40 °C under exclusion of moisture. The residue was treated with dry diethyl ether (100 mL), and the crystals of 2,5-oxazolidinedione **1228** were collected by filtration and dried over P_2O_5 in a vacuum desiccator. The crude product thus obtained, 16 g (89%), was recrystallized from ethyl acetate/petroleum ether to yield 14.3 g (77.2%) of pure material, which showed no melting point because of polymerization.

Typical procedure. *2-Isocyanatoacetyl chloride* **1231** from glycine and **phosgene** [447]: **Phosgene** (for *safe phosgenation*, see Chapter 7) was passed in a fine stream into a suspension of finely ground glycine (25 g) in dry dioxane (750 mL) at 45–50 °C with stirring. After 6 h, the mixture had become almost clear. The reaction was allowed to proceed for a further 3 h. The solution obtained was then filtered to remove a small amount of insoluble solid and concentrated under reduced pressure at a temperature below 50 °C. The residue, consisting of white crystals and a violet oil, was filtered with the aid of diethyl ether (50 mL). The crystals of 2,5-oxazolidinedione **1228** were collected, washed with dry diethyl ether, and dried over P_2O_5 in a vacuum desiccator. They weighed 5.5 g (16%). The filtrate was distilled to yield 12 g (30%) of an irritating colorless liquid, 2-isocyanatoacetyl chloride, **1231**.

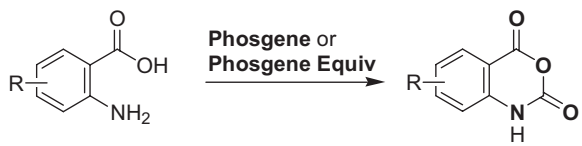
Other 2-isocyanatoacyl chlorides have also been prepared from the corresponding α-amino acids and **phosgene** by a similar procedure to that described above.

Typical procedure. *2-Isocyanatoacetyl chloride* **1231** from 2,5-oxazolidinedione, hydrogen chloride, and **phosgene** [447]: Into a solution of 2,5-oxazolidinedione **1228** (10 g) in dry dioxane (300 mL), **phosgene** (for *safe phosgenation*, see Chapter 7) and then hydrogen chloride were passed at 10 °C with stirring for 1 h each. The solution was then maintained at 50 °C and treated with **phosgene** for 7 h. After 2 days, the solution was concentrated under reduced pressure, and the residual brown liquid was distilled to yield 10.5 g (89.0%) of 2-isocyanatoacetyl chloride, bp 54.5–56.5 °C (22 mmHg).

Trichloroacetyl chloride in dioxane [859] and **nitrogen monoxide in DMSO** [906] have also been reported as reagents for the preparation of NCAs.

4.3.5.5 N,COOH Binucleophiles. Synthesis of 1*H*-Benzo[*d*][1,3]oxazine-2,4-diones (Isatoic Anhydrides)

1*H*-Benzo[*d*][1,3]oxazine-2,4-diones (isatoic anhydrides) have long been prepared from anthranilic acids **1232** using **ethyl chloroformate** [907, 908], **acetyl chloride** [909, 910], **$PhSO_2Cl$** and pyridine [911], **morpholine- or pyrrolidine-urea** derivatives [912], and **diphosgene** [161, 913].



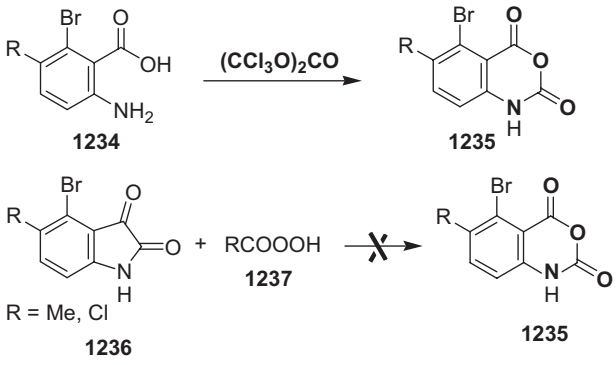
1232 **1233**

Under practically the same experimental conditions as those used to prepare NCAs of amino acids, **phosphorus tribromide** reacts with *N*-carbobenzoxyanthranilic acid to give nearly quantitative yields of isatoic anhydride [858].

Typical procedure. *Isatoic anhydride* [858]: **Phosphorus tribromide** (0.035 mol) was added to a solution of *N*-carbethoxy- or *N*-carbobenzoxy-anthranilic acid (0.1 mol;

prepared by coupling anthranilic acid with the corresponding carbalkoxy chloride in the usual way) in anhydrous diethyl ether (100 mL). After 24 h at room temperature, isatoic anhydride had separated as a microcrystalline product. It was collected by filtration, washed with dry diethyl ether, and recrystallized from ethanol. Yield ca. 90%.

Isatoic anhydrides **1235** were prepared from the corresponding anthranilic acids with **triphosgene** [914].

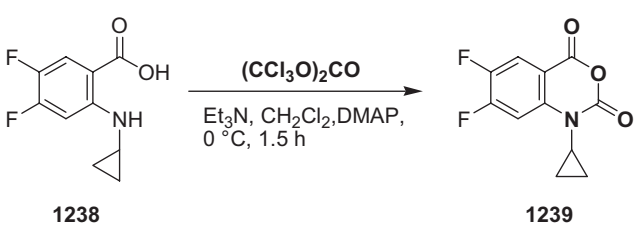


Attempts to synthesize isatoic anhydride **1235** directly from isatin **1236** by peracid oxidation with **1237** were unsuccessful.

Typical procedure. *5-Bromo-6-methyl-1H-benzo[d][1,3]oxazine-2,4-dione* **1235** (R = Me) [914]: Under anhydrous conditions, 6-bromo-5-methylanthranilic acid (2.3 g, 10 mmol) was stirred with **triphosgene** (1.0 g, 3.4 mmol) in THF (25 mL) for 12 h. The resultant solid was collected by filtration, washed with cold acetone, and dried in vacuo. Isatoic anhydride was isolated in quantitative yield and used without further purification.

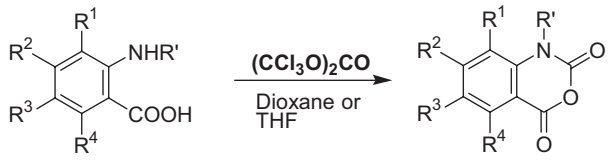
5-Bromo-6-chloro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione was prepared by reacting anthranilic acid and **triphosgene** as described above; yield 72% [914].

Cyclization of *N*-substituted anthranilic acids using **triphosgene**, **diphosgene**, or **chloroformates** has been claimed in patent literature [915]. For example 2-*N*-cyclopropylamino-4,5-difluorobenzoic acid **1238** was converted into *N*-cyclopropyl-6,7-difluoro-2*H*-1,3-benzoxazine-2,4(1*H*)-dione **1239** in quantitative yield.



Typical procedure. *N-Cyclopropyl-6,7-difluoro-2H-1,3-benzoxazine-2,4(1H)-dione* **1239** [915]: In a 10 mL single-necked, round-bottomed flask equipped with a septum and magnetic stirring bar was placed a solution of 2-*N*-cyclopropylamino-4,5-difluorobenzoic acid **1238** (100 mg, 0.46 mmol), and triethylamine (62 µL, 0.44 mmol) in dichloromethane (2 mL). The solution was cooled to 0 °C, and then treated with a solution of **triphosgene** (45 mg, 0.147 mmol) in dichloromethane (0.5 mL). Finally, a catalytic amount of dimethylaminopyridine (10 mg) was introduced as a solution in dichloromethane (0.5 mL). After stirring at 0 °C for 1.5 h, the reaction mixture was quenched by adding a small amount of 1 N hydrochloric acid. The organic phase was dried over sodium sulfate and then concentrated to a yellow oil to afford 114 mg of *N*-cyclopropyl-6,7-difluoro-2*H*-1,3-benzoxazine-2,4(1*H*)-dione **1239** in quantitative yield. The product was crystallized from hot ethanol.

Various substituted isatoic anhydrides **1241** have been prepared from the corresponding anthranilic acid **1240** and **triphosgene** in dioxane (better solvent) or THF at reflux temperatures; see Table 4.42 [916, 917].



1240 **1241**

Typical procedure. *Isatoic anhydride* **1241** [916]: Anthranilic acid (5 g, 0.036 mol) and **triphosgene** (7.1 g, 0.024 mol) were dissolved in dioxane (75 mL) and the so-

Tab. 4.42. Preparation of isatoic anhydrides with **triphosgene**.

Entry	R^1	R^2	R^3	R^4	R'	*Solvent*	*Time (h)*	*Yield (%)*
1	H	H	H	H	H	Dioxane	14	83.5
	H	H	H	H	H	THF	39	70.7
2	H	H	NO_2	H	H	Dioxane	17	91.3
	H	H	NO_2	H	H	THF	72	70.0
3	H	H	H	F	H	THF	50	93.5
4	H	H	H	Cl	H	THF	73	99.2
5	H	H	Br	H	H	THF	92	93.8
6	Br	H	Br	H	H	Dioxane	15	88.2
	Br	H	Br	H	H	THF	68	65.6
7	Br	H	Br	F	H	THF	36	75.4
8	Br	H	CH_3	H	H	THF	71	77.0
9	H	OCH_3	OCH_3	H	H	Dioxane	19	87.2
10	H	OCH_3	OCH_3	H	H	THF	56	97.0
11	OCH_3	OCH_3	OCH_3	H	H	THF	54	98.5
12	H	H	H	CH_3	H	THF	53	43.5
	H	H	H	H	CH_3	Dioxane	18	78.5

lution was heated to reflux temperature (approx. 100 °C) for 14 h. After cooling to room temperature and collection of the precipitate by filtration, 4.9 g of crude product **1241** was obtained; yield 83.5%. Recrystallization from THF (70 mL) gave 3.0 g (yield 51.1%) of brilliant white crystals of isatoic anhydride.

4.3.6
Chlorocarbonylation at Carbon Centers; Synthesis of Ketones

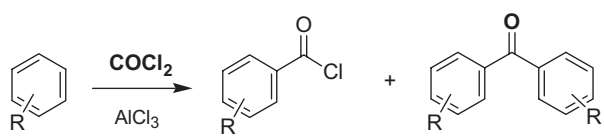
As illustrated in the general scheme in Section 4.1, intermediates of the type RY–COCl, obtained with **phosgene**, play a key role in stepwise COCl (chlorocarbonyl) transfer reactions to substrates of the type R–Y–H. The principal application of these processes is in generating chloroformates, carbamoyl chlorides, etc.

When RY–COCl is a carbonyl chloride (or an acid chloride), the intermediate assumes the character of a reactive substrate and undergoes further nucleophilic substitution to form symmetrical and unsymmetrical diaryl, dialkyl, or aryl alkyl ketones. Several **phosgene equivalents** (**triphosgene**, **oxalyl chloride**, ***N*-methoxy-*N*-methyl-2-pyridyl urethane**) bearing suitable leaving groups (equivalents to chlorine in phosgene) have proved to be interesting reagents for the preparation of ketones.

4.3.6.1 **Phosgene**

A wide variety of aromatic compounds **1242** react with **phosgene** in the presence of anhydrous aluminum trichloride. The normal product isolated is the corresponding benzophenone **1244** [918–928]. Other Lewis acids, such as BF_3/HF [929], $FeCl_3$ [930], $SbCl_3$ [931], and $ZnCl_2$ [932, 933], have also been used as catalysts. The intermediate aroyl chloride **1243** can only be isolated with hindered or particularly unreactive substrates or when a large excess of phosgene is used [1, 934].

As expected, when the hydrocarbon is used as the reaction solvent, the selectivity is lowest and benzene, toluene, xylenes, halobenzenes, alkoxybenzenes, and substituted anilines afford benzophenone derivatives as nearly the sole product. With electron-deficient aromatics, there is an increase in the amount of aroyl chlorides, especially when there is steric hindrance to further reaction. When the reaction is carried out in carbon disulfide, moderate yields of aroyl chlorides are obtained. The enhanced selectivity results from the general insolubility of the aroyl chloride/aluminum chloride complex in carbon disulfide, preventing further reaction. This approach does not work well for highly substituted benzenes, since their complexes are more soluble in the system.



1242 **1243** **1244**

Symmetrically disubstituted aliphatic ketones can also be prepared by the reaction of organolithiums with **phosgene** [935].

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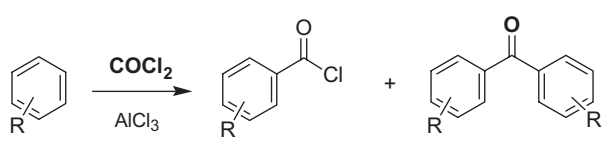


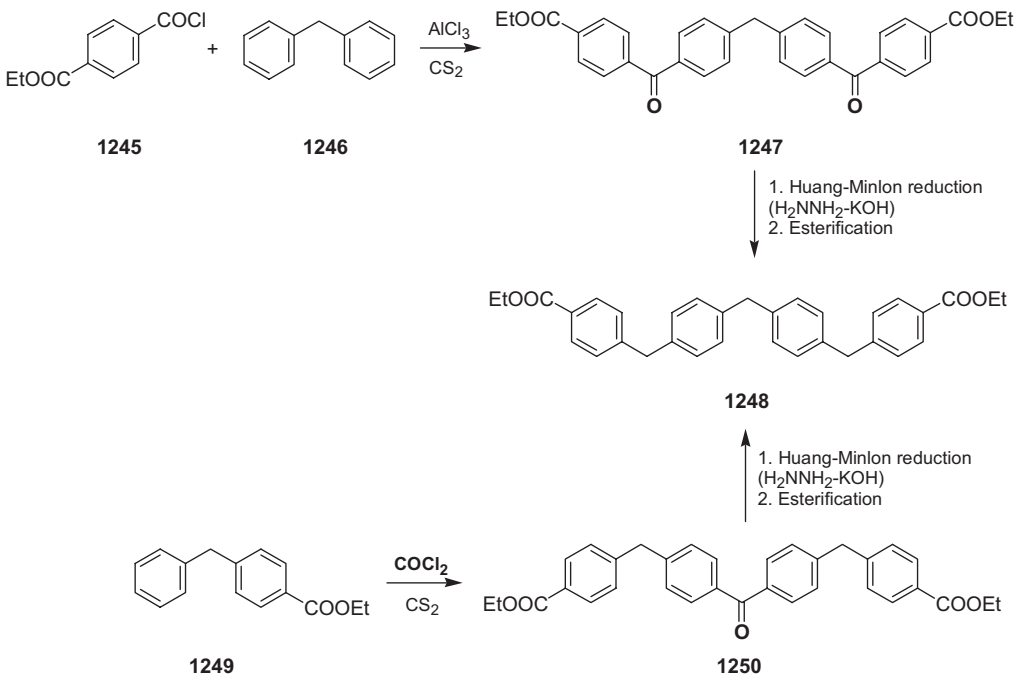
1242 **1243** **1244**

Symmetrically disubstituted aliphatic ketones can also be prepared by the reaction of organolithiums with **phosgene** [935].

Phosgenations – A Handbook. L. Cotarca, H. Eckert

ISBN: 3-527-29823-1

Ethyl 4-chloroformylbenzoate **1245** and diphenylmethane **1246** were treated with anhydrous aluminum chloride to give the diketo diester **1247** [936]. The carbonyl groups of diketo diester **1247** were then reduced according to the Huang–Minlon modification of the Wolff–Kishner reduction to give a dicarboxylic acid, which was esterified to give the corresponding diester **1248**. The same diester **1248** was also obtained by Friedel–Crafts acylation of ethyl 4-benzylbenzoate **1249** with **phosgene** and subsequent Huang–Minlon reduction and esterification.



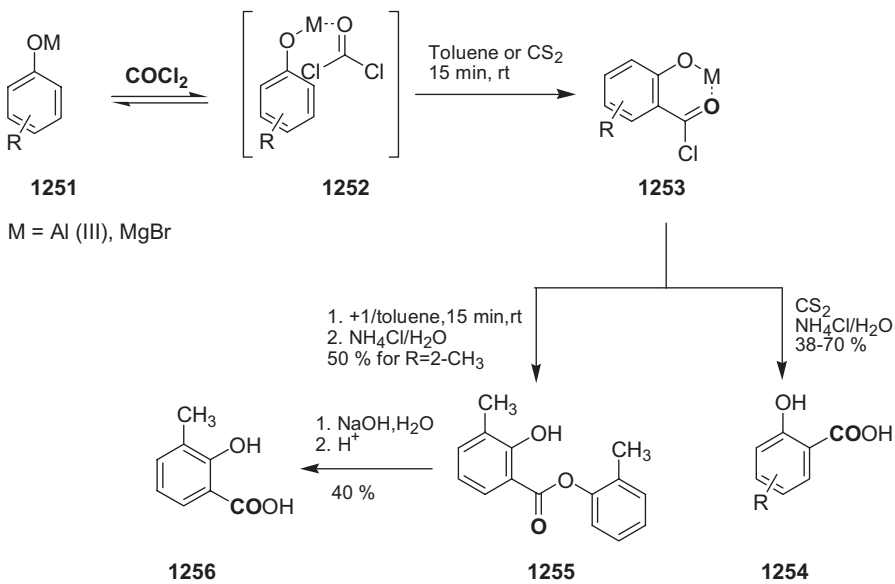
Typical procedure. *4,4′-Bis(4-ethoxycarbonylbenzyl) benzophenone* **1250** *with* **phosgene** [936]: A mixture of ethyl 4-benzylbenzoate **1249** (50 g) and powdered anhydrous aluminum chloride (80 g) in carbon disulfide (500 mL) was cooled to −15 °C, and then **phosgene** (10 g) was slowly stirred into the mixture at a temperature below −10 °C. The temperature was then allowed to rise slowly to ambient. After standard work-up, 44 g of the keto diester **1250** was obtained as a pale-yellow powder. This powder was used without further purification for the preparation of the corresponding dicarboxylic acid.

Typical procedure. *4,4′-Bis(4-ethoxycarbonylbenzoyl) diphenyl methane* **1247** *with* **carbon disulfide** [936]: An ice-cooled mixture of ethyl 4-chloroformylbenzoate **1245** (70 g) and powdered anhydrous aluminum chloride (200 g) in carbon disulfide (600 mL) was treated dropwise with a solution of diphenylmethane (27 g) in carbon disulfide (200 mL) at 0 °C. The reaction mixture was then refluxed for 5 h. Removal of the

carbon disulfide by distillation and addition of crushed ice and hydrochloric acid yielded **1247** as a pale-yellow powder, which was crystallized from ethanol to give 60 g (72% yield) of colorless needles; mp 130–130.5 °C.

In general, **phosgene** reacts with phenols at oxygen to produce aryl chloroformates and carbonates [1]. Only a few cases have been reported in which, using highly hindered phenols, some 4-chlorocarbonylation was observed [937]. On the basis of these results, **phosgene** can be considered as the simplest member of the *ortho*-C reactive acyl chlorides.

A direct synthesis of **salicylic acid chlorides** can be achieved through "metal-driven" intra-complex acylation of bromomagnesium and aluminum phenoxides with **phosgene** [938]. The products can be reacted further, without purification, with convenient nucleophilic compounds, thus facilitating a one-pot approach to a range of phenolic derivatives such as esters, amides, and ketones. Treatment of bromomagnesium or aluminum phenoxide with an excess of **phosgene** in poorly solvating media (toluene or carbon disulfide) results in exclusive *ortho*-chlorocarbonylation of the phenol.



The chelation effect of the highly coordinating metal ion is responsible for the activation and selectivity of the process.

General procedure. *Salicylic acids* **1254** [938]: ***Method A***: A dry 100 mL three-necked, round-bottomed flask containing a magnetic stirring bar, equipped with a reflux condenser and a pressure-equalizing dropping funnel, was fitted with a gas-inlet tube and thoroughly purged with dry nitrogen. To the flask were added magnesium turnings (0.24 g, 0.01 mol) and dry diethyl ether (20 mL). A solution of

EtBr (1.62 g, 0.015 mol) in dry diethyl ether (10 mL) was then added dropwise with stirring. Stirring was continued until all the magnesium had dissolved. A solution of the appropriate phenol (0.01 mol) in dry diethyl ether (25 mL) was then added dropwise with stirring at room temperature under nitrogen, and stirring was maintained for a further 15 min. The diethyl ether was then completely removed in vacuo at room temperature. The resulting white powder was kept under high vacuum for 3 h, and then suspended in dry CS_2 (25 mL). The resulting slurry was cooled to 0 °C, whereupon a solution of **phosgene** (for a *safe source*, see Chapter 7) (2.94 g, 0.03 mol) in dry CS_2 (25 mL) was rapidly added, thereby producing the salicylic acid/magnesium bromide adduct **1253**. Stirring was continued for 15 min, and then the mixture was poured into 10% aq. NH_4Cl solution (100 mL) and extracted with diethyl ether (2 × 100 mL). The aqueous layer was washed with diethyl ether (50 mL), then acidified with 10% aq. HCl, and the resulting mixture was extracted with diethyl ether (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated to afford the pure substituted salicylic acid **1254** (yield 38–70%).

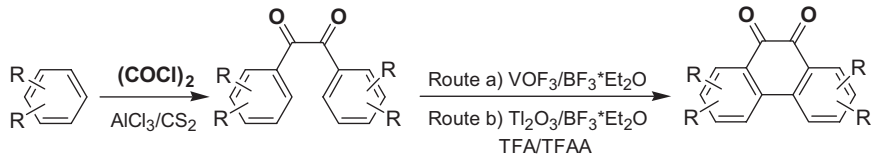
Method B: A dry 100-mL three-necked, round-bottomed flask containing a magnetic stirring bar, equipped with a reflux condenser and a pressure-equalizing dropping funnel, was fitted with a gas-inlet tube and thoroughly purged with dry nitrogen. To the flask were added the appropriate phenol (0.01 mol) and dry diethyl ether (20 mL). The solution was cooled to 0 °C, whereupon Et_3Al (0.38 g; 3.4 mL of a 1 M solution in hexane, 0.0034 mol) was added by means of a syringe with stirring under nitrogen. Stirring was continued until the evolution of gas had ceased (~10 min). Diethyl ether and hexanes were then completely removed in vacuo at room temperature. The resulting white powder was kept under high vacuum for 3 h and then suspended in dry CS_2 (25 mL). The resulting slurry was cooled to 0 °C, whereupon a solution of **phosgene** (for a *safe source*, see Chapter 7) (2.94 g, 0.03 mol) in dry CS_2 (25 mL) was rapidly added, and stirring was continued for 15 min. The mixture was then poured into 10% aq. NH_4Cl solution (100 mL) and extracted with diethyl ether (2 × 100 mL). The combined ethereal extracts were treated with 10% aq. $NaHCO_3$ (2 × 100 mL). The combined aqueous layers were washed with diethyl ether (50 mL) and acidified with 10% aq. HCl. The resulting mixture was extracted with diethyl ether (2 × 100 mL), and the combined organic extracts were dried (Na_2SO_4). Removal of the solvent gave the pure substituted salicylic acid **1254**.

4.3.6.2 Oxalyl Chloride

Benzils with oxalyl chlorides

The formation of aromatic α-diketo compounds through either inter- [939] or intramolecular [940, 941] Friedel–Crafts reaction with **oxalyl chloride** is limited to just a few examples.

Intermolecular Friedel–Crafts acylation of various substituted alkyl alkoxybenzenes **1257** with **oxalyl chloride** using 1,2-dichloroethane [942] or carbon disulfide [943] as solvent gives rise to benzils **1258**.



1257 **1258** **1259**

R = CH_3, 44 %, C_6H_{13}, 42%, OCH_3, 1.7 %, O-i-C_5H_{11}, 45 %

Subsequent intramolecular oxidative coupling with either vanadium(V) oxyfluoride/boron trifluoride diethyl ether etherate or thallium(III) oxide/trifluoracetic acid resulted in the corresponding phenanthrene-9,10-diones **1259**. It has been shown that oxygen functionalities at the 3-, 3′-, 4-, and 4′-positions are necessary for coupling to occur. These substituted benzils and phenanthrene-9,10-diones constitute precursors for ligands in the field of discotic metallomesogens or polymeric mesogens.

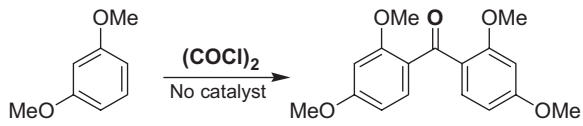
General procedure. *Alkyl-alkoxy-substituted benzils* **1258** [943]. Solvents and glassware used in this synthesis were thoroughly dried prior to use. To a mechanically stirred suspension of the alkyl- or alkoxybenzene **1257** (200 mmol) and aluminum chloride (28.3 g, 220 mmol) in carbon disulfide (500 mL) at 0 °C, a solution of **oxalyl chloride** (15.2 g, 120 mmol) in carbon disulfide (100 mL) was added over a period of 4 h under a constant stream of argon. Stirring was continued for a further 18 h. The resulting brown mixture was then poured onto 500 mL of ice and the yellow organic phase was separated. The aqueous phase was extracted with dichloromethane and the combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. The resulting orange residue was chromatographed on a bed of silica gel using dichloromethane as eluent to remove carboxylic acids and inorganic residues. The obtained material **1258** was then recrystallized from ethanol or acetone. Final purification was achieved by column chromatography (silica gel) with dichloromethane as eluent.

Benzophenones with oxalyl chloride

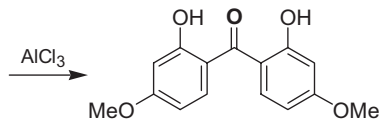
The product of intermolecular reaction of 1,3-dimethoxybenzene with **oxalyl chloride**, in CS_2 or 1,2-dichloroethane, with $AlCl_3$, 2,2′,4,4′-tetramethoxybenzil (mp 129–130 °C), was formerly erroneously identified by Staudinger as 2,2′,4,4′-tetramethoxybenzophenone (mp 135–136 °C) **1261** [942, 944].

2,2′,4,4′-Tetramethoxybenzophenone **1261** was obtained by Van Allan [942] by mixing **oxalyl chloride** and 1,3-dimethoxybenzene; the solution became reddish-yellow and hydrogen chloride was slowly evolved. Heating accelerated this evolution of gas. In order to determine the nature of this reaction, the components were heated for a few hours, and the reaction mixture was distilled. The distillate was recrystallized from ethanol to give a substance having a melting point of 135–136 °C, which, from its elemental analysis, methoxyl determination, and Grignard analysis, proved to be 2,2′,4,4′-tetramethoxybenzophenone **1261**. Demethylation

with aluminum chloride gave 2,2′-dihydroxy-4,4′-dimethoxybenzophenone **1262**, identical to that obtained from 1,3-dimethoxybenzene **1260** and **phosgene** in the presence of aluminum chloride.

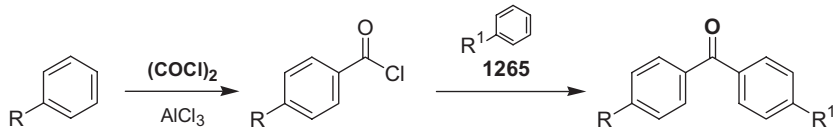


1260 **1261**



1262

The $AlCl_3$-mediated chlorocarbonylation of arenes with **oxalyl chloride** has been used in the preparation of symmetrical and unsymmetrical diaryl ketones **1266** [945, 946].



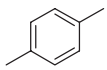
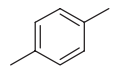
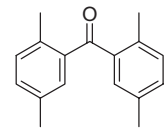
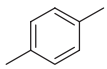
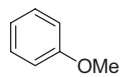
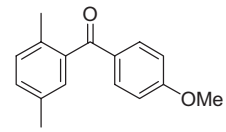
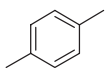
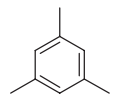
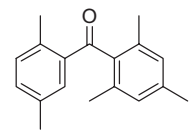
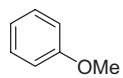
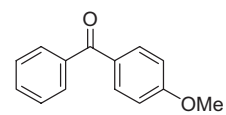
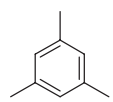
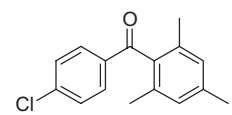
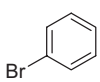
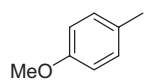
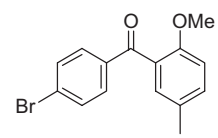
1263 **1264** **1266**

Apparently, success in this reaction is strongly curtailed by the distinct tendency of oxalyl chloride to form [$COCl_2$] or [$COCl^{\bullet}$], which subsequently substitutes hydrogen atoms (aliphatic or aromatic) by chlorocarbonylation [947]. Chlorocarbonylation is especially favored under free radical conditions and in chlorinated solvents, such as trichloroethene or dichloromethane. Neubart and Fishel reported the reaction of alkylbenzenes with **oxalyl chloride** and $AlCl_3$ under these conditions, resulting in 4-alkylbenzoyl chlorides in yields of up to 80%, depending on the length of the alkyl substituent [948].

A recent application of enzyme catalysis (**oxalyl chloride**, 50 U aminoacylase E.C. 3.5.1.14, hexane, 4 days, 20 °C) for the synthesis of *unsymmetrical* diaryl ketones has been reported [949].

The best results were obtained when the less activated substrate was used in the initial acylation and the more activated arene was used as the subsequent acceptor. With less activated substrates, such as chloro- and bromobenzenes, the chlorocarbonylation required a longer time and higher temperatures. Yields of 54–77% were obtained (Table 4.43) using 1.0 equiv. of each arene, rather than the several fold excess of one or the other often previously employed [950]. Moreover, the conditions of the second Friedel–Crafts reaction are sufficiently mild that even an *o*-

Tab. 4.43. Synthesis of *diaryl ketones* with **oxalyl chloride** [946].

Arene A	*Chlorocarbonylation*	*Arene B*	*Acylation*	*Product*	*Yield* %
	30 min, 10 °C		14 h, rt		77
	30 min, 10 °C		1 h, rt		74
	30 min, 10 °C		14 h, rt		68
	2 h, rt		14 h, rt		72
	14 h, rt		5 h, rt		70
	14 h, rt		14 h, rt		54

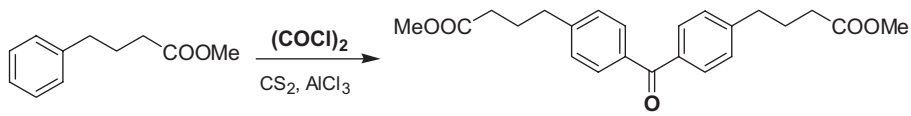
methoxy ketone, often demethylated under Friedel–Crafts conditions [951], could be prepared in satisfactory yield.

Typical procedure. *Symmetrical diaryl ketone* [946]: In a 100-mL round-bottomed flask with a side-arm, **oxalyl chloride** (1.05 mL, 12 mmol) was added dropwise over a period of 5 min to a solution of *p*-xylene (1.23 mL, 10 mmol) in dichloromethane (50 mL) at 5 °C. Aluminum chloride (1.33 g, 10 mmol) was then added portionwise over 5 min to give a yellow suspension. The reaction mixture was allowed to warm to room temperature and stirred for 1 h, during which time dissolution of the solid and gas evolution were observed. A second equivalent of *p*-xylene (1.23 mL, 10 mmol) was then added dropwise over a period of 5 min, and the reaction mixture was stirred for 13 h at room temperature. It was then chilled in an ice/water bath, and water (25 mL) was added dropwise over a period of 10 min. The layers were separated, and the aqueous layer was extracted twice with dichloro-

methane. The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was chromatographed to give the corresponding *diaryl ketone* as a clear oil (1.84 g, 77% yield).

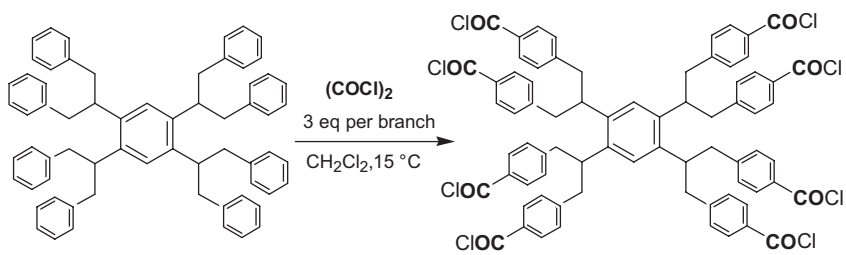
A procedure for preparing 4,4′-disubstituted benzophenones **1266** using **oxalyl chloride** was described by Cram [952].

Typical procedure. *4,4′-Bis[(3-carbomethoxy)propyl]benzophenone* **1268** [952]: By a standard esterification procedure, 4-phenylbutyric acid was converted to its methyl ester **1267** in 92% yield. To carbon disulfide (100 mL) was added 50 g of this ester, followed by **oxalyl chloride** (17.4 g). The solution was cooled to 0 °C and anhydrous aluminum chloride (74 g) was slowly added. The mixture was then stirred at 25 °C for 3.5 h. The solvent was subsequently decanted from the heavy brown syrup that separated, and the syrup was stirred with 2 kg of ice. This mixture was extracted with diethyl ether, and the ethereal layer was washed with water, dried, and concentrated to a thick orange liquid, which was distilled to give 38.8 g (73%) of faintly yellow liquid; bp 280–285 °C/2 mmHg.



1267 **1268**

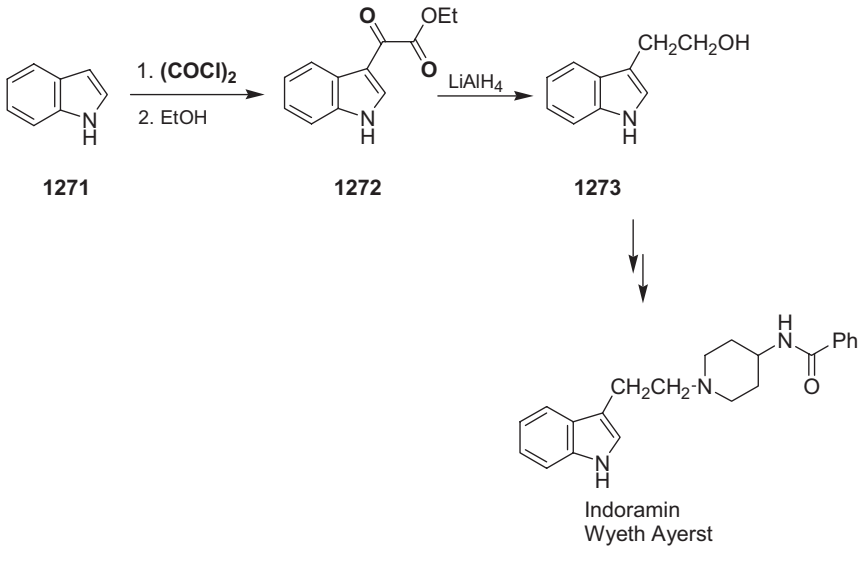
Regioselective chlorocarbonylation with **oxalyl chloride** and $AlCl_3$ in dichloromethane at 15 °C of polybenzyl cores **1269** resulting from the $CpFe^+$-induced octabenzylation of durene has been reported [953]. Reaction of the resulting polychlorinated cores with amines and alcohol nucleophiles has opened new rapid synthetic routes toward dendritic materials.



1269 **1270**

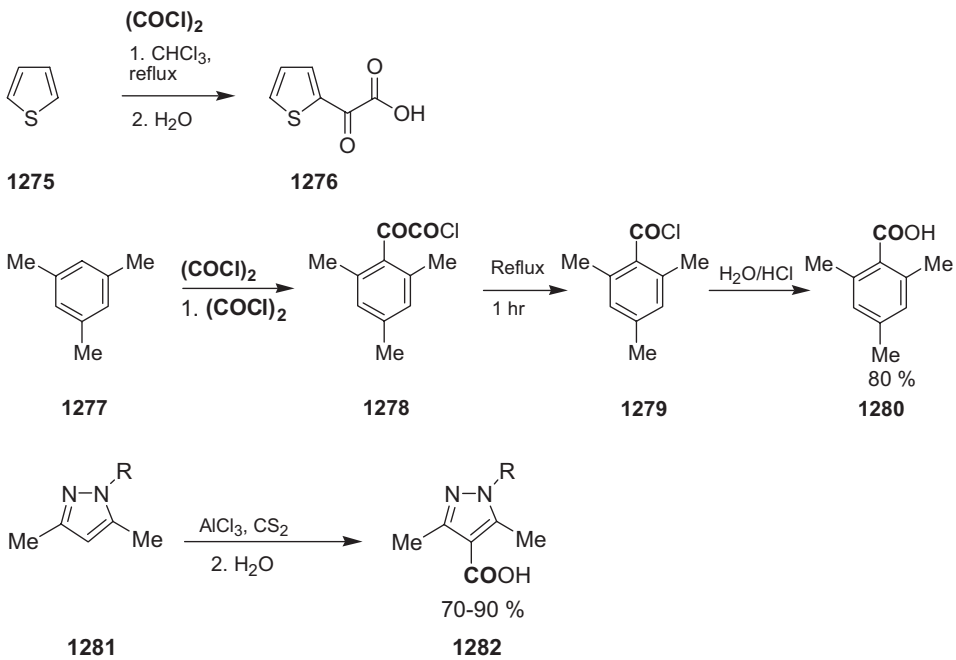
Photochemical chlorocarbonylation of heptacyclo[6.6.0.0.^{2,6}0.^{3,13}0.^{4,11}0^{5,9}.0^{10,14}]-tetradecane (“HCTD”) was performed by irradiating a solution of **oxalyl chloride** and this substrate in benzene [954].

Other applications of this type of reaction include the formation of glyoxylate esters **1272** and **1276**, which are useful intermediates for the manufacture of pharmaceuticals and in the synthesis of glyoxylic acid derivatives [955–957].



1271 **1272** **1273** **1274**

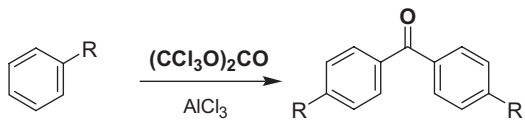
The Friedel–Crafts reaction of **oxalyl chloride** with aromatic compounds offers a useful means of generating aromatic carboxylic acids. The reaction essentially proceeds via a chloroglyoxylate intermediate **1278**, which decomposes on heating to give the corresponding acid chloride **1279**. The similar preparation of heteroaryl carboxylic acids **1282** from substrates **1281** is also reported. Yields are generally high [958].



1275 **1276** **1277** **1278** **1279** **1280** **1281** **1282**

4.3.6.3 Triphosgene

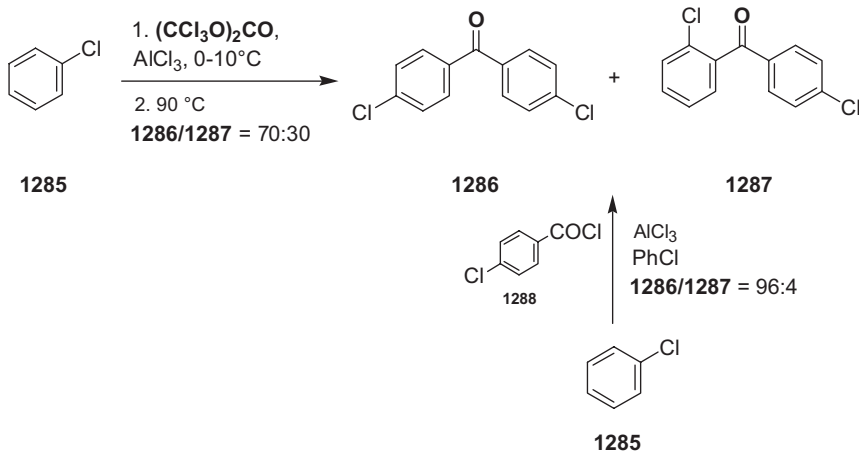
Triphosgene has been employed as a *phosgene equivalent* in the preparation of benzophenones **1284** [959].



1283 **1284**

R = H, Cl, CH_3, $(CH_3)_2N$

By adding aluminum trichloride to a solution of **triphosgene** in chlorobenzene **1285** at 0–10 °C and gradually heating to 90 °C, a mixture of two benzophenones, **1286** and **1287**, is formed [960]. Regioselective formation of 4,4′-dichlorobenzophenone can be achieved by the reaction of 4-chlorobenzoyl chloride **1288** with chlorobenzene.



1285 **1286** **1287**

1288

1285

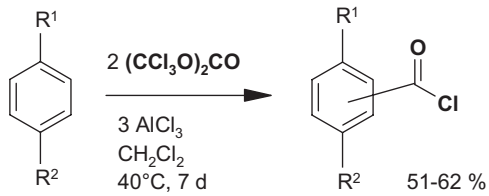
Triphosgene is able to chlorocarbonylate activated aromatic compounds such as toluene **1289a**, anisole **1289b**, 1,4-dimethoxybenzene **1289c**, and *N*-ethyl-*N*-cyclohexyl aniline **1289d** under special conditions (molar excess of **triphosgene** and $AlCl_3$) to form *substituted benzoic acid chlorides* **1290a–d** in moderate yields (51–62%, Table 4.44) [961, 962].

This chlorocarbonylation reaction proceeds satisfactorily in refluxing dichloromethane, with a molar ratio of **1289**/**triphosgene**/$AlCl_3$ of 1:2:3, although long reaction times are required (Table 4.44).

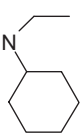
Typical procedure. *2,5-Dimethoxybenzoyl chloride* **1290c** [962]: $AlCl_3$ (4.0 g, 30 mmol) was suspended in dichloromethane (30 mL). To this mixture, a solution of 1,4-dimethoxybenzene (1.38 g, 10 mmol) and **triphosgene** (5.94 g, 20 mmol) in dichloromethane (30 mL) was added dropwise over a period of 30 min. The resulting

Tab. 4.44. Chlorocarbonylation of aromatic compounds **1289a–d** with **triphosgene**: o/p-ratios and yields of products **1290a–d** [962].

Compound 1290	*Reaction Time [h]*	*Ratio o/p*	*Product yield [%]*
a	48	0.20	62
b	40	1.13	51
c	168	–	60
d	168	0.15	61



1289a-d **1290a-d**

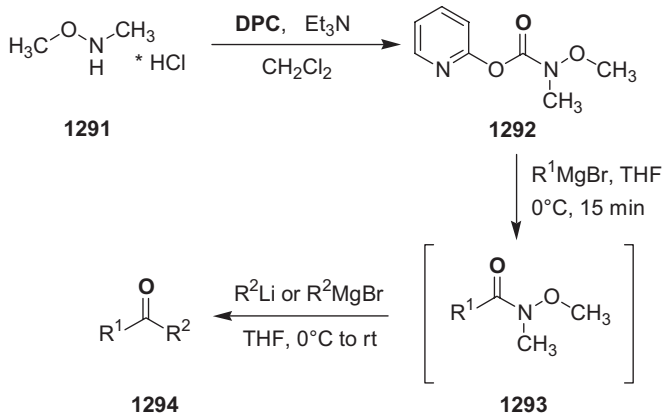
a $R^1 = H$, $R^2 = Me$
b $R^1 = H$, $R^2 = OMe$
c $R^1 = R^2 = OMe$
d $R^1 = H$, $R^2 =$ 

mixture was stirred under reflux for 7 days. It was then poured into crushed ice/water (50 mL) and stirred with pyridine (0.5 mL) at 0 °C for 10 min. The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with ice-cold 0.5 M HCl (30 mL) and with ice-cold water (2 × 10 mL), and dried over sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel, eluting with hexane/ethyl acetate (4:1 → 3:1 → 2:1 → 1:1), to afford 1.23 g (60%) of 2,5-dimethoxybenzoyl chloride; R_f (hexane/ethyl acetate, 3:1) = 0.48; IR (KBr): $\nu_{max} = 1770\ cm^{-1}$.

4.3.6.4 *N*-Methoxy-*N*-methyl-2-pyridyl Urethane

The one-pot reaction of *N*-methoxy-*N*-methyl-2-pyridyl urethane **1292** with Grignard and organolithium reagents provides an efficient method for the preparation of unsymmetrical ketones **1294** [963].

The reagent **1292** can be conveniently prepared in 94% yield by the addition of *N*,*O*-dimethylhydroxylamine hydrochloride **1291** and triethylamine to a solution of **di-2-pyridyl carbonate** (**DPC**) in dichloromethane at 0 °C. It is easily separated by aqueous work-up (2-hydroxypyridine is very soluble in water) and purified by column chromatography on silica gel or kugelrohr vacuum distillation (bp 116–120 °C/0.20 mmHg). This **phosgene equivalent** shows no sign of decomposition when kept for two months in a refrigerator.



Successful one-pot preparation of unsymmetrical ketones **1294** using **1292** largely depends on the initial selective substitution of the 2-pyridyloxy group without concomitant displacement of the *N*-methoxy-*N*-methylamino group. Selective substitution of the 2-pyridyloxy group in **1292** proceeds cleanly even at 0 °C, in contrast to the cases of *N*-methoxy-*N*,*N*′,*N*′-trimethylurea and *N*,*N*′-dimethoxy-*N*,*N*′-dimethylurea, where selective substitution of the *N*,*N*′-dimethylamino and *N*-methoxy-*N*-methylamino groups only occurs at −78 °C and −78 → ∼22 °C, respectively.

First attempts at selective substitution of the 2-pyridyloxy group in **1292** with an organolithium reagent (for example, phenyllithium, 1 equiv.) were not successful, affording mixtures of benzophenone (45%) and *N*-methoxy-*N*-methylbenzamide (22%), along with 21% recovery of the starting material. However, it proved possible to prepare symmetrical ketones by treating **1292** with 2 equiv. of the organolithium reagent.

Coupling reactions between **1292** and Grignard/organolithium reagents were carried out in one pot by reacting **1292** with the first Grignard reagent to provide the corresponding *N*-methoxy-*N*-methylamide intermediate **1293** *in situ* at 0 °C, and then this was converted into the ketone (Table 4.45) by treatment with the second Grignard or organolithium reagent between 0 °C and room temperature followed by acid hydrolysis (1 N HCl). The second step of the reaction worked well with organolithium as well as Grignard reagents.

Typical procedure. *p-Methoxyvalerophenone* **1294k** [963]: *Preparation of* ***N-Methoxy-N-methyl-2-pyridyl urethane*** **1292**: To a solution of **di-2-pyridyl carbonate** (2.162 g, 10 mmol) in dichloromethane (30 mL), *N*,*O*-dimethylhydroxylamine hydrochloride **1289** (975.5 mg, 10 mmol) and triethylamine (1.42 mL, 10.2 mmol) were added at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was allowed to warm to room temperature over a period of 1 h. It was then poured into saturated aq. $NaHCO_3$ solution (60 mL) and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to dryness in vacuo. The crude product was purified by

Tab. 4.45. Preparation of unsymmetrical ketones **1294** from **N-methoxy-N-methyl-2-pyridyl urethane 1292** and Grignard/Organolithium reagents [963].

Compound R^1COR^2 1294	*Step 1 R^1MgBr*	*Step 2[b] R^2MgBr*	*Reaction time, h[d]*	*Yield of R^1COR^2 1294 [%]*
a	$CH_3(CH_2)_4$	PhC≡CLi	0.5	85
b	$CH_3(CH_2)_4$	PhLi	0.5	76
c	$CH_3(CH_2)_4$	2-ThLi[c]	1	86
d	$Ph(CH_2)_3$	CH_2=CHMgBr	0.5	77
e	$Ph(CH_2)_3$	*t*-BuLi (1.5 eq)	1	54
f	*c*-C_6H_{11}[a]	*n*-BuLi	0.5	73
g	*c*-C_6H_{11}	*sec*-BuLi (2 eq)	4	45
h	*c*-C_6H_{11}	PhLi (1.5 eq)	0.5	83
i	*p*-MeC_6H_4	MeLi	0.5	86
j	*p*-MeC_6H_4	$CH_3(CH_2)_4MgBr$	2	93
k	*p*-$MeOC_6H_4$	*n*-BuLi	0.2	96
l	*p*-$MeOC_6H_4$	2-ThLi (1.5 eq)	0.5	88
m	*p*-ClC_6H_4	MeLi	0.2	84
n	*p*-ClC_6H_4	*n*-BuLi	0.2	94
o	*p*-ClC_6H_4	*sec*-BuLi (1.5 eq)	1	75

[a] Cyclohexylmagnesium chloride was used; [b] The reaction was carried out with 1.2 equiv. of organometallic reagent between 0 °C and rt; [c] 2-Thienyllithium; [d] Reaction time indicates step 2.

column chromatography on silica gel (EtOAc/*n*-hexane, 1:1) to give 1.712 g (94%) of ***N*-methoxy-*N*-methyl-2-pyridyl urethane 1292**.

Preparation of p-methoxyvalerophenone **1294k**: To a solution of ***N*-methoxy-*N*-methyl-2-pyridyl urethane 1292** (364.4 mg, 2 mmol) in THF (6 mL), *p*-methoxyphenylmagnesium bromide (0.25 M in THF, 8 mL, 2 mmol) was added dropwise over a period of 10 min at 0 °C under nitrogen atmosphere. Stirring was maintained for a further 5 min and then *n*-butyllithium (1.60 M in hexane, 1.5 mL, 2.4 mmol) was added directly to the mixture (one-pot process). The reaction mixture was stirred for 0.5 h, while warming to room temperature, and was then quenched with 1 N HCl (5 mL). After evaporation of the THF, the concentrated mixture was poured into 1 N HCl (30 mL) and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to dryness in vacuo. The crude product was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:4) to give 369.1 mg (96%) of *p*-methoxyvalerophenone **1294k**.

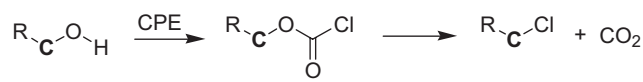
4.4 Chlorination Reactions

Section 4.2 reviewed reactions of oxygen, sulfur, and nitrogen nucleophilic compounds with phosgene equivalents (giving chloroformates, thiochloroformates, and

carbamoyl chlorides, respectively), in which the main process is chloroformylation, e.g. reactions involving COCl group transfer. In the present Section, we extend our survey to chlorination using **phosgene** or **phosgene equivalents**.

Chlorination of various monofunctional substrates (e.g. reactions with alcohols giving alkyl chlorides, or with carboxylic acids giving acid chlorides or anhydrides) using **chlorinated phosgene equivalents** (i.e. compounds able to transfer an electrophilic COCl group; chloroformylating agents) is a multi-stage process involving the formation of chlorocarbonyl functionalized intermediates rather than a one-step direct substitution reaction. Due to the relatively high reactivity of chloroformylated intermediate species, often the literature makes no distinction between the synthesis of chloroformylated intermediates and their further transformation into chlorides, carbonates, isocyanates, ureas, etc., as the final "pseudophosgenation" reaction products.

The reactivity is typical of that for tricoordinated carbonic acid derivatives, involving an addition–elimination reaction sequence.



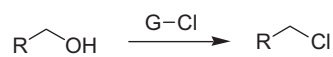
1295 **1296** **1297**

C = aliphatic primary, secondary or tertiary carbon atom,
aryl or heteroaryl carbon atom
carbonyl carbon atom
CPE = chlorinated phosgene equivalent

The chlorocarbonyl functionalized intermediates **1296** usually have limited stability. Under the reaction conditions, they are not isolable and easily eliminate carbon dioxide (in the case of O-containing nucleophiles, e.g. alcohols or carboxylic acid substrates), or benzyl chloride (in the case of N-dealkylation of *tertiary* benzylamines).

4.4.1 Alkyl Chlorides. Chlorination of Alcohols to give Alkyl Chlorides

A practical and convenient route to a number of chlorinated compounds **1300** is the direct chlorination of alcohols **1298** [964].



1298 **1300**

G = H, SOCl, PCl_2, COCl

Various chlorinating agents, such as **thionyl chloride** [965], **phosphorus trichloride** [966], **PPh_3/tetrachloromethane** [967], **PPh_3/hexachloroacetone** [968], **phosgene** [969–973] or, more economically, **phosgene with HCl gas** in the presence of an amine or a quaternary ammonium salt as catalyst [974–977], have been described.

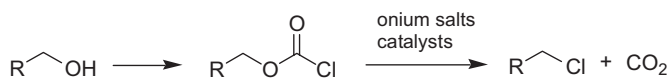
Primary, secondary, and benzylic alcohols are converted into the corresponding chlorides when treated with **tetrachlorosilane** in the presence of potassium carbonate at room temperature. For example, benzyl alcohol, 1-octanol, 2-hexanol, cyclohexanol, cinnamyl alcohol, borneol, and *tert*-butyl alcohol were treated with K_2CO_3 and **$SiCl_4$** in dichloromethane at room temperature for 50–70 min to give benzyl chloride, 1-chlorooctane, 2-chlorohexane, chlorocyclohexane, cinnamyl chloride, bornyl chloride, and *tert*-butyl chloride, respectively, in 94–97% yield [978].

Potassium carbonate reacts with tetrachlorosilane to form trichlorosilyloxycarbonyl chloride ($Cl_3SiOCOCl$), which subsequently reacts with another mole of tetrachlorosilane leading eventually to **phosgene** in chlorinated solvents. **Trichlorosilyloxycarbonyl chloride** or **phosgene** generated *in situ* in this way have proved to be very effective for the chlorination of a wide variety of alcohols to give the corresponding chlorides [978].

Activated alcohols can be converted to alkyl chlorides by reaction with **phosgene** in the presence of *N*,*N*-dimethylformamide [971].

Because of the thermal instability of certain chloroformates, the production of halides can often occur in the absence of a catalyst [1, 969, 970, 972]. Most chloroformates are amenable to facile decomposition in the presence of appropriate catalysts [973].

Decarboxylation of alkyl chloroformates **1299** in the presence of onium salts as catalysts has been extensively studied [974, 979–981].



1298 **1299** **1300**

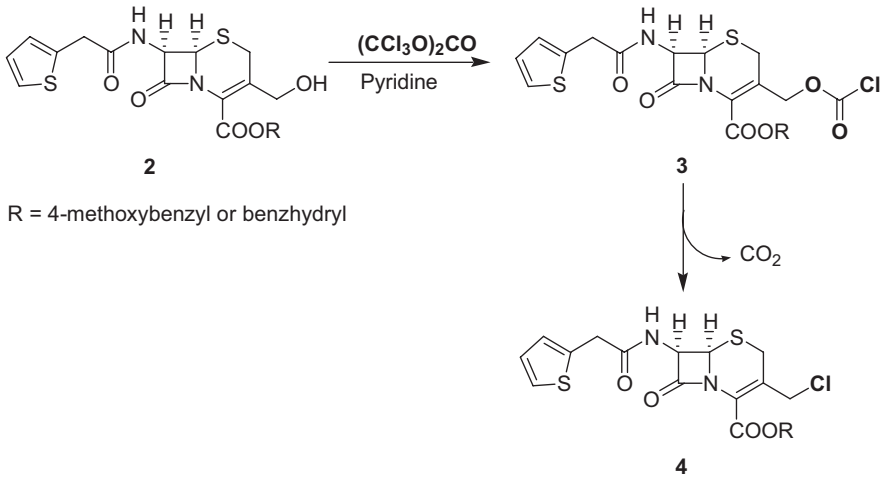
The advantages of the partial chlorination of alcohols (60–95% conversion) with HCl and completion of the chlorination by a catalytic phosgenation and subsequent decarboxylation of the resulting chloroformates have been combined in a two-stage process [974, 982]. Only small amounts of dialkyl ethers, alkenes, isomeric chloroalkanes, or dialkyl carbonates are claimed to be formed as side products.

The availability of **triphosgene** as a stable solid alternative to phosgene together with a quantification of the intermediate chloroformates gave the reaction a more preparative character.

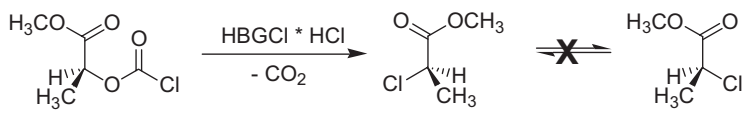
A clean conversion to cephem chloride **4** has been observed by chlorinating the cephem nucleus **2** at the C-3 position using **triphosgene** [13]. The reaction is thought to proceed through the unstable cephem chloroformate **3** (reaction and experimental procedure described in Section 4.2.1).

The reaction proceeds primarily according to an S_N2 mechanism, with some contribution from S_N1 and/or S_Ni mechanisms, as discussed in Section 4.2.1.

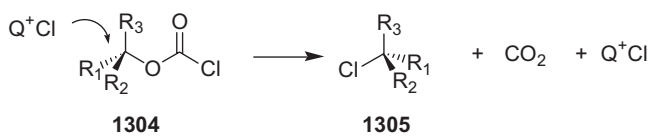
Recently, SNPE reported that the inversion of configuration that occurs in bimolecular nucleophilic substitutions is being used to prepare chiral 2-chloropropionates **1302**.



When methyl (*S*)-(−)-2-(chlorocarbonyloxy)propionate **1301** (prepared by phosgenation of methyl (*S*)-(−)-lactate) decomposes in the presence of hexabutylguanidinium chloride hydrochloride, methyl (*R*)-(+)-2-chloropropionate **1302** is formed in up to 90% yield and with up to 98% *ee*.

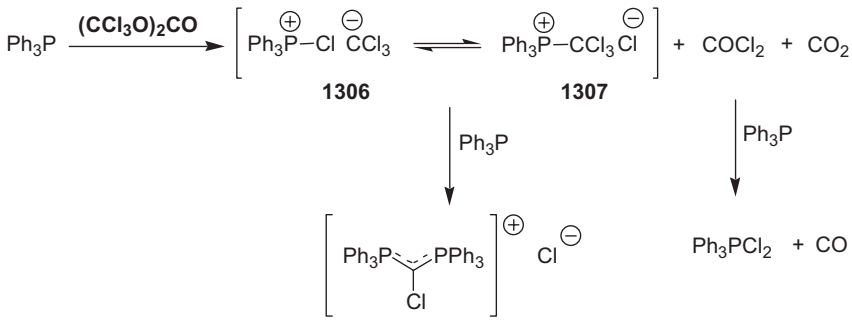


Continuous attack by chloride ion on either side of the substitution site in **1304** can occur, and the exchange between the chloride ion from the catalyst and the chlorine atom of the substrate follows an S_N2 mechanism, resulting in a racemate [983]. However, continuous removal of the inversion products prevents this from happening. This chemistry is currently being practiced on a 100-kg scale [984].



A very efficient reagent for converting primary and secondary alcohols to the corresponding chlorides at room temperature is a mixture of **triphosgene** and **triphenylphosphine** [985]. It was previously reported that chloroformate esters react with PPh_3 to give the corresponding chlorides at elevated temperatures (>100 °C) [986].

The authors postulated phosphonium salts **1306** and **1307** as the reactive intermediates in this reaction, similar to those seen in chlorination with **hexachloroacetone**/**PPh_3** [968, 985, 987].



However, further investigations [988] demonstrated that phosphonium salts are not formed and that **Ph_3PCl_2** ($\delta^{31}P = +66.1$) is the only phosphorus-containing product, thus providing a very clean and quantitative method for the synthesis of **Ph_3PCl_2** (see the section below on phosphorus compounds).

Table 4.46 lists the yields obtained in chlorinations of various alcohols with the **triphosgene**/**triphenylphosphine** reagent [985].

General procedure. *Chlorination with* **triphosgene/triphenylphosphine** *(4-methoxybenzyl chloride)* [985]: To a stirred solution of **triphenylphosphine** (1.67 g, 6.37 mmol) in dry dichloromethane (25 mL) at 0 °C, **triphosgene** (0.686 g, 2.45 mmol) was added portionwise over a period of 5 min. After the vigorous gas evolution had subsided (warning: phosgene is released!), the mixture was stirred for an additional 5 min. The solvent was removed under reduced pressure, and the residue was treated dropwise with a solution of 4-methoxybenzyl alcohol (0.8 g, 5.79 mmol) in dry di-

Tab. 4.46. Chlorination of alcohols with **triphosgene**/**triphenylphosphine** [985].

Alcohol	*Product*	*Yield (%)*
4-Methoxybenzyl alcohol	4-Methoxybenzyl chloride	96
Cynnamyl alcohol	Cynnamyl chloride	98
sec-Phenethyl alcohol	*sec*-Phenethyl chloride	85
Benzyl alcohol	Benzyl chloride	95
Allyl alcohol	Allyl chloride	94
2-Methyl-2-propen-1-ol	3-Chloro-2-methylpropene	97
Propargyl alcohol	Propargyl chloride	96
1-Pentanol	1-Chloropentane	98
1-Octanol	1-Chlorooctane	98
3-Pentanol	3-Chloropentane	91
5-Nonanol	5-Chlorononane	92
2-Methyl-2-propanol	2-Chloro-2-methylpropane	89
2-Methyl-2-butanol	2-Chloro-2-methylbutane	90

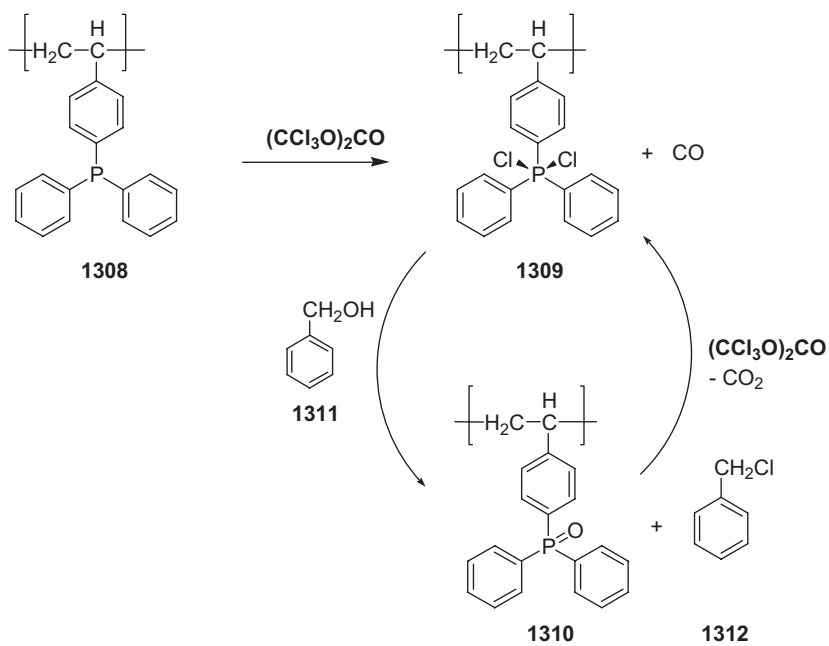
chloromethane (10 mL). The resulting mixture was stirred for 20 min at room temperature. The solvent was then removed under reduced pressure and the residue was extracted with pentane (2 × 25 mL). The combined organic phases were dried over Na_2SO_4 and subjected to bulb-to-bulb distillation using a Büchi GKR-51 oven to give 4-methoxybenzyl chloride (0.868 g, 96%).

Based on the above findings, a new methodology was described for the synthesis of polymer-bound triphenylphosphine dichloride **1309** by the use of **triphosgene** [988, 989]. This type of resin has attracted a lot of attention due to the simplicity of separating the product from the resulting phosphine oxide [990].

The addition of one-third of an equivalent of **triphosgene** (based on milliequivalent per gram P) to a suspension of Ph_2P resin **1308**, followed by the addition of a substrate after gas evolution had ceased, gave the expected product in comparable yield to free Ph_3PCl_2. Examination of recovered resins by FT-IR confirmed the expected conversion of the Ph_2P group into Ph_2PO [988].

These materials showed high efficiency in the conversion of benzyl alcohol to benzyl chloride at room temperature. In 1 h, yields of 94–100% were achieved using reactive copolymers having DVB contents below 25% [990]. These results contribute in finding a solution to two of the major drawbacks concerning the application of reactive polymers in column reactions, namely the high reaction temperatures required (reflux) and the low cross-link density that leads to very soft materials, which make column reactions unsuitable.

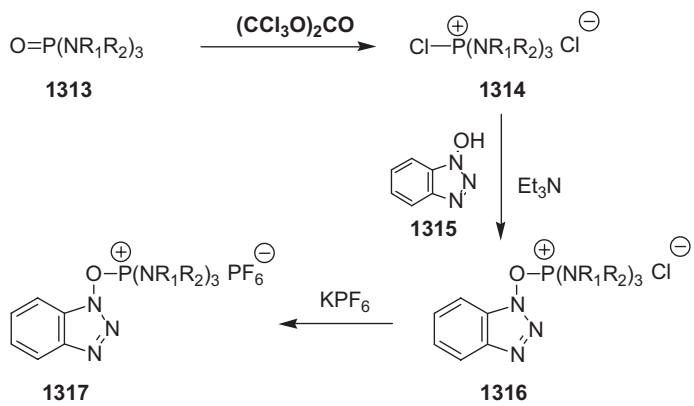
The functional groups can be easily and efficiently regenerated using 1.0 mol of **triphosgene** for every 2.6 moles of phosphine in the polymer. Preliminary results showed up to 40% conversion of benzyl alcohol in column reactions using regenerated polymers with 5 to 10 min contact times.



The synthesis of benzotriazolyloxy tris(dimethylamino)phosphonium hexafluorophosphate **1317** (BOP), an excellent peptide coupling reagent, has been traditionally performed by saturating hexamethylphosphoric triamide (HMPA) **1313** ($R_1 = R_2 = Me$) with **phosgene** and subsequently treating this mixture first with hydroxybenzotriazole **1315** and then with KPF_6. Peptide coupling is often carried out in DMF in the presence of BOP, whereby the reaction goes to completion within 2 h [991–994].

Two modified inexpensive synthetic routes to **BOP** were later reported by the same authors. One uses commercially available **phosgene** in toluene (20%)/HPPA [992], the other **$POCl_3$**/HMPA [993]. More recently, a new coupling agent, **PyBOP**, derived from tris(pyrrolidino)phosphine oxide/**$POCl_3$**, has been developed [995], which avoids the use of toxic HMPA.

Triphosgene (less moisture-sensitive than **$POCl_3$**) has been successfully used in the synthesis of **BOP** (**1317**, $R_1 = R_2 = Me$) and PyBOP (**1317**, $R_1 = R_2 = (CH_2)_4$), making the route reasonably attractive when compared to the **$POCl_3$**/HMPA or **$POCl_3$**/tris(pyrrolidino)phosphonium chloride methods [996].

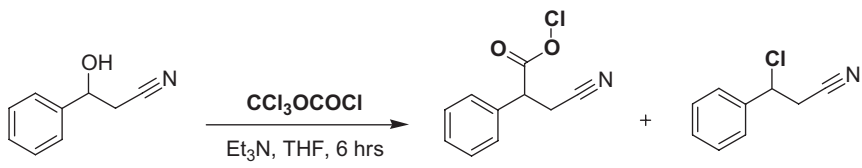


BOP $R_1 = R_2 = Me$
PyBOP $R_1 = R_2 = (CH_2)_4$

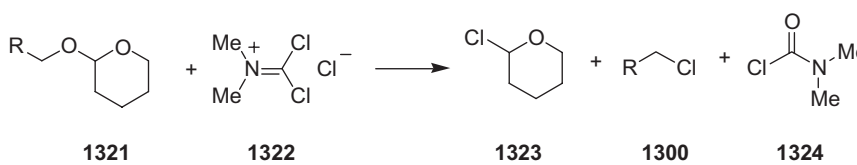
Typical procedure. *Benzotriazolyl-N-oxytris(dimethylamino)phosphonium hexafluorophosphate* (**1317**, **BOP**) [996]: To vigorously stirred HMPA (15.0 g, 83.7 mmol) at 0 °C, a solution of **triphosgene** (11.28 g, 38.01 mmol) in dichloromethane (15 mL) was added over a period of 40 min. The ice bath was then removed and the mixture was stirred at room temperature. At various intervals, small aliquots were removed in order to follow the disappearance of the HMPA spectroscopically. After 3 h, the solvent was removed under reduced pressure to leave a residue. This residue was redissolved in dry dichloromethane (40 mL) and solid hydroxybenzotriazole monohydrate (12.76 g, 94.4 mmol) was added with stirring. The resulting solution was cooled to about −5 °C with an acetone/ice bath, whereupon triethylamine (8.42 g, 83.4 mmol) was added over a period of 15 min and stirring was continued at −5 °C

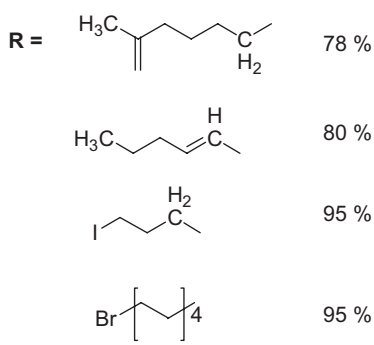
for 4 h. The residue was dissolved in water (50 mL) and mixed with a filtered solution of potassium hexafluorophosphate (16.68 g, 90.6 mmol) in water (120 mL) to give benzotriazolyl-*N*-oxytris(dimethylamino)phosphonium hexafluorophosphate **1317** (**BOP**) as a crystalline solid (28.91 g, 78%).

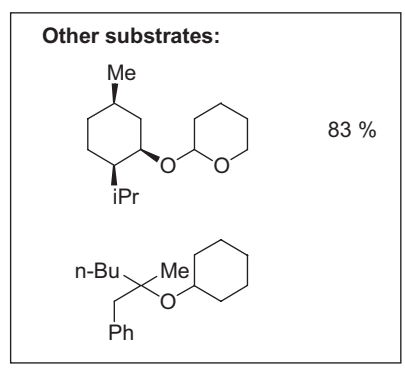
Chloroformates **1319** and chlorides **1320** are also formed when secondary benzyl alcohols **1318** are treated with **trichloromethyl chloroformate** (**diphosgene**) in the presence of triethylamine [16]. The distribution of products can be controlled.



Reactions of tetrahydropyranylated alcohols **1321** with ***N,N*-dimethylphosgeniminium chloride** (''**Viehe salt**'') **1322** give the corresponding alkyl chloride **1300** in good yields [997]. This conversion can be conveniently accomplished by adding the ''**Viehe salt**'' (1.05 equiv.) as a solid to a solution of the THP-protected alcohol (1 equiv.) in anhydrous dichloromethane (0.3 M) under argon at 0 °C. After completion of the reaction and aqueous work-up, the crude alkyl chlorides are purified by column chromatography.

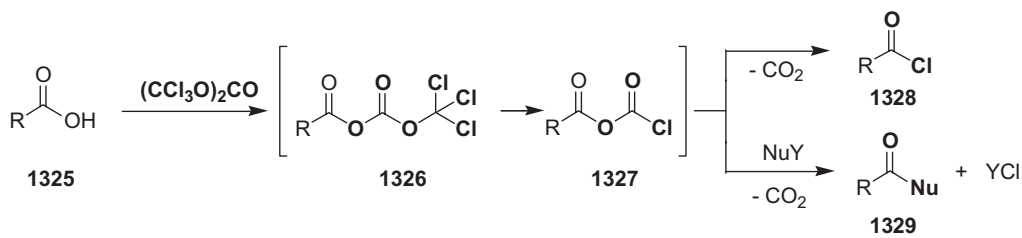






4.4.2
Acid Chlorides. Chlorination of Carboxylic Acids

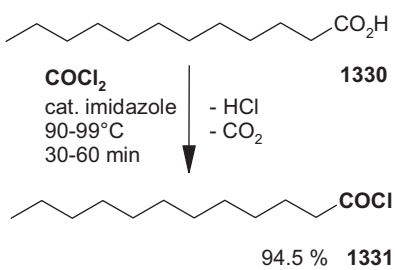
Phosgene and its equivalents (**triphosgene**, for example) react with carboxylic acids **1325** to give an acyl haloalkyl carbonate **1326** or acyl chloroformate **1327**. Depending on the reaction conditions, the predicted intermediates, which are of limited stability, readily lose carbon dioxide to give an *acid chloride* **1328** as a more stable carbonic acid derivative, or react with a nucleophile (for example, the acid carboxylate) to give the corresponding product of nucleophilic substitution **1329**.



Various chlorinating agents have been used to convert carboxylic acids or their anhydrides into acid chlorides. The most commonly reported methods employ **thionyl chloride**, **phosphorus trichloride**, or **phosphorus pentachloride**. However, the unsatisfactory degree of purity of the final acid chlorides, due to inherent contamination with sulfur or phosphorus by-products, has stimulated a search for new reagents and catalysts.

4.4.2.1 Phosgene

Phosgene as a chlorinating agent, together with *N*,*N*-dialkyl carboxamides, amidinium salts, or tetralkyl ureas as catalysts, has proved to be an economical alternative to the large-scale manufacture of acid chlorides [998–1001]. Comprehensive catalyst screening studies to achieve high reaction rates and conversions have been reported [1002–1004].

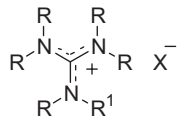


Typical procedure. *Lauroyl chloride* **1331** [1002]. ***Equipment***: A 500-mL, round-bottomed flask was fitted with a paddle stirrer, a gas inlet tube, a thermowell, and a

dry ice/acetone deflamator (dry-ice condenser). The flask and fittings were arranged so that gaseous phosgene could be fed in below the surface of the stirred reaction medium, and that phosgene escaping from the hot medium could be condensed on the dry-ice/acetone deflamator and returned directly to the medium as a liquid. The deflamator was connected to two dry-ice/acetone traps in series, which, in turn, were connected to a water scrubber, and the scrubber was open to the atmosphere within the confines of a fume hood. (Caution! Phosgene is not sufficiently irritating at time of exposure to give warning of lethal amounts.) As by-products, hydrogen chloride and carbon dioxide were evolved from the reaction medium; they passed up through the deflamator, through the dry-ice/acetone trap, and into the top of the water scrubber. In the scrubber, the gases reacted with a steady stream of water and passed down through a long glass column (4 ft) packed with glass beads. If the rate of phosgenation was too rapid, e.g. an excessive reaction temperature occurred, phosgene entrained in the by-product gases was no longer adequately condensed by the deflamator and began to appear in the dry ice/acetone trap. To this end, the incorporation of these traps in the off-gas system helps to establish facile reaction conditions.

Reaction: The flask was charged with lauric acid **1330** (200 g, 1.0 mol) and catalyst (imidazole, 2-methyl imidazole, 2.0 mol% based on the acid), and the mixture was heated with stirring to 90 °C. The stirred mixture was maintained at 90 °C for 1 h, at which time **gaseous phosgene** (for a *source* and for *safe phosgenation*, see Chapter 7) was introduced below the surface of the liquid at such a rate as to maintain a gentle **phosgene** reflux from the deflamator. **Phosgene** addition was regulated and calculated with the aid of a tubular flowmeter. The reaction was continued, generally within the temperature range 80–100 °C, until hydrogen chloride was no longer evolved (cessation of heat generation at the top of the water scrubber). The **phosgene** feed was stopped and the reaction mixture was kept at 85–95 °C with gentle **phosgene** reflux from the deflamator until the evolution of carbon dioxide had ceased (30–60 min, as evidenced by cessation of the gas entering at the base of the scrubber column). Occasionally, additional **phosgene** was required during this period to maintain phosgene reflux and to complete the reaction. Following complete reaction, the deflamator was replaced by a 10-in. (25 cm) glass helix packed distillation column fitted with a total reflux head, and dissolved **phosgene** was removed from the stirred reaction product by purging with dry nitrogen at 90 °C for 2 h. The product was distilled at 10 mmHg as a single fraction. Yield: 91–94.5% of lauroyl chloride **1331**.

The SNPE Group has developed efficient catalysts and a clean technology for the industrial manufacture of acid chlorides with **phosgene** [979, 1004–1006]. Mechanistic studies demonstrated that the activity of the catalysts is related to the nucleophilicity of the chloride anion [979, 1007]. Based on these findings, hexaalkylguanidinium chlorides **1332** proved to be efficient and powerful phosgenation catalysts (**HBGCl**) for converting either carboxylic acids or their anhydrides to acid chlorides. Particularly well-suited for chlorination reactions with **phosgene** is the silica-supported catalyst **PBGSiCl** [979].



1332

X = Cl
R = R^1 = nBu :**HBGCl**
R = R^1 = Me : **HMGCl**
R = nBu, R^1 = nPr: **PBGSiCl**
(silica-supported **PBPGCl**)

General procedure. *Chlorination of carboxylic acids (stearic acid)* [979]: (Caution: Hood! Review phosgene safety precautions before repeating). The carboxylic acid (0.2 mol) and the **PBGSiCl** catalyst **1332** (10 g, 2 mmol Cl^-) were heated at 100–120 °C. After stabilization of the temperature, **gaseous phosgene** (for a *safe source* and *safe phosgenation*, see Chapter 7) was bubbled into the suspension and condensed in a trapping funnel by a dichloromethane/dry-ice mixture. The reaction was monitored by GC. After complete consumption of the carboxylic acid (6–8 h), heating was stopped and the reaction mixture was degassed by a nitrogen stream. The catalyst was then separated by filtration and the product was analyzed. Spectral data for the products were consistent with those of commercial acyl chloride samples.

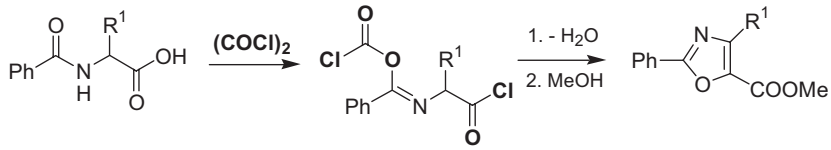
Several **phosgene equivalents** have been reported to bring about clean and efficient activation of the carboxylic group as an acid chloride.

4.4.2.2 Oxalyl Chloride

Pure **2-cyanoacryloyl chloride**, which is useful for the preparation of esters suitable for contaminant-free adhesives, is manufactured by reacting 2-cyanoacrylic acid with a chlorinating agent under conditions inhibiting side reactions and polymerization. **Oxalyl chloride**, **thionyl chloride**, **trifluoroacetyl chloride**, and **phosgene**, which form only volatile by-products, are the preferred chlorinating agents. The polymerization is inhibited, for example, by using a catalyst which forms an intermediate complex with the chlorinating agent, thereby preventing the formation of a mixed anhydride.

Typical procedure. *2-Cyanoacryloyl chloride* [1008]: 2-Cyanoacrylic acid (2.0 g) was dissolved in hot *p*-xylene (250 mL) containing γ-propanesultone (1 mg). Some 50 mL of the xylene was then removed by distillation, and the concentrated solution was filtered and cooled to 40 °C. Me_2NCHO (5 mg; stock solution in benzene) was added, and then **oxalyl chloride** (6 mL) was added dropwise with stirring under a continuous flow of Ar. The mixture was stirred for 12 h at room temperature, then ethyl furfurylidenecyanoacetate (5 mg) was added and the volatiles (along with a part of the solvent) were removed in vacuo to give 100 mL of a clear yellow solution of 2-cyanoacryloyl chloride in xylene.

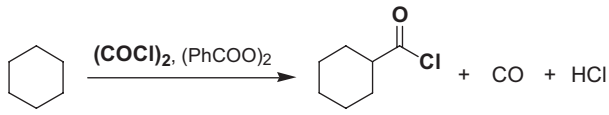
N-Benzoyl amino acids **1333** react with excess **oxalyl chloride** at room temperature to form intermediates **1334**, treatment of which with alcohols affords 4-substituted 2-phenyloxazole-5-carboxylates **1335** [1009].



1333 **1334** **1335**

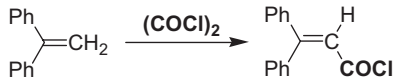
Acid chlorides are also formed when **oxalyl chloride** reacts with some saturated hydrocarbons in the presence of light or a peroxide. Replacement of hydrogen by **COCl** occurs [954, 1010].

Thus, when a mixture of cyclohexane **1336** (0.3 mol), **oxalyl chloride** (0.2 mol), and dibenzoyl peroxide (1.2 g) was refluxed for 24 h, the cyclohexanecarboxylic acid chloride **1337** was obtained in modest yield.



1336 **1337**

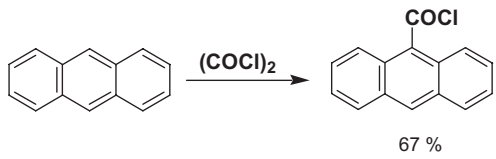
In some cases, an olefinic hydrogen can be displaced by **COCl** [1011].



1338 **1339**

Typical procedure. [1012]: On refluxing 1,1-diphenylethylene **1338** (6.5 g) with **oxalyl chloride** (4.5 g) for 3–4 h, the acid chloride **1339** was obtained in 50% yield. The yield of this reaction could be raised to 95% by using 5 mol of **oxalyl chloride** per mol of alkene. Neither light nor peroxides have any effect on this reaction, which is apparently ionic.

Cyclohexene and trimethylethylene failed to react. Anthracene **1340** undergoes substitution without catalysis [1013].



1340 **1341**

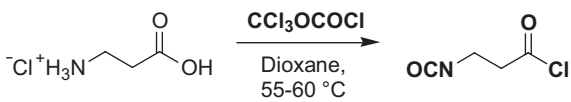
Typical procedure. *Anthracene 9-carboxylic acid chloride* **1341** [1013]: A solution of anthracene **1340** (5 g) and **oxalyl chloride** (30 mL) in nitrobenzene (150 mL) was heated to 120 °C, and then the temperature was raised to 240 °C over a period of 5–6 h. The corresponding acid chloride **1341** was obtained in 67% yield.

Under Friedel–Crafts conditions ($AlCl_3$, CS_2), **oxalyl chloride** reacts with aromatic hydrocarbons to give carbonyl chlorides, which are hydrolyzed by water to give carboxylic acids. The $AlCl_3$-mediated chlorocarbonylation of arenes with **oxalyl chloride** has been used in the preparation of symmetrical and unsymmetrical diaryl ketones [946] (see also Section 4.3.6).

4.4.2.3 Diphosgene

Isocyanato acid chlorides, such as 3-isocyanatopropanoyl chloride **1343**, having two different, highly reactive electrophilic groups, are efficient reagents for introducing amino acid residues into organic compounds [161] and polymers [1014]. 3-Isocyanatopropanoyl chloride **1343** has been prepared by the reaction of 3-aminopropanoic acid hydrochloride **1342** with **phosgene** [1015]. However, the yield is only 36%, and hydrogen chloride must be introduced to increase the yield to 92%. 6-Isocyanatohexanoyl chloride can only be prepared in trace amounts with phosgene unless additional hydrogen chloride is used.

A procedure using **trichloromethyl chloroformate** (**diphosgene**) has been successfully applied in the synthesis of isocyanato acid chlorides and isocyanato chloroformates from amino acids and amino alcohols, respectively [161, 1016].



1342 **1343**

Typical procedure. *3-Isocyanatopropanoyl chloride* **1343** [1016]: *Caution! Diphosgene is toxic. The reaction should be carried out in a well-ventilated hood.* A 500-mL, two-necked flask was equipped with a thermometer and a reflux condenser protected at the top by a calcium chloride guard tube. A Teflon-coated magnetic stirring bar, anhydrous dioxane (250 mL), finely pulverized 3-aminopropanoic acid hydrochloride **1342** (*β*-alanine·HCl) (12.6 g, 0.1 mol), and **diphosgene** (23.8 g, 14.4 mL, 0.12 mol) were placed in the flask in the order specified. The mixture was stirred and heated at 55–60 °C. After ca. 5 h, the solid had completely dissolved to give a clear solution. Heating was discontinued after a total of 7 h and the solvent was removed under reduced pressure. The residual oil was rapidly distilled under reduced pressure and a distillate amounting to 11.2–12.4 g (84–93%) was collected at 75–85 °C/20 mmHg. Redistillation afforded 10.5–11.8 g (79–88%) of 3-isocyanatopropanoyl chloride **1343** as a colorless liquid (bp 92–94 °C/25 mmHg). ***Comment***: *Although the reaction can be carried out with an equimolar amount of trichloromethyl chloroformate, a longer time (15–20 h) is required to reach completion, and the yield is somewhat reduced. If a 1.5–2.0-fold excess of trichloromethyl chloro-*

formate is used, the reaction time is decreased to ca. 5 h and the yield is increased to 90–95%.

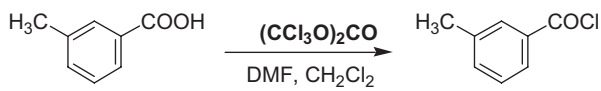
Organic acid chlorides have been prepared with **diphosgene** in the presence of DMF as a catalyst [1017].

Typical procedure. *Octanoyl chloride* [1017]: **Diphosgene** (108.8 g) was added to a mixture of octanoic acid (144.2 g) and DMF (1.5 L) at 70 °C. The mixture was left to stand for 1 h, and then nitrogen was bubbled through it for 30 min at 100 °C to give 96.9% of octanoyl chloride (purity 99.99%). Benzoyl chloride and terephthaloyl chloride were similarly prepared.

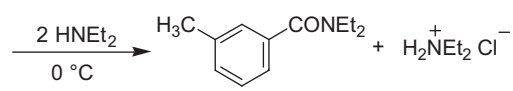
4.4.2.4 Triphosgene

Alkyl vinyl ethers have been converted into acid chlorides with **triphosgene** or **diphosgene** [1018].

m-Toluic acid **1344** has been converted into *m*-toluyl chloride **1345** with **triphosgene** [1019]. **Triphosgene** offers several advantages over **thionyl chloride**, giving a cleaner reaction without the formation of SO_2 or dark-colored impurities. The synthesis is the first stage in the preparation of *N*,*N*-diethyl-*m*-toluamide (*Deet*) **1346**, the active ingredient in many commercial insect repellents.



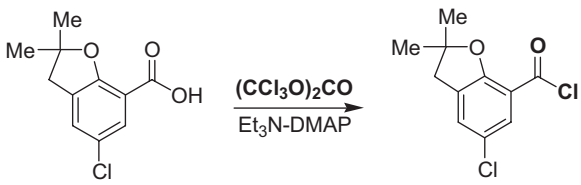
1344 **1345**



1346

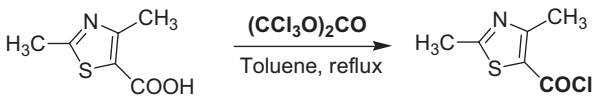
Typical procedure. *m-Toluyl chloride* **1345** with **triphosgene** [1019]: A micro-reflux condenser, a $CaCl_2$ drying tube, a micro-Claisen head, and a 3-mL conical vial containing a spin vane were oven-dried. They were then left to cool to room temperature in a desiccator. The vial was charged with pure *m*-toluic acid (136 mg, 1.00 mmol) and dichloromethane (0.50 mL) and the mixture was stirred until the solid had dissolved. To this solution were added **triphosgene** (100 mg, 0.34 mmol) and one drop of dry dimethylformamide. The vial was fitted with the Claisen head. The opening above the vial was capped and the condenser (fitted with the drying tube) was attached at the other opening. A piece of Tygon tubing was used to connect the drying tube to a small, inverted glass funnel placed just under the surface of a 10% NaOH solution in a beaker to neutralize the HCl generated during the preparation of *m*-toluyl chloride. The solution was heated to reflux in a sand bath for 1 h. Bubbles of CO_2 and HCl could be observed in the gas trap shortly after the reaction had begun. The acid chloride was not isolated, but was reacted in situ with diethylamine to give *N*,*N*-diethyl-*m*-toluamide (Deet) in an average overall yield of 51%.

5-Chloro-2,3-dihydro-2,2-dimethylbenzofuran-7-carboxylic acid **1347** was activated for esterification by reaction with either **triphosgene/Et_3N/DMAP** or **diphosgene/Et_3N** [1020].



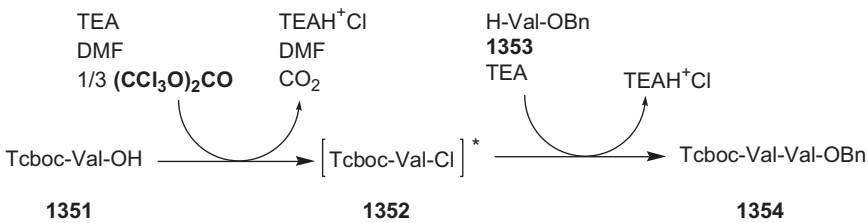
1347 **1348**

Thiazolecarbonyl chloride was prepared in 88% yield by adding **triphosgene** to a suspension of the corresponding acid in toluene and refluxing the mixture for 15 h [1021].



1349 **1350**

The use of **triphosgene** as an acid activator has been reported in several recent applications. Eckert and Seidel activated the N-protected amino acid Tcboc-valine **1351** (Tcboc = 2,2,2-trichloro-*tert*-butyloxycarbonyl [1022]; for a *preparation*, see also Section 4.3.2.1) with **triphosgene/DMF/TEA** for racemization-free coupling with valine benzyl ester to afford Tcboc–Val–Val–OBn in 85% yield [1023, 1024].



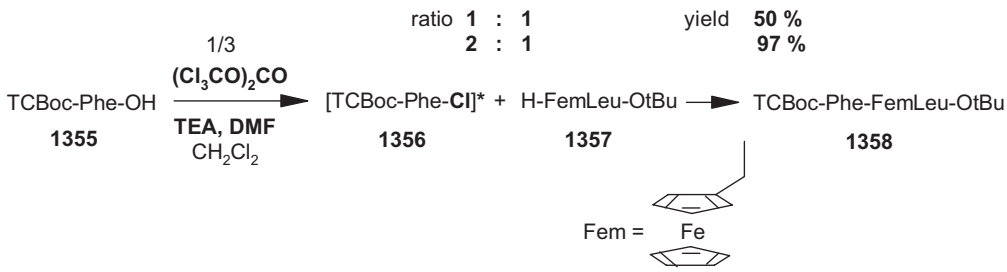
1351 **1352** **1354**

Tcboc = 2,2,2-trichloro-tert-butyloxycarbonyl

The method is particularly well-suited for coupling *N*-alkyl amino acids. Tcboc–Phe–OH **1355** and FemLeu–O*t*Bu **1357** (Fem = ferrocenylmethyl [1025, 1026]) can be coupled with **triphosgene/DMF/TEA** to afford moderate to excellent yields (50–97%) of Tcboc–Phe–FemLeu–O*t*Bu **1358**, depending on the excess of the activated component **1356** [1023, 1024].

An original process has been reported in which **triphosgene** is used as an efficient and effective coupling reagent for peptide synthesis through in situ genera-

tion of the amino acid chloride from a protected (Fmoc) amino acid. In the original method, the amino acid was activated with **triphosgene** and collidine in THF and reacted with a peptidyl resin for 1 h at 50 °C. This process is particularly useful for coupling to sterically hindered amino acid residues and for other difficult couplings. Furthermore, the same reagent can be used for the derivatization of peptides by formation of an amide bond between a free amine on a peptide and a carboxylic acid or for the coupling of an amino acid to a solid support [1027, 1028].



Racemization-free, **triphosgene-mediated** coupling in the solid phase was recently used by Thern and Jung in a total synthesis of the nematicidal cyclododecapeptide *Omphalotin A* **1359** [1029].

Omphalotin A:

1 2 3 4 5 6 7 8 9 10 11 12
Cyclo(Trp–MeVal–Ile–MeVal–MeVal–Sar–MeVal–MeIle–Sar–Val–MeIle–Sar)

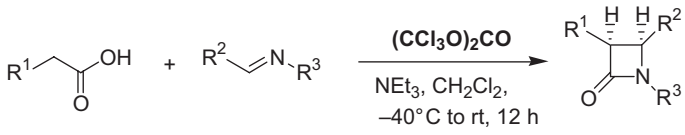
1359

The following protocol was developed: the *N*-Fmoc-deprotected peptidyl-TCP resin (trityl linker) was pre-treated with diisopropylethylamine (DIEA), and the Fmoc-*N*-methyl amino acid was activated at room temperature in THF by the addition of triphosgene and collidine. The procedure enables the use of **triphosgene** on acid-labile TCP resin. Premature cleavage from the resin was prevented by limiting the pre-treatment of the resin with DIEA, as well as the Fmoc deprotection with piperidine, to the shortest possible duration. An elevated temperature during the coupling reaction was unnecessary as the presence of the strong base DIEA appears to accelerate the coupling reaction. By applying these modifications, the formation of by-products was almost completely eliminated and the amount of Fmoc amino acid needed per coupling reaction could be reduced from 5 to 3.5 equivalents without any loss of coupling efficiency.

Typical procedure. *Coupling with* **triphosgene** [1029]: Fmoc peptidyl resin was deprotected with 20% piperidine/DMF (2 min + 8 min). After washing, the resin was treated with dry THF (1 mL) for 15 min. Meanwhile, the requisite Fmoc amino acid (483 μmol, 3.5 equiv.) was added to a 68 mM solution of **triphosgene** in dry THF (2.4 mL; 1.15 equiv. **triphosgene**). *sym*-Collidine (180 μL, 10 equiv.) was added

to the clear solution, whereupon a precipitate of collidinium chloride was formed. DIEA (190 μL, 8 equiv.) was added to the resin, followed, immediately thereafter, by the suspension. The mixture was shaken for the required reaction time, then filtered and washed.

Triphosgene activation has been used for the construction of β-lactams through ketene–imine cycloaddition reactions (Staudinger reaction) [1030]. In all the studied cases, the cycloaddition reaction was found to be stereoselective and only *cis*-β-lactams **1362** were formed.



65-95 %

1360 **1361** **1362**

R^1, R^2, R^3 = PhO, MeO, Ph, Styryl, etc

Typical procedure. *β-Lactams* **1362** [1030]: To a solution of acid **1360** (1.5 mmol), imine **1361** (1 mmol), and triethylamine (6 mmol) in dry dichloromethane (10 mL) at −40 °C, a solution of **triphosgene** (1 mmol) in dry dichloromethane (5 mL) was added over a period of 20 min. The mixture was allowed to warm to room temperature and stirred for 12 h. It was then washed successively with water (20 mL), saturated $NaHCO_3$ solution (20 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered through a short column of silica gel, and the solvent was removed to give the crude product, which was purified either by crystallization or column chromatography to give the β-lactams **1362** in yields of 65–95%.

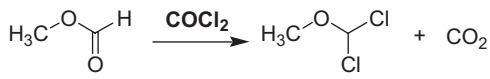
4.4.2.5 1,1-Dichlorodimethyl Ether (Chloromyl®)

Addition of **phosgene** to the carbonyl group of a carboxylic ester, e.g. methyl formate, followed by elimination of carbon dioxide, generates **1,1-dichlorodimethyl ether** (**Chloromyl®**) **1364**, a liquid **phosgene equivalent** (bp 85 °C). **Chloromyl®** is capable of a wide range of reactions, including conversion of organic acids to acid chlorides, formylation of aromatics, and the generation of methoxycarbene [1031–1033].

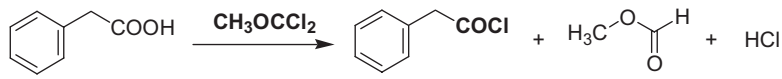
Using **Chloromyl®**, phenylacetic and adipic acids (e.g. **1365**) or α-keto acids (e.g. **1368**) are converted to their acid chlorides with volatilization of hydrogen chloride and methyl formate **1367** (bp 32 °C) [1033].

4.4.3 Symmetric Anhydrides and Esters. Nucleophilic Substitution of Acyl Chloroformates

Anhydrides are typically prepared by the reaction of an **acyl halide** and a carboxylate salt [1034], or by the reaction of a carboxylic acid with P_2O_5 [1035], **methoxyacetylene** [1036], or a **carbodiimide** [1037–1039].

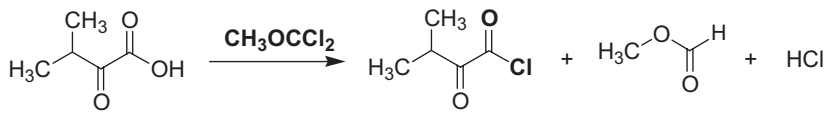


1363 1364



92.5 %

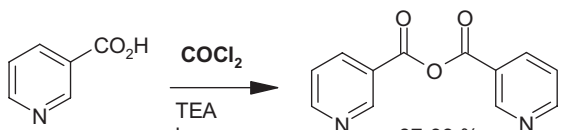
1365 1366 1367



98 %

1368 1369 1367

A report of the synthesis of acid anhydrides using **phosgene** gas has also appeared in the literature [1040, 1041]. Nicotinic anhydride **1371** was prepared from nicotinic acid **1370** with **phosgene** in 87–93% yield, as described in a very detailed procedure [1041].

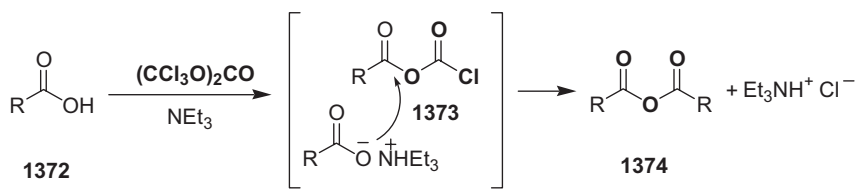


1370 **1371**

Typical procedure. *Nicotinic anhydride* **1371** [1041]: Nicotinic acid **1370** (10 g, 0.081 mol) and anhydrous benzene (275 mL) were placed in a 500-mL, three-necked, round-bottomed flask (dried overnight in an oven at 200 °C) fitted with a sealed Hershberg stirrer, a dropping funnel with a pressure-equalizing tube, and a stillhead connected to a condenser. In order to remove traces of moisture introduced with the nicotinic acid, the mixture was heated until about 75 mL of the benzene had distilled. The stillhead was then replaced by a Claisen head fitted with a thermometer and a calcium chloride guard tube, and the mixture was cooled to 5 °C by stirring in an ice bath. To the cold suspension of nicotinic acid, freshly distilled triethylamine (8.65 g, 0.086 mol, 5% excess) was added in a single portion. The resulting clear solution was stirred with continued cooling while **phosgene** (for a *safe source* and for *safe phosgenation*, see Chapter 7) (34 g of a 12.5% solution in benzene, 0.043 mol, 5% excess) was added from the dropping funnel. The rate of addition was regulated so that the temperature of the reaction mixture did not exceed 7 °C. Triethylamine hydrochloride precipitated immediately. After the addi-

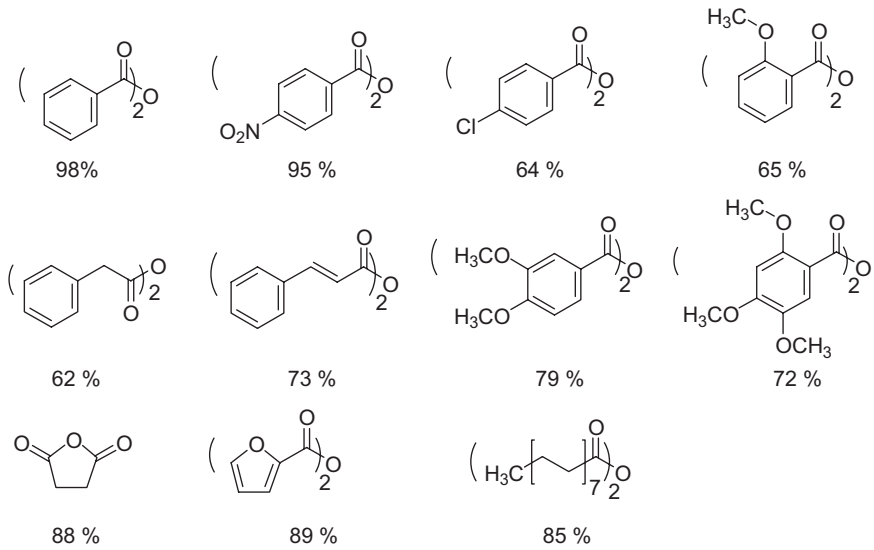
tion of **phosgene**, the mixture was stirred at room temperature for 45 min, heated to the boiling point, and filtered under slightly reduced pressure while still hot. The triethylamine hydrochloride cake was washed on the filter with warm (60 °C) benzene (3 × 25 mL). The combined filtrate and washings were transferred to a 500-mL round-bottomed flask and concentrated to dryness in a rotary evaporator at low temperature and pressure. The dry residue was gently boiled with anhydrous benzene (75 mL), and the mixture was again filtered while still hot. The triethylamine hydrochloride cake was washed with cold benzene (2 × 5 mL), and the combined filtrate and washings were left to stand at 20 °C for 2–3 h. The crystalline product was collected on a filter, washed with cold anhydrous benzene (2 × 4 mL), and dried in vacuo. The yield of nicotinic anhydride **1371**, mp 122–125 °C, was 6.25 g (68%). The combined filtrate and washings were concentrated to dryness in a rotary evaporator. The residue was gently boiled with 175 mL of a mixture of benzene and cyclohexane (2:3), and a small amount of insoluble material was removed by filtration of the hot mixture. The filtrate was stored at 5 °C for 18 h; the crystalline deposit obtained was collected, washed with 3 mL of a cold benzene/cyclohexane mixture, and dried in vacuo. An additional 2.4 g (25%) of colorless product; mp 122–123 °C, was thus obtained. The total yield of nicotinic anhydride **1371** was 8.05–8.65 g (87–93%).

The formation of **symmetric anhydrides** from the corresponding carboxylic acids and **triphosgene** has also been reported [1042].



The triethylamine salt of a carboxylic acid, prepared by the reaction of triethylamine and a carboxylic acid **1372**, undergoes reaction with one-sixth of an equivalent of **triphosgene** to give an equimolar mixture of the carboxylate and the predicted intermediate acyl chloroformate **1373** [1042]. Nucleophilic displacement of the chloroformate function by the carboxylate affords the desired anhydride **1374**, with concomitant formation of triethylammonium chloride as a precipitate and carbon dioxide gas. The reaction reaches completion in minutes. The solvents of choice have been THF or ethyl acetate, and no evidence for the formation of diacyl carbonates as potential by-products of the reaction has been found. The reaction has been used to prepare the anhydrides from both electron-rich and electron-deficient carboxylic acids (see below) [1042].

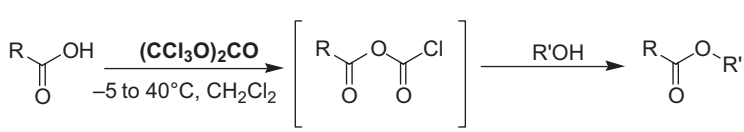
This **triphosgene-mediated** reaction for the synthesis of anhydrides has a number of advantages over the existing methods, in that the reaction is carried out under neutral conditions and does not use highly toxic or allergenic (as with carbodiimides) reagents. Furthermore, no elaborate apparatus is needed for this one-pot reaction, which proceeds conveniently to completion in minutes at ice-water temperature.



Typical procedure. *o-Anisic anhydride* [1042]: A solution of *o*-anisic acid (500 mg, 1.8 mmol) and distilled triethylamine (0.25 mL, 1.8 mmol) in ethyl acetate (35 mL) was stirred in an ice bath. **Triphosgene** (90 mg, 0.3 mmol) was then added in one portion, whereupon the immediate precipitation of $Et_3N{\cdot}HCl$ was observed. The reaction mixture was kept in the ice bath for 10 min, and then stirred for a further 15 min at room temperature. The solid ($Et_3N{\cdot}HCl$) was filtered off and washed with ethyl acetate (10 mL). The combined filtrate and washings were concentrated to dryness, and the residue obtained was recrystallized from ethyl acetate and hexane at room temperature to give the title compound as clear crystals (330 mg, 65%).

Typical procedure. *Succinic anhydride* [1042]: A solution of succinic acid (500 mg, 42 mmol) and triethylamine (1.23 mL, 42 mmol) in anhydrous THF (120 mL) was allowed to react with **triphosgene** (42 mg, 7.0 mmol) at ice-water temperature for 10 min. The reaction mixture was subsequently stirred for a further 15 min at room temperature. The solution was then filtered, and the filtrate was concentrated to dryness. The residue was crystallized from ethyl acetate to afford the desired product as white crystals (370 mg, 85%).

A similar activation method using **triphosgene** has recently been applied for the esterification of monocarboxylic acids and amino acids [1043].



1375 **1376**

General procedure. *Methyl 3,5-dimethoxybenzoate* **1312** (R = 3,5-dimethoxyphenyl, R′ = Me) [1043]: A mixture of 3,5-dimethoxybenzoic acid (3.32 g, 18.22 mmol) and methanol (5.90 mL, 145.8 mmol), was cooled to −5 to −10 °C in an ice-salt bath. A solution of **triphosgene** (1.98 g, 20.00 mmol) in dichloromethane (5 mL) was then added dropwise. The resulting mixture was warmed to 40 °C and stirred for 2 h. Excess solvent was then removed in vacuo, leaving a white residue. The solid was neutralized with 5% aq. NaOH solution, and the two-phase system was extracted with ethyl acetate (2 × 50 mL). The combined organic phases were dried (Na_2SO_4), and removal of the solvent under reduced pressure gave the product. The crude solid consisted only of the pure ester.

4.5 Dehydration Reactions

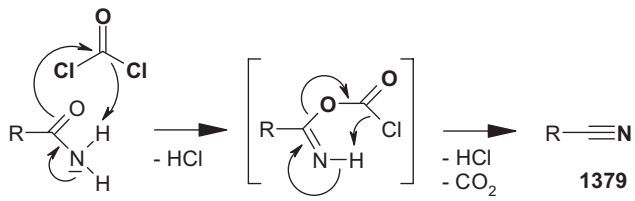
This section differs from the preceding sections in that during the dehydration reaction no part of **phosgene** is transferred to the reaction partner; in the other three typical reactions of **phosgene** (chlorocarbonylation, carbonylation, chlorination), parts of it are transferred to another molecule. Herein, the formal dehydration product, a *symmetrical acid anhydride*, is not presented, since the true intermediate in the phosgenation of a carboxylic acid is the acid chloride (having similar reactivity). We prefer to classify the process as chlorination rather than a dehydration by **phosgene** or phosgene equivalents. Reviews on dehydration reactions can be found under the relevant functional groups, such as cyanides, isocyanides, and carbodiimides. A general overview on dehydration reactions in the context of mild chemical methods is given in [1044].

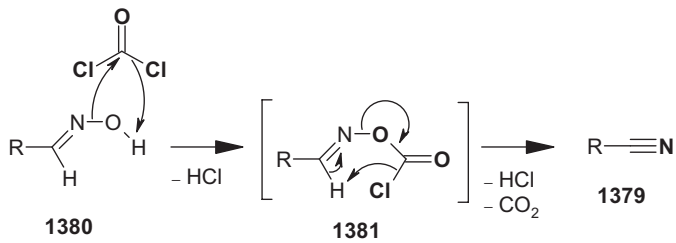
4.5.1 Cyanides

The preparation of *cyanides* by dehydration is best accomplished from *aldoximes* (standard method) rather than from *carboxamides*, because the former require milder reaction conditions. However, carboxamides, as carboxylic acid derivatives, are more easily accessible. **Phosgene** has been applied in the dehydration of carboxamides rather than of aldoximes.

Dehydration of carboxamides **1377**, for example with **phosgene**, can be envisaged as involving nucleophilic attack of the electron-rich carbonyl function of the carboxamide group on the strongly activated carbonyl function of **phosgene** forming an *azaanhydride* of *chlorocarbonic acid* **1378**. This high-energy species then stabilizes by decomposition, driven by the good leaving group ability of the chloride anion and by the formation of the low-energy, small, stable molecule CO_2, thereby affording *cyanides* **1379**.

An analogous mechanism can be given for the dehydration of aldoximes **1380** with **phosgene**.





Some reviews on the preparation of cyanides from aldoximes [1045, 1046] and from carboxamides [1047, 1048] are available. Often used dehydration reagents are **acetic anhydride** for aldoximes and **phosphorus pentoxide** for carboxamides. In the following sections, dehydration reactions affording cyanides are described with various dehydration reagents, classified into *acidic* and *basic* reagents.

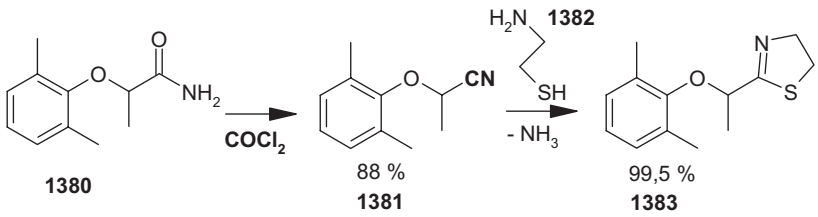
4.5.1.1 Acidic Reagents

Acidic reagents seem to offer milder conditions. Dehydration reactions forming cyanides can be performed with **phosgene** [1049–1052], **diphosgene** [1053–1055], **triphosgene** [1056], **phenyl chloroformate** [1057], **oxalyl chloride** [1058, 1059], **trichloroacetyl chloride** [1060–1062], **acetic anhydride** [1063–1074], **TFAA** [1075–1082], **phosphorus oxides** [1083–1088], **phosphorus oxychloride** [1089–1098], **phosphorus pentachloride** [1099], **triphenylphosphine/haloalkanes** [1100–1103], **thionyl chloride** [1104–1118], ***p*-tosyl chloride** [1119–1124], **triflic anhydride** [1125–1127], **chlorosulfonyl isocyanate** [1128], the **Burgess reagent** [1129], **phenyl chlorothionoformate** [1130], **cyanuric chloride** [1131–1134], **carbodiimides** [1135, 1136], **CDC** [1137], **PyBOP** [1138], **$AlCl_3$/NaI** [1139], and **acetonitrile/aldehyde** [1140], and by **pyrolysis** [1141].

Phosgene

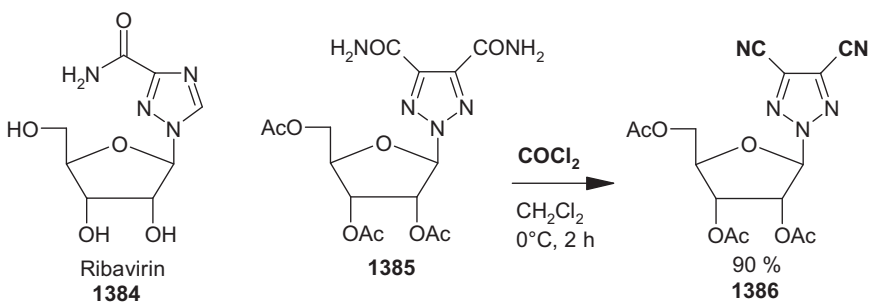
In a series of syntheses of potential antisecretory antidiarrheals, the thiazoline moiety in **1383** was constructed by condensation of 2-aminoethanethiol **1382** with the cyano group in **1381**, which was generated from the carboxamide group in **1380** by dehydration with **phosgene** in 88% yield [1049].

Typical procedure. *2-(2,6-Dimethylphenoxy)propionitrile* **1381** [1049]: Carboxamide **1380** (18.9 g, 0.097 mol) and triethylamine (37.8 mL, 0.25 mol) were dissolved in



toluene (200 mL) and dichloromethane (50 mL) and the solution was cooled in an ice bath. A 12% solution of **phosgene** in toluene (for a *safe source*, see Chapter 7) (100.0 mL; 0.13 mol) was added dropwise at such a rate as to keep the temperature below 10 °C. The reaction mixture was then allowed to warm to room temperature and water (50 mL) was added. The organic layer was washed with dilute aq. HCl and water, dried, and concentrated to yield 15.1 g (0.085 mol, 88%) of **1381** as an oil.

2-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,3-triazole-4,5-dicarbonitrile **1386**, an analogue of the human myeloid leukemia cell growth inhibitor Ribavirin **1384**, has been prepared from its carboxamide **1385** by dehydration with **phosgene** [1050].



Typical procedure. *2-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-1,2,3-triazole-4,5-dicarbonitrile* **1386** [1050]: To a cold (−5 °C) solution of carboxamide **1385** (4.7 g, 11.4 mmol) in anhydrous dichloromethane (75 mL) and pyridine (10 mL), a solution of 20% **phosgene** in toluene (for a *safe source*, see Chapter 7) (14.7 mL, 30 mmol) was added dropwise with stirring. After the addition was complete (30 min), the reaction mixture was stirred at 0 °C for 2 h. The resulting brown solution was poured onto crushed ice (200 g) and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed successively with cold 1 N HCl (10 mL), 10% aqueous $NaHCO_3$ (2 × 100 mL), and water (2 × 50 mL), and then dried (Na_2SO_4) and concentrated to dryness. Crystallization of the residue from EtOH furnished 3.9 g (90%) of 2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,3-triazole-4,5-dicarbonitrile **1386**; mp 121 °C.

2,3-Dicyanopyridine has been prepared from the corresponding quinolinic acid diamide with **phosgene** in 64% yield [1051]. Asparagine and glutamine react with

phosgene at their ω-carboxamide functions forming ω-cyano groups, with concomitant dehydration of the α-carboxylic functions to *N*-carboxylic anhydrides [1052] (see Section 4.6 "Divalent Compounds").

Diphosgene

An article entitled "*Facile Conversion of Carboxamides to Nitriles*" [1053] describes the ready conversion of alkyl, benzylic, aryl, and heteroaryl carboxamides bearing various functionalities to the corresponding nitriles in good yields of 76–96% using liquid **diphosgene** (trichloromethyl chloroformate) as the dehydrating agent. In many cases, the procedure does not require an extraction step, and hence offers a very simple work-up.

Typical procedure. *3,5-Dinitrobenzonitrile* [1053]: In a well-ventilated hood, **diphosgene** (2 mL) was added dropwise to a cold (0–5 °C), stirred solution of 3,5-dinitrobenzamide (2.1 g, 10 mmol) in trimethyl phosphate (6.3 mL). The reaction mixture was then slowly heated to 60 °C for 5 min to ensure completion of the reaction and also to distil off any generated phosgene. After cooling in an ice/water bath, the reaction mixture was vigorously stirred and iced water (10 mL) was added to destroy any traces of phosgene or chloroformate. The precipitated solid product was collected by filtration, washed with water to eliminate traces of HCl and trimethyl phosphate, and air-dried; yield: 1.88 g (96%), mp 127–129 °C. Recrystallization from diisopropyl ether gave an analytically pure product, mp 130–131 °C.

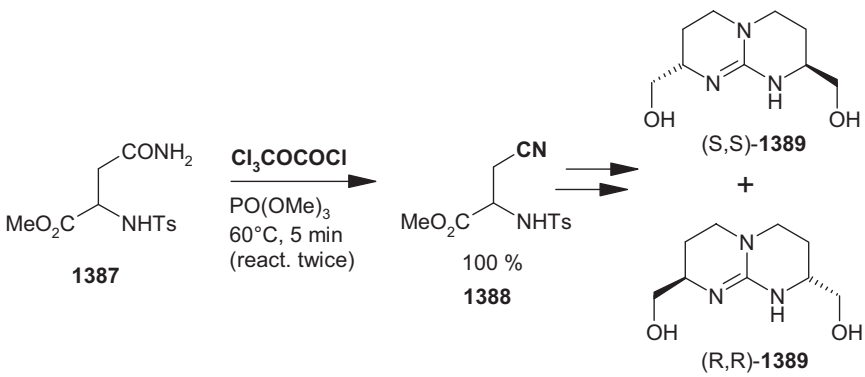
The same authors also reported that alkyl, benzylic, aryl, and heteroaryl aldoximes bearing various functionalities could be readily converted to the corresponding nitriles using **diphosgene** in good yields of 82–96% [1054].

General procedure. *Nitriles from aldoximes* [1054]: In a well-ventilated hood, **diphosgene** (32.1 g, 0.15 mol) was added dropwise to a stirred solution of the aldoxime (0.1 mol) in acetonitrile (50 mL). An increase in temperature was observed. After stirring for 5 min, iced water (200 mL) was slowly added to the reaction mixture to destroy any excess **diphosgene** and the generated phosgene. *Caution*: Phosgene is hydrolyzed by water only slowly. Stirring must therefore be continued until no phosgene remains (see Merck Index for details on the detection of phosgene).

Isolation and purification: In the case of solid nitriles, the solid precipitate is collected by filtration, washed with water, air-dried, and recrystallized from diisopropyl ether to afford an analytically pure product.

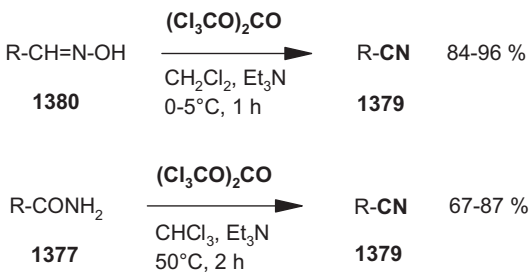
In the case of liquid nitriles, diethyl ether (200 mL) is added to the mixture, and the organic layer is separated, washed successively with water, 5% sodium hydrogen carbonate solution, and brine, dried over magnesium sulfate, and concentrated to an oil. If desired, the oil may be distilled to afford the pure nitrile.

A chiral bicyclic guanidinium compound **1389**, derived from L- or D-asparagine, has been synthesized as an anion receptor [1055]. The cyano function in **1388** is generated in about 100% yield by dehydration of the γ-carboxamide **1387** with **diphosgene**.



Triphosgene

Alkyl, benzylic, aryl, and heteroaryl aldoximes **1380** and carboxamides **1377** are dehydrated to the corresponding cyanides **1379** in yields of 84–96% and 67–87%, respectively, with **triphosgene** in the presence of triethylamine under mild conditions [1056]. The dehydration of aldoximes requires cooling of the reaction mixture to 0–5 °C, whereas that of carboxamides requires heating to 50 °C due to the lower reactivity of the latter.



General procedure. *Cyanides* **1379** *from aldoximes* **1380** [1056]: To an ice-cold, stirred solution of aldoxime **1380** (3 mmol) and triethylamine (1.2 mL, 8 mmol) in absolute dichloromethane (25 mL), a solution of **triphosgene** (0.33 g, 1.1 mmol) in dichloromethane (20 mL) was added dropwise at 0–5 °C over a period of 15 min. The mixture was stirred at the same temperature for 1 h, and then washed successively with water (10 mL), 0.1 N aq. HCl (20 mL), 10% aq. $NaHCO_3$ (20 mL), and brine (15 mL). The separated organic layer was dried (Na_2SO_4) and concentrated, and the crude product was purified by passage through a short column of silica gel.

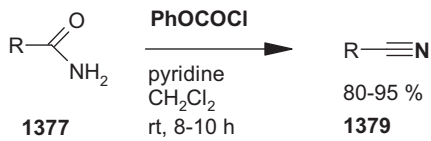
Liquid products were distilled in vacuo, while solid products were recrystallized from benzene/petroleum ether.

General procedure. *Cyanides* **1379** *from carboxamides* **1377** [1056]: To a stirred solution of an amide (4 mmol) and **triphosgene** (0.6 g, 2 mmol) in absolute chloroform (40 mL), a solution of triethylamine (1.7 mL, 12 mmol) in absolute chloroform

(10 mL) was added dropwise over a period of 10 min. As the reaction was exothermic, the reaction temperature gradually increased to 50 °C and the mixture was kept at this temperature for 2 h. After standard work-up as described above, the products **1379** obtained were purified by passage through a short silica gel column followed by distillation or recrystallization from benzene/petroleum ether.

Phenyl chloroformate

A mild and general synthetic method for the facile conversion of alkyl, benzylic, aryl, and heteroaryl primary amides to the corresponding nitriles in high yields of 80–95% uses **phenyl chloroformate** in the presence of pyridine at room temperature [1057].



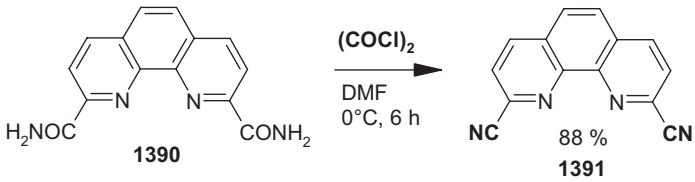
General procedure. *Cyanides* **1379** *from carboxamides* **1377** [1057]: **Phenyl chloroformate** (5.5 mmol) was added dropwise to a stirred, ice-cooled solution (or suspension) of the amide/thioamide (5.0 mmol) in dry dichloromethane (25 mL) and anhydrous pyridine (10.0 mmol) at such a rate that the temperature remained below 5 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 8–10 h (completion of the reaction was verified by TLC). It was then quenched with water (8 mL) and extracted with dichloromethane (2 × 25 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and the solvent was removed in vacuo to afford the crude product, which was purified by column chromatography on silica gel. Pure cyanides **1379** were obtained in yields of 80–95%.

Oxalyl chloride

Oxalyl chloride has been used as a dehydration reagent in the preparation of 2,9-dicarbonitrile-1,10-phenanthroline **1391**, which serves as a starting material in the synthesis of macrocyclic compounds [1058].

Typical procedure. *2,9-Dicyano-1,10-phenanthroline* **1391** [1058]: To DMF (200 mL), **oxalyl chloride** (5.7 mL, 0.066 mol) was added with stirring at 0 °C under argon atmosphere. A white precipitate formed immediately, which was accompanied by gas evolution. When the gas evolution had ceased, a solution of the diamide **1390** (7.0 g, 0.026 mol) in DMF (150 mL) was added to the reaction flask. The resulting yellow mixture was stirred for 6 h at 0 °C. Pyridine (9.4 mL, 0.116 mol) was then added and, after stirring for a further 30 min, the mixture was neutralized with saturated aq. Na_2CO_3 solution (500 mL). Some precipitate was formed, and precipitation was completed by adding water (700 mL). After filtration, the pale-yellow

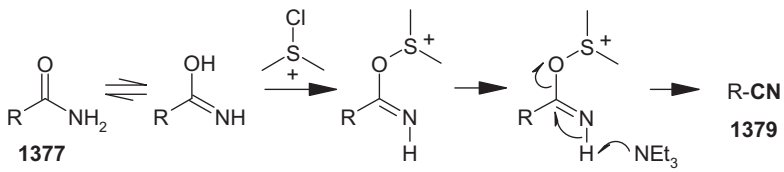
product was dried, first in air and then over P_2O_5 in vacuo, to give 5.2 g (88%) of 2,9-dicarbonitrile-1,10-phenanthroline **1391**, mp >300 °C.



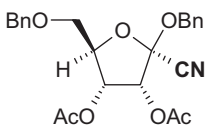
1390 **1391**

The use of oxalyl chloride as a dehydrating agent has been developed into a general procedure for preparing cyanides from carboxamides under *Swern oxidation conditions*, affording a great variety of structures such as **1392–1396** in mostly excellent yields [1059]. The proposed mechanism is outlined.

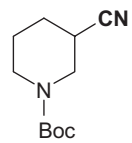
Typical procedure. *Nitrile* **1397** *from the carboxamide* [1059]: A solution of **oxalyl chloride** (67 μL, 0.77 mmol) in dichloromethane (0.5 mL) was added to a solution of the corresponding carboxamide (142.0 mg, 0.55 mmol) and DMSO (78 μL, 1.1 mmol) in dichloromethane (1.5 mL) at −78 °C. After stirring for 15 min at −78 °C, triethylamine (0.23 mL, 1.65 mmol) was added dropwise. The reaction mixture was stirred for 15 min at −78 °C, and then quenched by the addition of water (5 mL). After allowing the mixture to warm to room temperature, the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), and filtered. Concentration of the filtrate in vacuo followed by purification by column chromatography on silica gel (hexane/EtOAc, 2:1) and kugelrohr distillation gave nitrile **1397** as a colorless oil (123.3 mg, 93%).



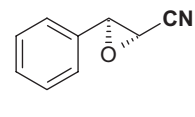
1377 **1379**



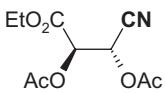
1392 94 %



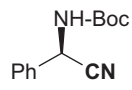
1393 89 %



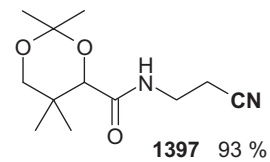
1394 87 %



1395 91 %



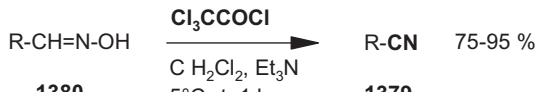
1396 81 %

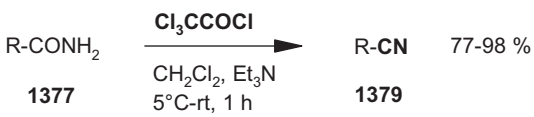


1397 93 %

Trichoroacetyl chloride

Among activated acyl chlorides, **trichloroacetyl chloride** is also suitable for dehydrating alkyl, benzylic, aryl, and heteroaryl carboxaldoximes [1060] and carboxamides [1061] to the corresponding cyanides in the presence of triethylamine, affording high product yields of 75–98%.





General procedure. *Nitriles* **1379** *from carboxaldoximes* **1380** [1060]: To a stirred solution of the aldoxime **1380** (20 mmol) and triethylamine (4 g, 40 mmol; distilled from calcium hydride) in dichloromethane (20 mL; distilled from phosphorus pentoxide) in a suitable flask topped with a calcium chloride guard tube, a solution of redistilled **trichloroacetyl chloride** (3.82 g, 21 mmol) in dichloromethane (20 mL) was added dropwise at 5–10 °C. The mixture was allowed to warm to room temperature and was stirred for 1 h. The dichloromethane was then removed using a rotary evaporator and diethyl ether (100 mL) was added to the residue. After swirling, the mixture was filtered, the filtrate was washed with water (2 × 30 mL) and saturated sodium chloride solution (30 mL), and dried with sodium sulfate. The ether was removed using a rotary evaporator and the residue was chromatographed on a short column of alumina (20 g) eluting with benzene (50–70 mL is usually required). Most of the benzene was distilled off; last traces of volatile material were removed in vacuo. The residual nitrile **1379** was distilled or recrystallized.

General procedure. *Nitriles* **1379** *from carboxamides* **1377** [1061]. ***Method A***: To a stirred mixture of the carboxamide (20 mmol), triethylamine (40 mmol; distilled from calcium hydride), and dichloromethane (30 mL; distilled from phosphorus pentoxide), a solution of redistilled **trichloroacetyl chloride** (4 g, 22 mmol) in dried dichloromethane (20 mL) is added dropwise at 0–5 °C. After completion of the addition, the mixture is treated sequentially with ice-cold water (25 mL), 5% aq. sodium hydroxide solution (30 mL), 5% aq. sulfuric acid (30 mL), and finally with water (25 mL). After each treatment, the aqueous phase is washed with dichloromethane (10 mL). The final organic solution is dried with anhydrous sodium sulfate. The dichloromethane is then removed by distillation (or evaporation) and the residue is purified. In cases where the nitrile formed is acid- or base-sensitive, the solution of the nitrile is only washed three times with water.

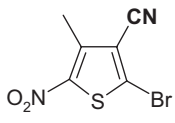
Method B *(for nitriles that are soluble in water)*: To a stirred mixture of the carboxamide (20 mmol), triethylamine (40 mmol), and dichloromethane (30 mL; distilled from phosphorus pentoxide) in a suitable flask topped with a calcium chlo-

ride guard tube, a solution of redistilled **trichloroacetyl chloride** (3.82 g, 21 mmol) in dichloromethane (20 mL) is added dropwise at 0–5 °C. The mixture is allowed to warm to room temperature and is stirred for 1 h. The dichloromethane is then removed using a rotary evaporator, and diethyl ether (10 mL) is added to the residue. After filtration, the ether is removed. The residue is chromatographed on a short column of alumina (20 g) eluting with dry benzene or petroleum ether/ethyl acetate. After removal of the solvent, the nitrile is distilled or crystallized.

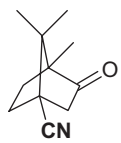
According to the above method, cyclopropanone cyanohydrins are synthesized in excellent yields [1062].

Acetic anhydride

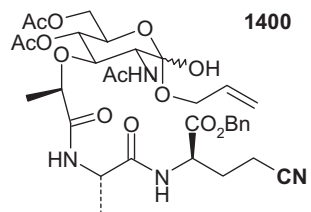
In some preparations, **acetic anhydride** has been used as a dehydration agent for carboxamides, although the required reaction conditions are rather rigid. 2-Bromo-4-methyl-5-nitrothiophene-3-carbonitrile **1398** is prepared in this way from its corresponding carboxamide [1063].



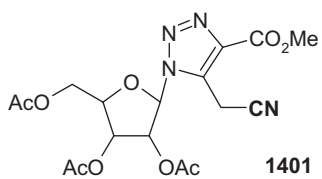
1398



1399



1400

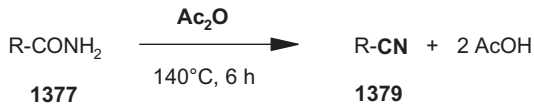


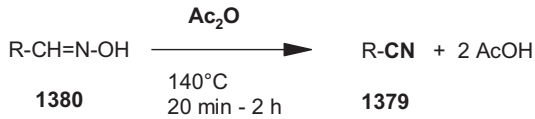
1401

Typical procedure. *2-Bromo-4-methyl-5-nitrothiophene-3-carbonitrile* **1398** [1063]: A solution of 2-bromo-4-methyl-5-nitrothiophene-3-carboxamide (2.2 g) in **acetic anhydride** (33 mL) was refluxed for 6 h. The reaction mixture was then concentrated under reduced pressure and the residue was chromatographed on a column of silica gel eluting with benzene. The nitrile obtained was crystallized from methanol; mp 125–126 °C (no yield quoted).

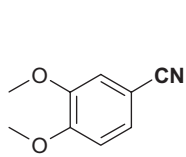
The method has also been applied to the synthesis of 4-cyanocamphor **1399** [1064], triazolo-5-cyanomethyl-4-methoxycarbonyl-1-nucleoside **1401** [1065], and (2*R*)-benzyl 2-[*N*-(2′-*N*-acetyl-1′-α-*O*-allyl-4′,6′-*O*-acetylmuramyl)amino]-4-cyanobutanoate **1400** [1066] from their corresponding carboxamides.

Dehydration of carboxaldoximes is often accomplished by the **acetic anhydride** method as it is a convenient and low-cost reagent. Veratronitrile **1402** is prepared from veratraldoxime by dehydration with **acetic anhydride** in 72–78% yield according to a procedure from the year 1935 [1067].

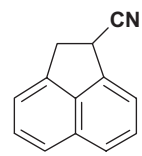




Typical procedure. *Veratronitrile (3,4-dimethoxybenzonitrile)* **1402** [1067]: Veratraldoxime [1067] (88–89 g, 0.45 mol) was combined with **acetic anhydride** (100 g) in a 300-mL round-bottomed flask equipped with a ground-glass air condenser, and the mixture was cautiously heated. A vigorous reaction took place, at which point the flame (*heating by oil bath; the author*) was removed. After the reaction had subsided, the solution was gently refluxed for 2 h and then carefully poured, with stirring, into cold water (300 mL). Stirring was continued, and on cooling the nitrile separated as small, almost colorless crystals; these were collected by filtration and dried in air. The veratronitrile thus obtained was quite pure; yield 57–62 g (72–76%); mp 66–67 °C.



1402 72-78 %



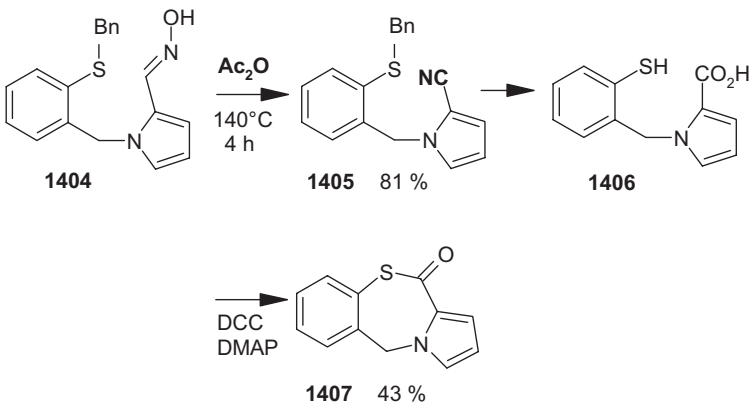
1403 87 %

1-Cyanoacenaphthene **1403** can be synthesized from its carbaldoxime by dehydration with **acetic anhydride** in 87% yield [1068]. Whereas acetic anhydride usually serves as the solvent as well as the reactant, this procedure is performed in *n*-octane.

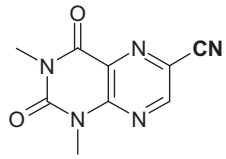
Typical procedure. *1-Cyanoacenaphthene* **1403** [1068]: A stirred suspension of the corresponding oxime (2.38 g, 12.1 mmol) in *n*-octane (25 mL) and **acetic anhydride** (5 mL) was gently heated until a vigorous reaction commenced. The mixture was then kept at reflux temperature for about 1 h to complete dissolution of the oxime. After cooling, the mixture was poured with swirling into ice-cold water (100 mL). The red-orange oil was extracted with diethyl ether (3 × 15 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was removed in vacuo and the remaining viscous red-brown oil was chromatographed on a column of silica gel (about 30 g) eluting with benzene to give the nitrile **1403** as a pale-yellow solid; yield: 1.88 g (87%). An analytical sample was obtained by recrystallization from *n*-octane; colorless crystals, mp 66 °C; IR (KBr): $\nu_{max} = 2240\ cm^{-1}$ (CN).

In the construction of a structure of pharmacological interest with a 1,4-thiazepine moiety, 11-oxo-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **1407** is obtained by a ring-closure reaction between the thiol and carboxy functions in **1406**. Intermediate **1406** is obtained from the nitrile **1405**, which, in turn, is obtained from the corresponding carbaldoxime **1404** by dehydration with **acetic anhydride** in 81% yield [1069].

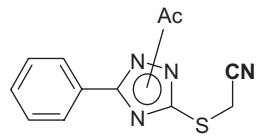
Typical procedure. *1-(2-Benzylthiobenzyl)pyrrole-2-carbonitrile* **1405** [1069]: A solution of 1-(2-benzylthiobenzyl)pyrrole-2-carbaldoxime **1404** (14.5 g, 0.045 mol) in **acetic anhydride** (140 mL) was heated at 140 °C for 4 h. After cooling to room temperature, the reaction mixture was poured onto crushed ice and sodium hydrogen carbonate was added in small portions to neutralize the acetic acid formed. The resulting mixture was extracted with diethyl ether and the combined extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated to give a brownish oil, which was purified by passage through a column of silica gel using chloroform as eluent. Concentration of the appropriate fraction of the eluate in vacuo afforded 10.8 g (81%) of a thick oil, which was distilled to give **1405** as a pale-yellow oil (bp 173–175 °C/0.11 mmHg); IR: $\nu_{max} = 2205\ cm^{-1}$ (CN).



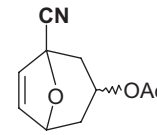
The cyanides **1408–1412** have all been synthesized by dehydrating their carboxaldoximes with **acetic anhydride** [1070–1074]. A pteridine synthesis yielded 75% of *6-cyano-1,3-dimethyllumazine* **1408** [1070]. *N*-Acetyl (3-phenyl-1,2,4-triazolo-5-yl)-thiolacetonitrile **1409** was obtained as the condensation product from a triazole derivative and chloro acetaldehyde, followed by oximation and dehydration, in 79% yield [1071]. *endo*-1-Cyano-3-acetoxy-8-oxabicyclo[3.2.1]oct-6-ene **1410** (89%) is an intermediate in the synthesis of *11-oxatricyclo[5.3.1.0^{2,6}]undecane* [1072]. A synthesis of *1α,25-dihydroxy-18-norvitamin D_3 and 1α,25-dihydroxy-18,19-dinorvitamin D_3* requires the 8*β*-acetoxy-des-A,B-cholestane-18-nitrile **1411** (86%) [1073]. A new route to *spirooxindoles*, a tricyclic system found in a number of interesting natural products, requires the cyanide **1412** (72%) as a key intermediate [1074].



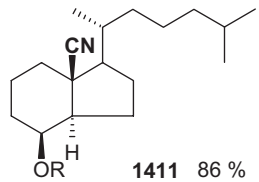
1408 75 %



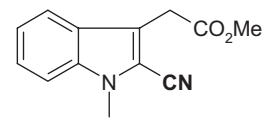
1409 79 %



1410 89 %



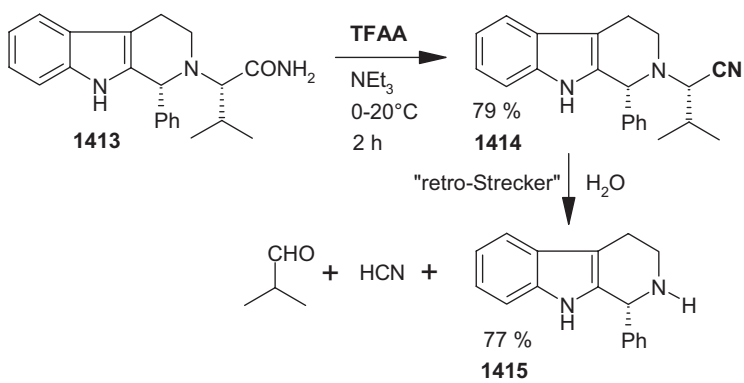
1411 86 %



1412 72 %

Trifluoroacetic anhydride (TFAA)

Trifluoroacetic anhydride (**TFAA**) is widely used for dehydrating carboxamides to the corresponding cyanides, because the highly activated **TFAA** permits the use of mild reaction conditions. To enable the following reaction sequence, compound **1413** was first constructed by an asymmetric Pictet–Spengler reaction using amino acid esters as chiral auxiliaries. After conversion of the carboxamide **1413** to the α-amino nitrile **1414** with **TFAA** at room temperature, a retro-Strecker reaction affords the desired cyclic secondary amine **1415** [1075, 1076].



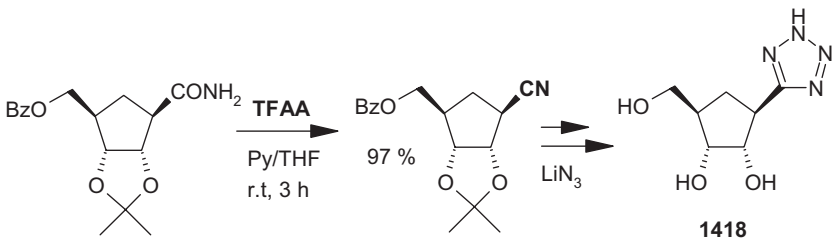
1413 **1414** **1415**

Typical procedure. *2-((S)-1-Cyano-3-methylbutyl)-1-(R)-phenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole* **1414** [1076]: A solution of the amide **1413** (0.48 g, 1.33 mmol) and triethylamine (0.4 mL, 2.86 mmol) in dry dichloromethane (50 mL) was cooled to 0 °C and treated with **TFAA** (0.2 mL, 1.41 mmol). The mixture was allowed to warm to ambient temperature, stirred for 2 h, and then extracted with saturated aq. $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and concentrated in vacuo (bath temperature < 30 °C). Recrystallization of the residue from diethyl

ether/petroleum ether afforded 0.36 g (79%) of the cyanide **1414**; $[\alpha]_D{}^{22} = -165.6$ ($c = 1.0$, $CHCl_3$); mp 138 °C.

Boc-aminoalkanenitriles are prepared by a similar procedure using **TFAA**. They are intermediates in the synthesis of mono-Boc-alkanediamines from Boc-ω-amino acids [1077]. The **TFAA** method has also been applied to *exo*-6-benzoyl-1-cyanobicyclo[2.2.2]oct-2-ene, an intermediate en route to a *non-peptide mimic of enkephalins* [1078].

An enantioselective synthesis of carbocyclic tetrazole C-ribonucleosides has been accomplished by first preparing the intermediate (1*S*,2*S*,3*R*,4*R*)-4-benzoyloxymethyl-2,3-isopropylidenedioxycyclopentene-1-carbonitrile **1417** from its carboxamide **1416** by dehydration with **TFAA** in 97% yield. Cyclization of **1417** with azide then gives the tetrazole **1418** [1079].



Typical procedure. *(1S,2S,3R,4R)-4-Benzoyloxymethyl-2,3-isopropylidenedioxycyclopentene-1-carbonitrile* **1417** [1079]: **TFAA** (4.8 mL, 36 mmol) was added dropwise to a stirred solution of carboxamide **1416** (10 g, 31 mmol) and pyridine (5.0 mL, 62 mmol) in THF (50 mL) at a temperature below 5 °C. The mixture was stirred at room temperature for 3 h, concentrated, and partitioned between dichloromethane (250 mL) and water (150 mL). The organic phase was dried (Na_2SO_4) and concentrated to give **1418** (9.12 g, 97%) as an oil, $[\alpha]_D{}^{22} = -31.7$ ($c = 1.49$, $CHCl_3$).

Dehydration of carboxaldoxime **1419** with **TFAA** at 5–15 °C furnishes the cyanide **1420** in 72% yield, which cyclizes with **1421** to form the isoquinoline moiety of *hypecumine* **1422** [1080].

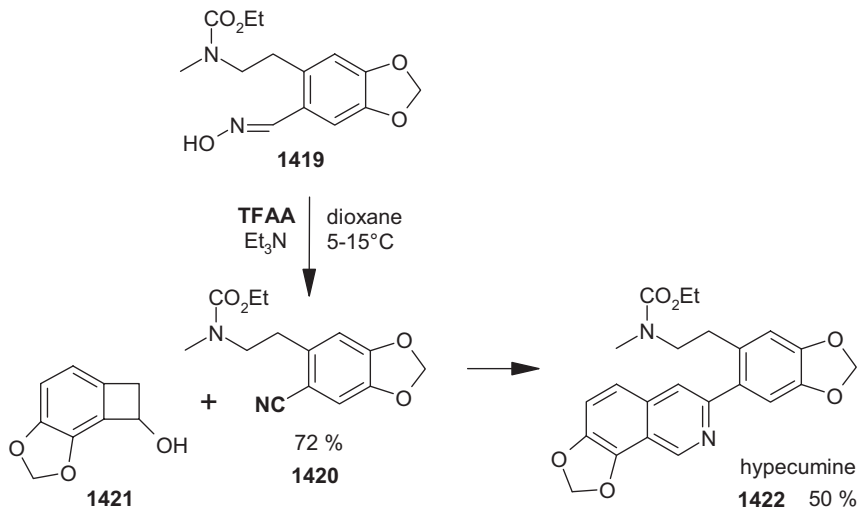
A route to bis-annulated pyranosides has been developed involving intermediate cyanides derived from aldoximes by dehydration with **TFAA** [1081].

In the course of research into orally active *GPIIb/IIIa antagonists*, the syntheses and biological activities of masked amidines as *prodrugs* were evaluated. In the synthetic studies, a 5-cyano-oxadiazole derivative was prepared from its corresponding carbaldoxime by dehydration with **TFAA**/pyridine [1082].

Phosphorus pentoxide and soluble polyphosphates

A frequently applied method for converting primary carboxamides into cyanides is dehydration with **phosphorus pentoxide**. It can be performed in two ways, the first in solution, and the second without any solvent in a two-phase solid/liquid or even a solid/solid phase reaction. Often, the nitrile can be easily distilled off. An *Organic*

Synthesis procedure is given for the first case, the preparation of **chloroacetonitrile** in 62–70% yield [1083].

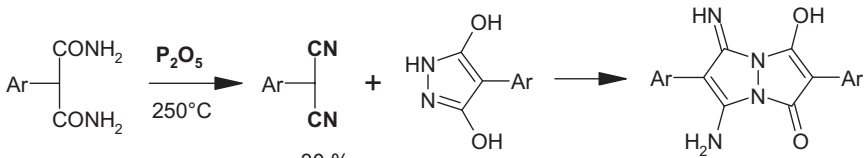


$$3\ ClCH_2CONH_2 + \mathbf{P_2O_5} \rightarrow 3\ ClCH_2\mathbf{CN} + 2\ H_3PO_4$$
1423 **1424**

Typical procedure. *Chloroacetonitrile* **1424** [1083]: In a 3-L round-bottomed, three-necked flask fitted with an efficient mechanical stirrer, a reflux condenser, and a thermometer were placed **phosphorus pentoxide** (170 g, 1.2 mol), chloroacetamide **1423** (187 g, 2 mol), and dry technical grade trimethylbenzene (800 mL). The mixture was gently refluxed with vigorous stirring for 1 h. It was then allowed to cool to about 100 °C with continuous stirring, and the reflux condenser was replaced with a distillation head fitted with a thermometer and a water-cooled condenser. The crude product and part of the solvent were distilled at atmospheric pressure. The yield of crude product boiling at 124–128 °C was 121–131 g (80–87%). In order to obtain a pure product, the crude chloroacetonitrile was mixed with **phosphorus pentoxide** (10 g) and redistilled through an efficient packed fractionating column. The yield of pure **chloroacetonitrile** distilling at 123–124 °C was 93–106 g (62–70%).

Similarly to the previous procedure, methyl 2-*exo*-cyano-bicyclo[6.1.0]non-4-ene-9-carboxylate was prepared in 80% yield [1084].

A variation on this preparative procedure, the second case mentioned above, is dehydration by **phosphorus pentoxide** under solvent-free conditions. An example of this is the synthesis of 2-ethyl-5-cyanomethyltetrazole, which is achieved in 61% yield [1085]. Also solvent-free is the preparation of the intermediate *p*-methoxyphenylmalonitrile **1426**, which is then condensed with **1427** to afford the corresponding pyrazolo[1,2-*a*]pyrazole **1428** [1086].

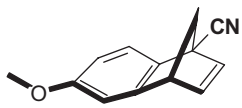


1425 30 % **1426** **1427** 40 % **1428**

Typical procedure. *p-Methoxyphenylmalonitrile* **1426** [1086]: This product was prepared by vacuum distillation (0.15 Torr) from a mixture of **phosphorus pentoxide** (20 g) and *p*-methoxyphenylmalonodiamide (10 g) at 250 °C. The resulting dinitrile **1426** was recrystallized from methanol/water; yield: 2.5 g (30%); mp 67 °C.

In modified methods, phosphorus pentoxide is rendered soluble by derivatizing it with a TMS group, resulting in polyphosphates. **Trimethylsilyl polyphosphate** (**TMS-PP**) has been employed to prepare 1-cyano-6-methoxy-benzonorbornadiene in 91% yield from the corresponding carboxamide [1087].

Typical procedure. *1-Cyano-6-methoxy-benzonorbornadiene* **1429** [1087]: A solution of **TMS-PP** was first prepared by refluxing **phosphorus pentoxide** (2 g) and hexamethyldisiloxane (5 mL) in dichloromethane (10 mL) for 1 h. The cooled solution was filtered to remove undissolved materials. This **TMS-PP** solution (5.5 mL) was then mixed with the appropriate carboxamide (134 mg, 0.332 mmol) in dichloromethane (2 mL) and the resulting mixture was heated at reflux temperature for 6 h. It was then cooled to room temperature, and diluted with dichloromethane and water. The organic phase was separated, and the aqueous layer was extracted with dichloromethane. The combined dichloromethane solutions were dried and concentrated to leave a colorless oil. Pure **1429** was obtained by spinning-plate chromatography on silica gel (eluting with 2.5% ethyl acetate in petroleum ether); 112 mg (91%).



1429

Another modification involving the attachment of a TMS group to **phosphorus pentoxide** is its reaction with TMS-sulfonate to give **trimethylsilyl sulfonyl polyphosphate** (**TMS-PP-OTs**). Several aryl, benzylic, and alkyl carboxamides have been dehydrated to their **nitriles**, either without (*Method A*) or with (*Method B*) the addition of triethylamine, in yields of 51–82% (*Method A*) or 66–96% (*Method B*) [1088].

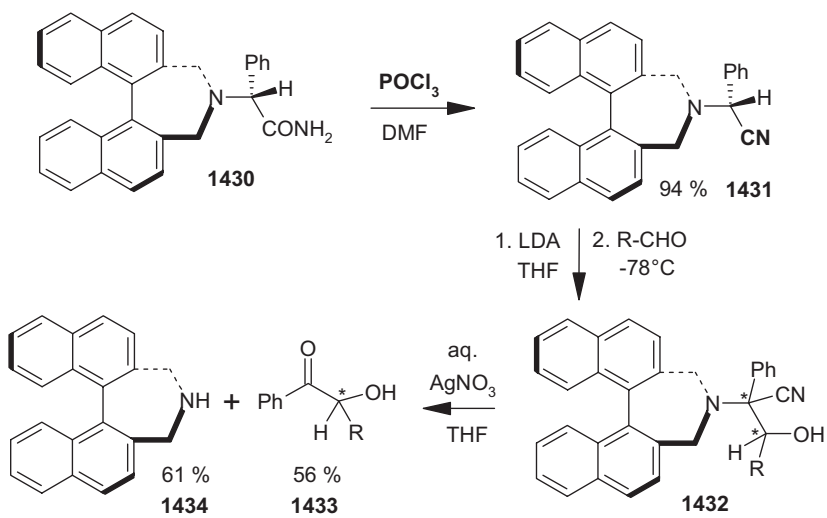
General procedure. *Cyanides with* **TMS-PP-OTs** [1088]. **Phosphorus pentoxide** (0.0075 mol) was treated at 20 °C with TMS-OTs (0.015 mol) and the stirred mixture was heated at 50 °C for 30 min.

Method A: The viscous liquid complex **TMS-PP-OTs** thus obtained was cooled to 30 °C, treated with the amide (0.01 mol), and the resulting mixture was stirred and heated at 70–75 °C for 3 h.

Method B: The **TMS-PP-OTs** was cooled in ice, treated first with triethylamine (0.015 mol) and then with the amide (0.01 mol), and then heated at 50 °C for 3 h. The reaction mixture was subsequently cooled in an ice bath and quenched with cold saturated aq. $NaHCO_3$ solution with stirring. The product was extracted into benzene or diethyl ether and the extract was passed through a bed of basic alumina to remove highly acidic P residues that would otherwise have contaminated the product even after distillation. After removal of the solvent, the **cyanides** were purified by kugelrohr distillation.

Phosphorus oxychloride

Another widely used dehydration agent for the synthesis of cyanides from amides is **phosphoryl chloride**. For example, the amide **1430** is dehydrated with this reagent to give *amino nitrile* **1431**, which is an auxiliary with a disymmetric tertiary amino group employed in an asymmetric nucleophilic acylation reaction with an aldehyde according to the following reaction sequence to afford chiral acetophenone **1433** [1089].



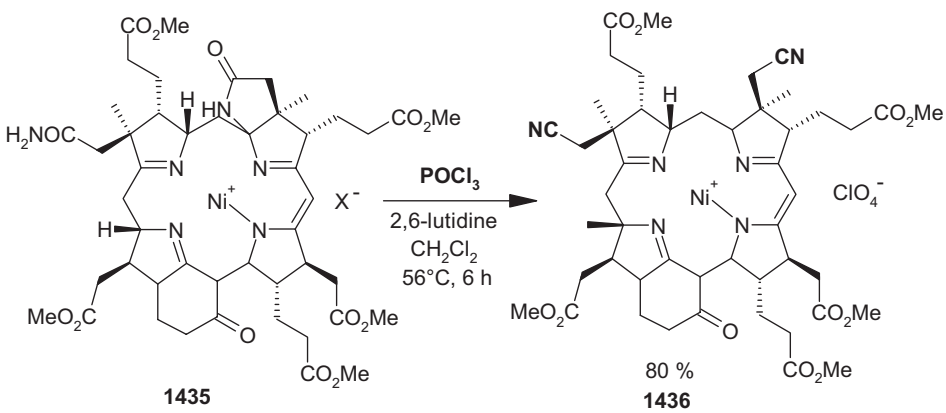
Typical procedure. *(S,R)-α-(2,7-Dihydrodinaphtho[2,1-c:1′,2′-e]azepinyl)-α-phenylacetonitrile* **1431** [1089]: To (*S*,*R*)-α-amino amide **1430** (4.44 g, 10.4 mmol) in DMF (100 mL) at 0 °C, a large excess of **$POCl_3$** (10 mL) was added dropwise over a period of 1 h. The resulting solution was magnetically stirred, first at 0 °C and then at room temperature overnight. It was subsequently poured into water (2 L) and the resulting precipitate was collected by filtration, washed with water, air-dried, dissolved in dichloromethane (100 mL), and chromatographed on a column of SiO_2 (silica gel 60) made up with dichloromethane. Elution with dichloromethane furnished pure

(*S*,*R*)-**1431** as a white crystalline solid: 4 g (94%); mp 215–218 °C (not recrystallized); $[\alpha]^{23}$ (λ) ($c = 1.2$, $CHCl_3$): +382.0 (589), +399.0 (578), +453.1 (546), +731.1 (436). The (*R*,*R*)-isomer was prepared in the same manner.

Tripeptides with a C-terminal nitrile moiety, which are employed in the inhibition of proteinases, have also been synthesized by the **phosphoryl chloride** method [1090].

Typical procedure. *N-Fmoc-D-Phe–L-Pro–D,L-1-amino-4-guanidinovaleronitrile hydrochloride* [1090]: Fmoc–D-Phe–L-Pro–L-Arg–OH (3.38 g, 5 mmol) and imidazole (680 mg, 10 mmol) were dissolved in pyridine (50 mL) and the solution was cooled to −20 °C. **Phosphoryl chloride** (1.92 mL, 7.5 mmol) was then added very slowly with vigorous stirring. The temperature was kept at −20 °C during this process and was subsequently allowed to rise to 20 °C over 1 h. The mixture was rotary evaporated and the residue was redissolved in chloroform (150 mL). This solution was washed with saturated sodium hydrogen carbonate solution (3 × 50 mL) and saturated brine (50 mL) and then dried over sodium sulfate. The chloroform solution was concentrated to a volume of about 30 mL and then poured into a mixture of diethyl ether and ethyl acetate (250 mL, 2:1, *v*/*v*). The precipitated product was collected, washed with diethyl ether, and dried in vacuo to give 2.93 g (87%); mp 105 °C (dec.); $R_f = 0.59$; $[\alpha]_D^{20} = -54.8$ ($c = 1$, methanol).

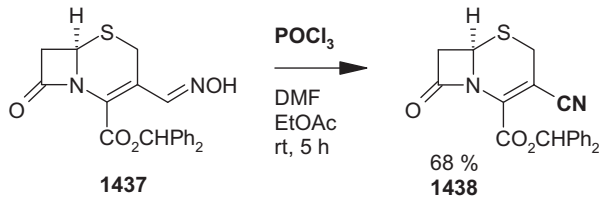
In a natural compound of rather high complexity, namely *factor F430* **1435** from methanogenic bacteria, the amide and lactam functions are converted into the *dinitrile* **1436** by dehydration with **phosphoryl chloride** [1091]. In a detailed evaluation of the experimental procedure, Eschenmoser and Pfaltz found that 2,6-lutidine works much better than pyridine as an auxiliary base (84% yield of dinitrile instead of 54%).



In a porphyrin synthesis, 2-cyanopyrrole derivatives were prepared by dehydration of the corresponding pyrrole-2-carbaldoxime with **phosphoryl chloride** [1092].

A 3-cyano-3-cephem derivative showing potent β-lactamase inhibitory activity has been prepared from its carbaldoxime by careful dehydration with **phosphoryl chlo-**

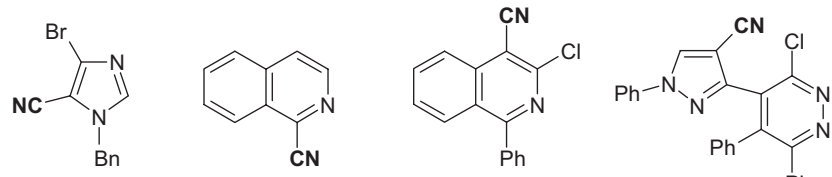
ride/DMF. Thus, dehydration of **1437** at room temperature for 5 h gave diphenylmethyl 3-cyano-3-cephem-4-carboxylate **1438** in 68% yield [1093].



1437 **1438**

Typical procedure. *Diphenylmethyl 3-cyano-3-cephem-4-carboxylate* **1438** [1093]: To a solution of DMF (0.065 mL, 0.84 mmol) in ethyl acetate (0.4 mL), **phosphoryl chloride** (0.088 mL, 0.84 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 30 min, and then a solution of **1437** (220 mg, 0.56 mmol) in ethyl acetate (4 mL) was added. The resulting mixture was stirred at room temperature for 5 h, poured into ice-cold 3% aqueous sodium hydrogen carbonate solution (20 mL), and extracted with ethyl acetate (30 mL). The organic layer was washed with water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was triturated with diethyl ether to give **1438** as a yellow, amorphous powder (143 mg, 68%); IR (Nujol): $\nu_{max} = 2220, 1785, 1730\ cm^{-1}$.

Syntheses of 1-benzyl-4-bromo-5-cyanoimidazole **1439** [1094], 1-cyanoisoquinoline **1440** [1095], 3-chloro-4-cyano-1-phenylisoquinoline **1441** [1096], and 4-[3-(4-cyano-1-phenyl)pyrazolo]-3-chloro-5,6-diphenylpyridazine **1442** [1097] have been accomplished by dehydrating their carbaldoximes with **phosphoryl chloride**.



83 % **1439** 95 % **1440** 96 % **1441** **1442**

Typical procedure. *1-Benzyl-4-bromo-5-cyanoimidazole* **1439** [1094]: A mixture of the requisite oxime (5.0 g, 17.86 mmol) and **phosphoryl chloride** (20 mL, excess) was heated under reflux for 30 min, then cooled and poured into ice/water. The precipitate was collected by filtration and recrystallized from ethyl acetate/light petroleum to give 1-benzyl-3-bromo-2-cyanoimidazole **1439** (3.9 g, 83%); mp 75–77 °C.

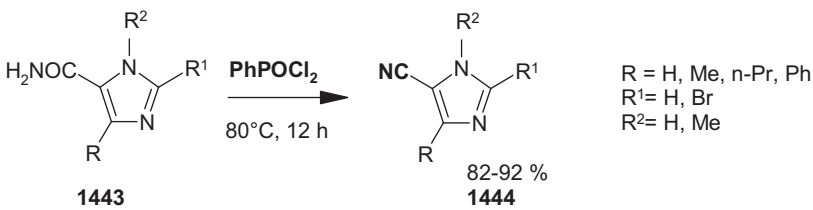
Typical procedure. *1-Cyanoisoquinoline* **1440** [1095]: **Phosphoryl chloride** (0.54 g, 3.5 mmol) in chloroform (5 mL) was added dropwise to a solution of the requisite carbaldoxime (0.2 g, 1.2 mmol) in chloroform (10 mL) under ice-cooling. The mixture was heated under reflux for 4 h, treated with iced water, and the resulting precipitate was filtered off. The filtrate was basified with 28% ammonia and then extracted with chloroform to give 1-cyanoisoquinoline **1440**; yield 0.17 g (95%).

Typical procedure. *3-Chloro-4-cyano-1-phenylisoquinoline* **1441** [1096]: To a solution of the appropriate carbaldoxime (7.6 g, 0.027 mol) in pyridine (100 mL), **phosphoryl chloride** (10.3 g, 0.067 mmol) was added dropwise at 0 °C. After 14 h at room temperature, a precipitate had formed. The reaction mixture was hydrolyzed by the addition of water and the precipitate was collected by filtration. Yield 6.9 g (96%); mp 191–193 °C (from ethanol).

For information on the scope and limitations of the **phosphoryl chloride method**, particularly with regard to the formation of insoluble precipitates of polyphosphorous acid, see Chapter 6. A modified method has been developed.

Dichlorophenylphosphine oxide (**$PhPOCl_2$**) has been applied to dehydrate variously substituted 4-imidazole carboxamides **1443** to the corresponding 4-cyanoimidazoles **1444** in yields of 82–92% [1098].

General procedure. *4-Cyanoimidazoles* **1444** [1098]: A mixture of ethyl 4-imidazolecarboxylate (33 g) and ammonium hydroxide (250 mL) was heated to 100 °C in a sealed glass vessel for 1–7 days. The mixture was then cooled and the solid 4-imidazolecarboxamide **1443** was recovered by filtration in near quantitative yield and air dried. *Dehydration* was carried out by heating a solution of 4-imidazolecarboxamide **1443** (5 g) in **$PhPOCl_2$** (25 mL) at 80 °C for 12 h. The cooled reaction mixture was then poured over ice (200 mL) and adjusted to pH 11 with 50% aqueous sodium hydroxide. The 4-cyanoimidazole **1444** was isolated by extraction with ethyl acetate and concentration of the extracts in vacuo.



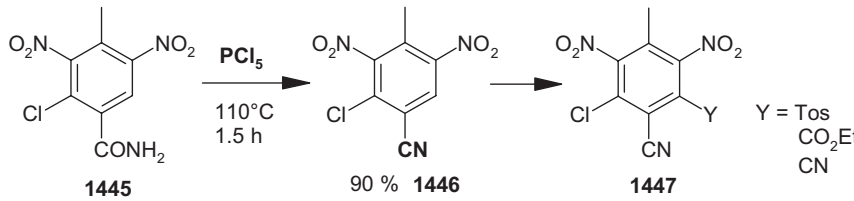
1443 **1444**

Phosphorus pentachloride

Phosphorus pentachloride is used as a dehydration agent in preparing the key intermediate 2-chloro-3,5-dinitro-4-methylbenzonitrile **1446** from its carboxamide **1445** in 90% yield. **1446** is employed in the synthesis of hexasubstituted nitrobenzene derivatives **1447** [1099].

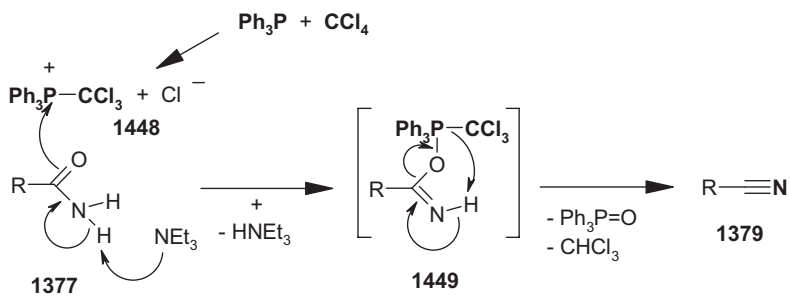
Typical procedure. *2-Chloro-3,5-dinitro-4-methylbenzonitrile* **1446** [1099]: A mixture of 2-chloro-3,5-dinitro-4-methylbenzamide **1445** (8.56 g, 0.033 mol) and **PCl_5** (13.76 g, 0.066 mol) was heated on an oil bath at 110 °C to a complete melt (1.5 h). After cooling, the reaction mixture was dissolved in dichloromethane (200 mL) and the resulting solution was slowly poured into iced water (600 mL). The organic layer was separated, washed with water, and dried with anhydrous $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (hexane/dichloromethane, 1:1). Recrystallization from dichloromethane gave 2-chloro-3,5-

dinitro-4-methylbenzonitrile **1446** as pale-yellow crystals (7.17 g, 90%); mp 133–134 °C.



Triphenylphosphine/haloalkanes

A versatile dehydration method has been presented by Appel in a review [1100]. The dehydration reagent is the two-component system **triphenylphosphine**/**tetrachloromethane**, and a key role is played by *(trichloromethyl)phosphonium chloride* **1448**. Due to its oxophilicity, **1448** forms the intermediate **1449**, which stabilizes by forming the small, low-energy molecules triphenylphosphine oxide, chloroform, and the desired cyanide **1379**.



Various carboxamides (and thiocarboxamides) can be dehydrated by this method under mild conditions affording cyanides in yields of 71–92% [1101].

General procedure. *Various cyanides* **1379** [1101]: Equimolar amounts (0.1 mol) of **tetrachloromethane**, triethylamine, carboxamide (thiocarboxamide) **1377**, and **triphenylphosphine** (in 25% excess) are warmed in absolute chloroform or 1,2-dichloroethane (100 mL) at 60 °C for 2.5 h or in absolute dichloromethane (100 mL) at 40 °C for 6 h. The reaction proceeds to completion, despite the fact that carboxamides **1377** are only partially dissolved at the beginning.

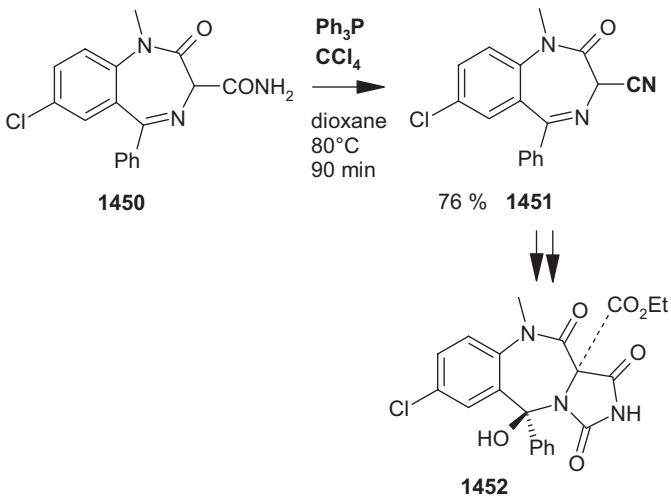
Work-up*; hydrogen cyanide (from 0.02 mol formamide)*: Solvent 1,2-dichloroethane (20 mL). To determine the yield of hydrogen cyanide, the reaction mixture was heated to reflux. A stream of nitrogen was passed through the flask to transfer the hydrogen cyanide into a solution of $AgNO_3$ in water/methanol; 1.36 g of AgCN was deposited (50.5%).

Work-up*; acetonitrile*: Solvent chloroform. The solvent was distilled off, chloroform was added to the residue, and this was distilled off again. The combined distillates were fractionated affording 3.8 g (92%) of acetonitrile.

***Work-up**; benzonitrile*: Solvent chloroform. The solvent was distilled off and the residue was extracted with petroleum ether (60–95 °C) in a Soxhlet apparatus for 16 h. After cooling, the crystallized triphenylphosphine oxide was filtered off and the filtrate was fractionated to give 9.3 g (90%) of benzonitrile (bp 70–72 °C/10 mmHg).

***Work-up**; 4-nitrobenzonitrile*: Solvent chloroform. The solvent was evaporated and the residue was steam-distilled; 10.5 g (71%) of 4-nitrobenzonitrile was collected; mp 148 °C.

This nitrile synthesis can be applied equally well to aliphatic and aromatic carboxamides. It is also applicable to the production of 7-chloro-3-cyano-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine **1451**, which is not accessible using the usual strongly acidic dehydrating agents [1100]. **1451** is produced as an intermediate in a synthesis of imidazo[5,1-*c*]benzodiazepine-1,4 **1452** by dehydration of the carbaldoxime **1450** with **triphenylphosphine**/**tetrachloromethane** in 76% yield [1102].

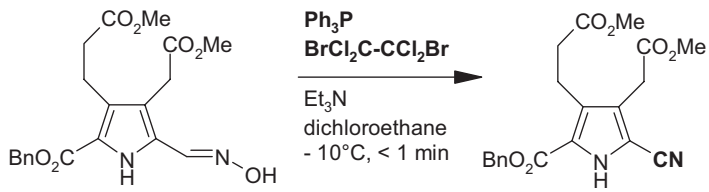


***Typical procedure**. 7-Chloro-3-cyano-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepine* **1451** [1102]: A mixture of **triphenylphosphine** (104.0 g, 0.4 mol), **tetrachloromethane** (350 mL), dioxane (400 mL), and the carboxamide **1450** (65.5 g, 0.2 mol) was stirred at 80 °C for 90 min, in the course of which the amide dissolved and the solution became orange. The solvent was then evaporated in vacuo and the residue was redissolved in dichloromethane. The organic solution was washed with water and then concentrated in vacuo. The resulting oil crystallized on trituration with a little diethyl ether. The crude product, which still contained some triphenylphosphine oxide, was recrystallized from ethanol to afford 47 g (76%) of pure product **1451**; mp 208–210 °C; IR: $\nu_{max} = 2266\ cm^{-1}$ (CN).

Systematic investigations have been performed to optimize the method by varying the haloalkane [1103, and refs. cited therein]. In particular, the reaction tem-

perature could be lowered significantly to −10 °C and the reaction time could be reduced *drastically* to less than 1 min [1103]. A 15% improvement in the yield from 67 to 82% could be achieved by using **1,2-dibromotetrachloroethane** instead of tetrachloromethane in the dehydration of carbaldoxime **1453** to the cyanide **1454** with **triphenylphosphine**.

Typical procedure. *5-Benzoxycarbonyl-2-cyano-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrole* **1454** [1103]: To a mixture of the oxime **1453** (402 mg, 1.0 mmol) and **triphenylphosphine** (524 mg, 2.0 mmol) in dry 1,2-dichloroethane (20 mL), a solution of **1,2-dibromotetrachloroethane** (652 mg, 2 mmol) and triethylamine (0.56 mL, 4.0 mmol) in dichloroethane (10 mL) was added at −10 °C. Removal of the precipitate by filtration and evaporation of the solvent under reduced pressure left an oily residue, which was passed through a short column of silica gel eluting with petroleum ether (bp 40–60 °C)/diethyl ether (1:2). Crystallization from ligroin afforded **1454**; yield: 316 mg (82%); mp 116 °C; IR (KBr): $\nu_{max} = 2215\ cm^{-1}$ (CN).



1453 82 % **1454**

Thionyl chloride

An often used dehydrating agent is **thionyl chloride**. It is very volatile, and thus any excess can easily be removed. However, its decomposition product is gaseous sulfur dioxide, which is severely disadvantageous owing to its ecological impact (see also Chapter 6). An *Organic Synthesis* procedure is given for the production of *2-ethylhexanonitrile* **1456** in yields of 86–94% [1104].

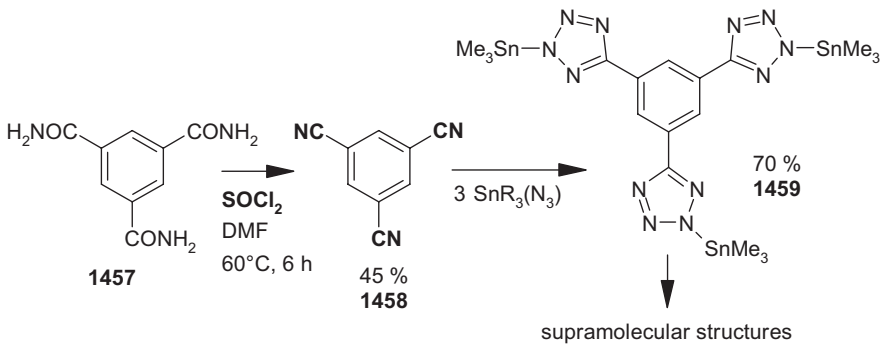
$$\underset{\textbf{1455}}{CH_3(CH_2)_3CH(C_2H_5)CONH_2} + \mathbf{SOCl_2} \rightarrow \underset{\textbf{1456}}{CH_3(CH_2)_3CH(C_2H_5)\mathbf{CN}} + SO_2 + 2\ HCl$$

Typical procedure. *2-Ethylhexanonitrile* **1456** [1104]: In a 1-L round-bottomed flask, fitted with an efficient reflux condenser, were placed 2-ethylhexaneamide **1455** (286 g, 2 mol), dry benzene (300 mL), and **thionyl chloride** (357 g, 218 mL, 3 mol). The flask was placed in a water bath, which was quickly heated to 75–80 °C and maintained at that temperature for 4.5 h. The reaction mixture was then transferred to a 1.5-L beaker and cooled in an ice bath. A mixture of crushed ice (100 g) and water (100 mL) was added to decompose the excess thionyl chloride. Cold 50% aq. potassium hydroxide solution was then added in small portions with stirring until the

mixture was alkaline to litmus. The basified mixture was then transferred to a separatory funnel, and the layers were separated. The aqueous portion was extracted with benzene (100 mL). The benzene solutions were combined and washed with 1% sodium carbonate solution (150 mL) and water (2 × 150 mL). The mixture was distilled from a modified Claisen flask, the bulk of the solvent being removed at atmospheric pressure. The yield of nitrile **1456** was 215–236 g (86–94%); bp 118–120 °C/100 mmHg.

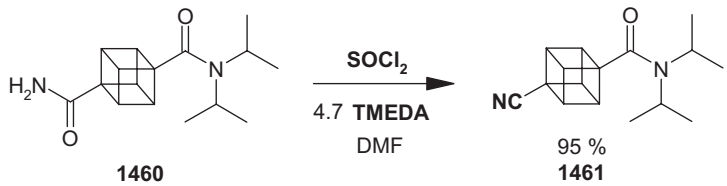
A key intermediate in the synthesis of tris(triorganostannyltetrazole)s **1459**, which are combined to generate *supramolecular structures*, is 1,3,5-tricyanobenzene **1458**. It is prepared by dehydrating the triamide **1457** with **thionyl chloride** in DMF, yielding 45% of **1458** [1105].

Typical procedure. *1,3,5-Tricyanobenzene* **1458** [1105]: To a stirred suspension of 1,3,5-tricarbamoylbenzene **1457** (4.6 g, 22.2 mmol) in DMF (35 mL), **thionyl chloride** (6 mL) was added over a period of 1 h, maintaining the temperature at 60 °C. Stirring at this temperature was maintained for 6 h, during which time complete dissolution occurred. The resulting solution was poured into dilute aq. HCl (100 mL) to decompose unreacted $SOCl_2$, giving a dense white precipitate. This solid was collected by filtration, washed with water until the washings were neutral to litmus, and dried at 120 °C for 14 h. Crystallization from ethanol and acetone yielded the product **1458** as colorless needles (1.50 g, 45%).



A similar procedure as above has been applied to the synthesis of 4-cyano-1-(*N*,*N*-diisopropylcarbamoyl)cubane in 95% yield from its amide by dehydration with **thionyl chloride** [1106]. It was found that treating the amide with thionyl chloride in DMF or under reflux conditions resulted in its decomposition. This could be avoided if TMEDA was added in 4.7-fold molar excess with respect to the amide. TMEDA seems to play a particular role; if triethylamine was used instead, substantial decomposition occurred.

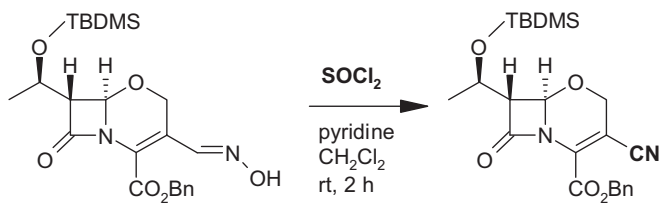
Pentagonal dodecahedranes bearing cyano groups have also been prepared by the **thionyl chloride** method in pyridine solution [1107, 1108].



1460 1461

Typical procedure. *Undecacyclo[9.9.0.0^{2,9}.0^{3,7}.0^{4,20}.0^{5,18}.0^{6,16}.0^{8,15}.0^{10,14}.0^{12,19}.0^{13,17}]-icosane-1,6-dicarbonitrile* [1107]: A solution of the requisite dicarboxamide (35 mg, 0.1 mmol) and **$SOCl_2$** (1 mL) in dry pyridine (3 mL) was stirred at room temperature for 24 h (total conversion; TLC). After sequential treatment with dilute aq. hydrochloric acid and aq. $NaHCO_3$, the organic phase was dried ($MgSO_4$), filtered through a pad of silica gel (CH_2Cl_2, $R_f = 0.38$), and concentrated to give 21 mg (69%) of crystals; mp 259 °C.

As part of a quest to develop novel concepts regarding the structure–activity relationships of *β*-lactam antibiotics, investigations were carried out in which the 7*α*-position of the oxacephem nucleus was derivatized with a 1-hydroxyethyl group. Thus, benzyl 7*α*-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-3-cyano-1-oxa-3-cephem-4-carboxylate **1463** was prepared in quantitative yield by dehydration of the corresponding carbaldoxime **1462** with **thionyl chloride** in the presence of pyridine at room temperature [1109].

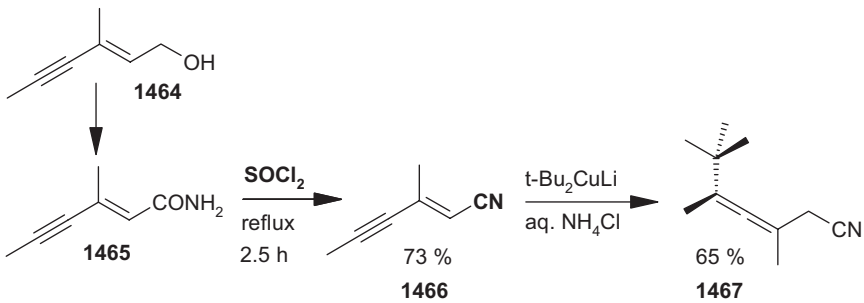


1462 1463

Typical procedure. *Benzyl 7α-[(1R)-1-tert-butyldimethylsilyloxyethyl]-3-cyano-1-oxa-3-cephem-4-carboxylate* **1463** [1109]: To a solution of the oxime **1462** (290 mg) in dichloromethane (3 mL) were added pyridine (373 mg) and **thionyl chloride** (187 mg), and the resulting mixture was stirred for 2 h at room temperature. It was then poured into cold 1 N aqueous HCl solution, and extracted with dichloromethane. The combined organic layers were washed with cold 5% aqueous $NaHCO_3$ solution and brine, dried, and concentrated. The residue was purified by column chromatography on silica gel to give nitrile **1463** (290 mg, 100%); IR: $\nu_{max} = 2205, 1792, 1722\ cm^{-1}$.

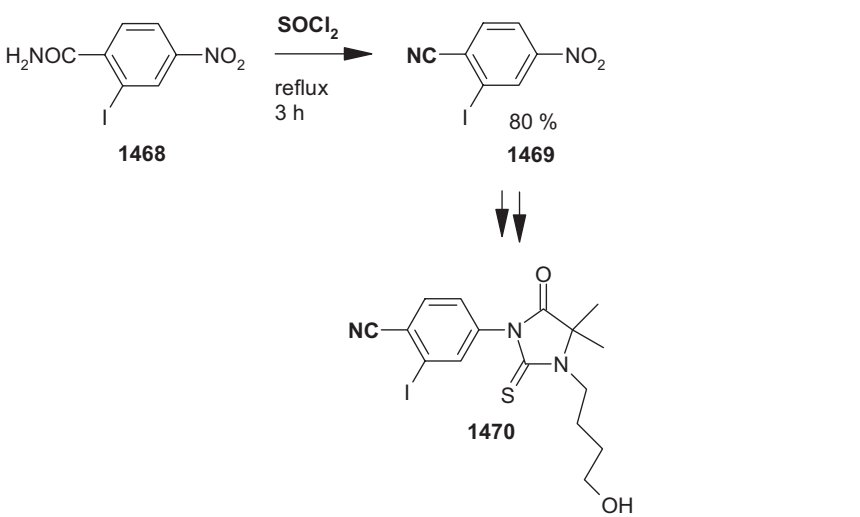
Further products prepared by the **thionyl chloride** method in solution are *Dolastatin*, a thiazole amino acid component (gln)Thz (70% yield) [1110], 4-phenyl-3-furoxanecarbonitrile (55% yield) [1111], ethyl 5-cyano-1-(1,1-dimethylethyl)-1*H*-pyrazolo-4-carboxylate (61% yield) [1112], ethyl 2-anilino-4-chloro-5-cyanothiophene-3-carboxylate (77% yield) [1113], and 4-cyanoisoxazole from its oxime tosylate (47% yield) [1114].

Solvent-free syntheses of cyanides using **thionyl chloride** are advantageous because of the simple work-up of merely evaporating the excess thionyl chloride. This method has been used to prepare acceptor-substituted enynes, which are employed in 1,6-additions of organocuprates to produce *allenes* **1467**. (*E*)-3-Methyl-2-hexen-4-ynenitrile **1466** was synthesized in 73% yield by dehydrating the carboxamide **1465** [1115].



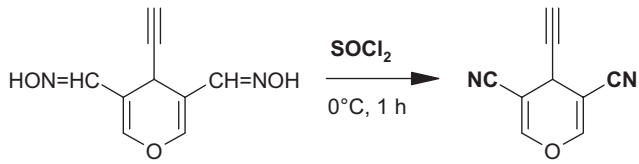
Typical procedure. *(E)-3-Methyl-2-hexen-4-ynenitrile* **1466** [1115]: To the amide **1465** (0.99 g, 8.0 mmol) was added **thionyl chloride** (4.76 g, 40.0 mmol) and the mixture was heated at reflux for 2.5 h with protection from moisture. A brown oil formed. Excess thionyl chloride was removed in vacuo and the crude product was purified by kugelrohr distillation to give 610 mg (73%) of the nitrile **1466** as a colorless liquid; bp 90 °C/12 mbar.

A high-affinity non-steroidal androgen receptor ligand **1470** has been designed, of which a fragment, 2-iodo-4-nitrobenzonitrile, has been synthesized from its carboxamide **1468** by dehydration with **thionyl chloride** in 80% yield [1116].



Typical procedure. *2-Iodo-4-nitrobenzonitrile* **1469** [1116]: A mixture of the carboxamide **1468** (5.5 g, 18.8 mmol) and **thionyl chloride** (35 mL) was refluxed for 3 h under argon and then concentrated under reduced pressure. The residue was purified by flash chromatography (20% EtOAc in hexane) to give 4.12 g (80%) of 2-iodo-4-nitrobenzonitrile **1469** as cream-colored crystals; mp 154–155.5 °C (EtOAc/hexane, 1:4).

4-Ethynyl-4*H*-pyran-3,5-dicarbonitrile **1472** has been prepared in 95% yield from the dicarbaldoxime **1471** by dehydration with **thionyl chloride** [1117].



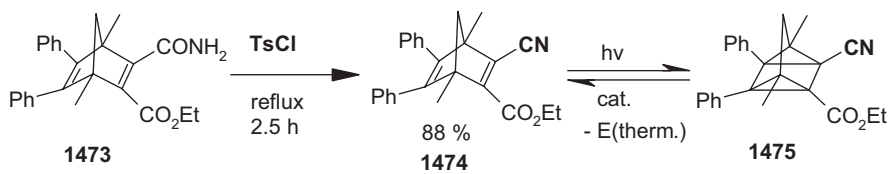
1471 95 % **1472**

Typical procedure. *4-Ethynyl-4H-pyran-3,5-dicarbonitrile* **1472** [1117]: Dicarbaldoxime **1471** (0.38 g, 2 mmol) was reacted under stirring with **thionyl chloride** (excess) at 0 °C for 1 h. After evaporating the excess thionyl chloride in vacuo, the residue was sublimed at 80 °C/1 Torr to give 0.30 g (95%) of **1472** as colorless needles; mp 91 °C.

The solvent-free **thionyl chloride** method has also been applied in the synthesis of *o*-azidobenzonitriles, which are employed in photoinduced ring-expansions to form 3-cyano- and 7-cyano-3*H*-azepin-2(1*H*)-ones [1118].

p-Toluenesulfonyl chloride (tosyl chloride)

***p*-Tosyl chloride** is used as a dehydration agent in preparing a cyano group from an amide to form the dienophile in a Diels–Alder reaction forming cyano norbornadienes, which can be reversibly converted into *quadrocyclanes*, affording a cycle in solar-energy storage [1119].

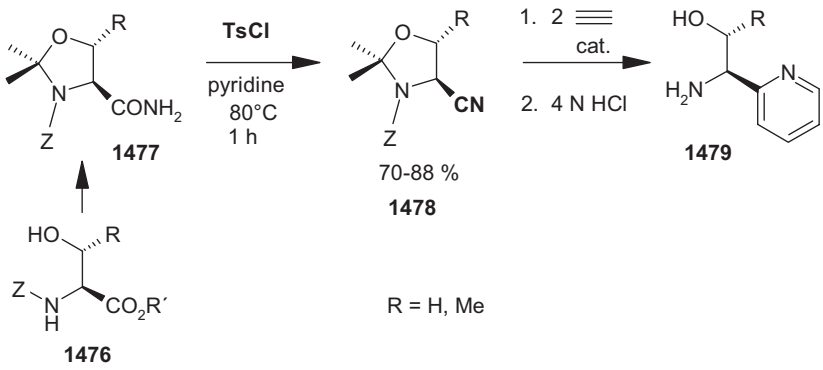


1473 88 % **1474** **1475**

Typical procedure. *1,4-Dimethyl-5,6-diphenyl-3-propionylbicyclo[2.2.1]hepta-2,5-diene-2-carbonitrile* **1474** [1119]: A solution of the amide **1473** (104.8 mg, 0.28 mmol) and ***p*-tosyl chloride** (119.8 mg, 0.63 mmol) in absolute pyridine (2 mL) was refluxed for 2.5 h. The mixture was then poured onto ice, acidified with 10% aq. HCl, and extracted with diethyl ether. The combined extracts were washed with 10% HCl and brine, dried, and concentrated to dryness. Chromatography on silica gel eluting

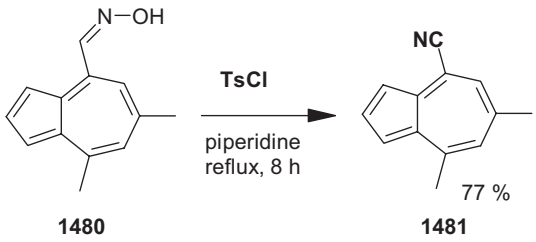
with hexane/ethyl acetate (10:1) yielded the nitrile **1474** (87.8 mg, 88%); mp 115 °C (from hexane).

According to the ***p*-tosyl chloride** method, chiral intermediates bearing cyano groups **1478** (R = H, Me) are prepared from amino acid starting materials **1476**. The intermediates **1478** can then be transformed to chiral 2-amino-2-(2′-pyridyl)-1-alkanols **1479** [1120] and *trans*-5-oxohexahydropyrrolo[3,2-*b*]pyrroles [1121], respectively.



General procedure. *(4R)-N-Benzyloxycarbonyl-4-cyano-2,2-dimethyl-1,3-oxazolidine and (4R,5R)-N-Benzyloxycarbonyl-4-cyano-2,2-dimethyl-5-methyl-1,3-oxazolidine* **1478** [1120]: A solution of the amide **1477** (36 mmol), ***p*-tosyl chloride** (10.29 g, 54 mmol), and pyridine (70 mL) was purged with Ar and stirred at 80 °C for 1 h. The crude mixture was then concentrated under reduced pressure and diluted with EtOAc (200 mL). The organic phase was washed with 2 N HCl (3 × 50 mL), water (3 × 50 mL), and saturated $NaHCO_3$ solution (3 × 50 mL), dried (Na_2SO_4), concentrated, and purified by flash chromatography (dichloromethane/hexane, 1:1); yield 70–88% of **1478**.

6,8-Dimethylazulene-4-carbonitrile **1481** has been prepared from the corresponding carbaldoxime **1480** by dehydration with ***p*-tosyl chloride** in 77% yield [1122].



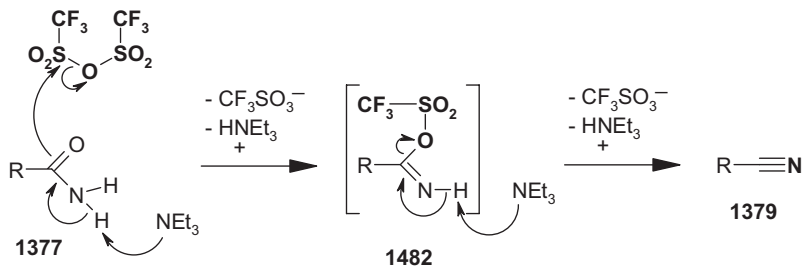
Typical procedure. *6,8-Dimethylazulene-4-carbonitrile* **1481** [1122]: A mixture of **1480** (996 mg, 5.0 mmol) and ***p*-tosyl chloride** (955 mg, 5.0 mmol) in dry piperidine (50 mL) was heated under reflux for 8 h. After evaporating the piperidine in vacuo,

the crude product was recrystallized from diethyl ether/hexane (1:1) to afford 700 mg (77%) of **1481** as dark-green crystals; mp 104 °C.

A key intermediate in a vitamin B_{12} synthesis, methyl (*S*)-4-cyano-5,5-dimethyl-6-heptynoate [1123], and a 6-cyano-1*H*-pyrano[2,3-c]pyrazol-4-one derivative [1124] have both been prepared from their carbaldoximes by dehydration with ***p*-tosyl chloride** in yields of 88% and 91%, respectively.

Trifluoromethanesulfonic anhydride (triflic anhydride, Tf_2O)

Trifluoromethanesulfonic anhydride (**triflic anhydride**) has been used as a dehydration reagent for the preparation of cyanides from primary amides. This has been developed into a preparative method for various types of structures, giving high yields of 84–95% in short reaction times (10–25 min) at low temperatures (<5 °C) [1125]. The mild conditions and fast reaction are attributable to the facile fragmentation of the intermediate **1482**, which stems from the fact that the trifluoromethanesulfonate anion is an extremely good leaving group.

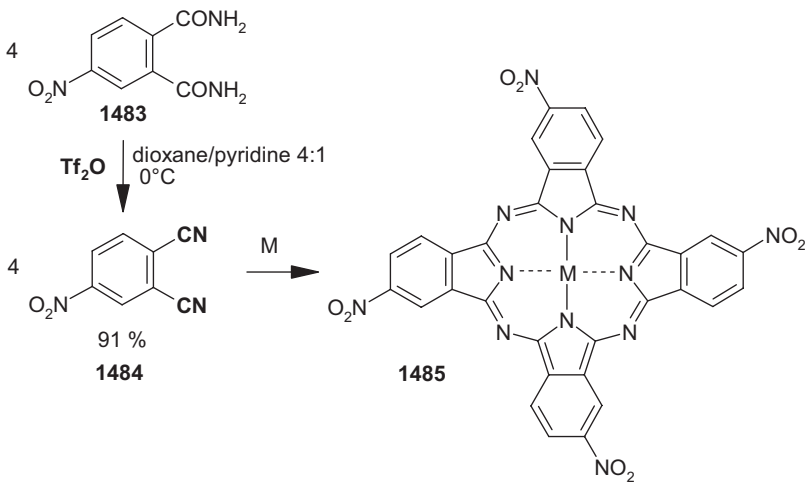


General procedure. *Nitriles* **1379** *from carboxamides* **1377** [1125]: **Triflic anhydride** (310 mg, 1.1 mmol) was added dropwise to a stirred, ice-cooled solution (or suspension) of the amide **1377** (1.0 mmol) in anhydrous dichloromethane (10 mL), and anhydrous triethylamine (202 mg, 2.0 mmol) at such a rate that the temperature was kept below 5 °C. The mixture was then allowed to warm to room temperature for the specified time (10–25 min), quenched with water (5 mL), and extracted with dichloromethane (2 × 15 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and the solvent was removed in vacuo to afford the crude product, which was purified by column chromatography on silica gel. Pure nitriles **1379** were obtained in yields of 84–95%.

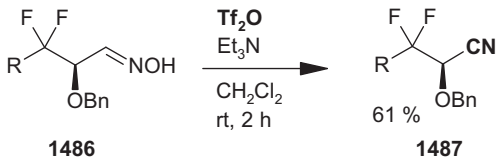
In the design of complex phthalocyanine structures with specific properties, substituted phthalocyanines play an important role. 4-Nitrophthalodinitrile **1484**, a key starting material in the synthesis of tetranitrophthalocyanine **1485**, is produced from 4-nitrophthalamide **1483** by dehydration with **triflic anhydride** in 91% yield [1126].

Typical procedure. *4-Nitrophthalodinitrile* **1484** [1126]: Under an argon atmosphere, 4-nitrophthalamide **1483** (12.27 g, 58.71 mmol) was suspended in dioxane/pyridine (4:1; 125 mL). The suspension was cooled in an ice-bath and **triflic anhydride** (20.6 mL) was added dropwise. When the addition was complete, the ice-bath was re-

moved and the reaction mixture was diluted to 2.5 times its original volume with water. The product was then extracted with EtOAc (4 × 75 mL). The combined organic phases were washed sequentially with water, 20% aq. HCl, water, and saturated brine. After drying over $MgSO_4$ and evaporation of the solvent, 4-nitrophthalodinitrile **1484** (9.26 g, 53.33 mmol, 91%) was obtained as a creamy white solid.



For the construction of difluoromethylene products (the difluoromethylene residue has been advantageously employed for the isosteric and isopolar replacement of methylene units), a useful building block is (*R*)-2-benzyloxy-3,3-difluoro-3-phenylpropionitrile **1487**, which has been prepared enantiomerically pure from its carbaldoxime **1486** by dehydration with **triflic anhydride** in 61% yield [1127].



Typical procedure. *(R)-2-Benzyloxy-3,3-difluoro-3-phenylpropionitrile* **1487** (R = Ph) [1127]: A solution of **triflic anhydride** (2.08 mL, 12.4 mmol) in dichloromethane (6.0 mL, freshly distilled from phosphoric anhydride) was added dropwise at −78 °C to a stirred solution of (*R*)-**1486** (3.61 g, 12.4 mmol) and triethylamine (4.28 mL, 37.20 mmol) in the same solvent (12.0 mL). After 2 h at room temperature, the mixture was washed with water and brine; the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was flash chromatographed, eluting with *n*-hexane/diethyl ether (4:1), to afford the nitrile (*R*)-**1487** in pure form (2.07 g, 61% yield); $[\alpha]^{20}_D = -93$ ($c = 1.00$, $CHCl_3$).

Chlorosulfonyl isocyanate

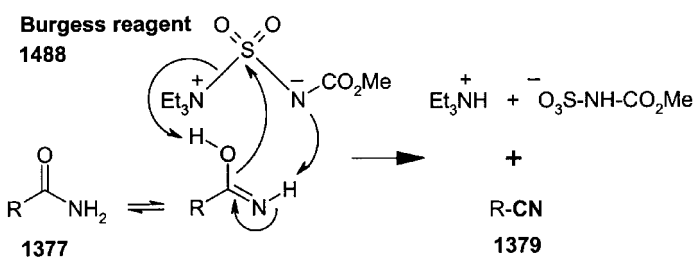
Chlorosulfonyl isocyanate, **Cl–SO_2–N=C=O**, is an effective dehydrating agent for the preparation of various aryl- and alkyl-nitriles from the corresponding amides and aldoximes in yields of 74–87% and 75–86%, respectively [1128].

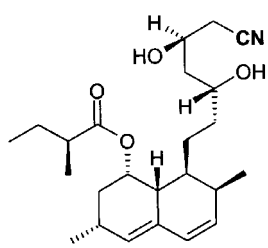
General procedure. *Nitriles from aldoximes* [1128]: To a magnetically stirred solution of the aldoxime (10 mmol) and dry triethylamine (20 mmol) in dry dichloromethane (10 mL), a solution of **chlorosulfonyl isocyanate** (15 mmol) in dichloromethane (10 mL) is added at 0 °C. The reaction mixture is stirred for 8 h at room temperature and then poured into water (caution!). The dichloromethane layer is separated and the aqueous layer is extracted with dichloromethane (3 × 25 mL). The organic layers are combined, washed with water, and dried over anhydrous sodium sulfate. Evaporation of the solvent gives the nitriles, which are purified by distillation or recrystallization.

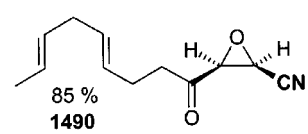
General procedure. *Nitriles from amides* [1128]: The procedure used for the dehydration of amides is the same as that described above, except that the reaction mixture is refluxed for 1 h after stirring for 8 h at room temperature. It is then cooled and worked-up as described above.

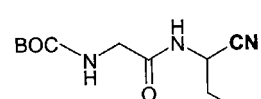
Methyl carboxysulfamoyl triethylammonium hydroxide inner salt (Burgess reagent)

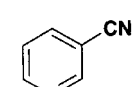
The **Burgess reagent 1488** can be viewed as an advancement of the **chlorosulfonyl isocyanate** method (see above). It is tailored to provide the required selectivity and reactivity for dehydration reactions. It can be widely applied as a dehydration agent for a great variety of structures, including those with several additional functions, to generate cyanides (e.g. **1489–1492**) from amides in good yields of 82–92% under mild conditions and with a rather simple work-up [1129]. Moreover, the **Burgess reagent** is chlorine-free.









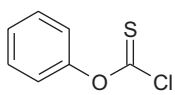


Typical procedure. *Mevinolin nitrile* **1489** [1129]: Mevinolin amide (125 mg, 0.30 mmol) was dissolved in anhydrous dichloromethane (1.5 mL; distilled from CaH_2) and the solution was stirred at 25 °C under argon. The **Burgess reagent** was then added in five 50 mg portions (1.05 mmol) over a period of 2 h. Stirring was continued for an additional 15 min, and then the mixture was applied directly to a column of silica gel. Flash chromatography (ethyl acetate/hexane, 1:1) gave 99 mg (82%) of mevinolin nitrile **1489** as a white crystalline solid.

Phenyl chlorothionoformate

A rather new method for the preparation of aromatic and aliphatic nitriles from amides on various structures, under mild conditions and with a simple work-up, was published in 1999. The reagent is **phenyl chlorothionoformate**, the reactions are performed at room temperature, reaction times are 5–9 h, and yields are high (81–95%) [1130].

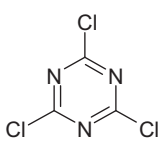
General procedure. *Nitriles from carboxamides (or thiocarboxamides)* [1130]: **Phenyl chlorothionoformate** (1.1 mmol) was added dropwise to a stirred, ice-cooled solution (or suspension) of the amide (1.0 mmol) in dry dichloromethane (5 mL) and anhydrous pyridine (2.0 mmol) at such a rate that the temperature was kept below 5 °C. The reaction mixture was then allowed to warm to room temperature for the requisite time and was then quenched with water (2 mL). The resulting mixture was extracted with dichloromethane (2×15 mL). The combined organic phases were washed with saturated brine, dried (Na_2SO_4), and the solvent was removed in vacuo to afford the crude product, which was purified by column chromatography on silica gel. Pure nitriles were obtained in yields of 80–95%.



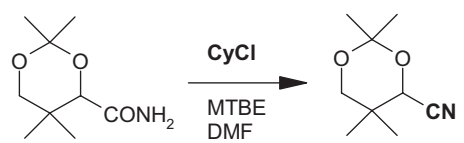
phenyl chlorothionoformate

Cyanuric chloride (CyCl)

Another new method for the conversion of primary amides to cyanides is dehydration with **cyanuric chloride** (**CyCl**), which is used for the preparation of enantiomerically pure cyanohydrins. (*S*)-2,2,5,5-Tetramethyl-1,3-dioxane-4-carbonitrile **1494** has been synthesized from the corresponding amide **1493** in 94% yield [1131]. In practice, it is found that only two of the potential three units of **CyCl** function as dehydration equivalents [1132].



CyCl

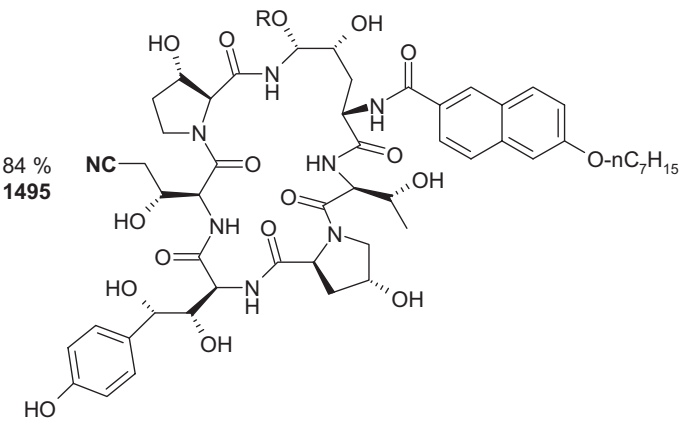


1493 **1494** 95 %

Typical procedure. *(S)-2,2,5,5-Tetramethyl-1,3-dioxane-4-carbonitrile* **1494** [1131]: A solution of **CyCl** (7.38 g, 40 mmol) in *tert*-butyl methyl ether (150 mL) was added to a solution of (*S*)-amide **1493** (15.15 g, 80 mmol) in DMF (50 mL). The mixture was stirred at room temperature for 1 h, in the course of which the solution turned into a yellow suspension. The mixture was neutralized with 28% aq. NaOH, and the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 20 mL). The combined organic phases were washed with distilled water, dried (Na_2SO_4), and filtered. The solvent was removed on a rotary evaporator to give **1494** as a colorless liquid; yield: 12.73 g (94%); bp 148.9 °C/760 Torr; $[\alpha]^{20}_D = +1.80$.

This method has also been applied to the preparation of a rather complex intermediate bearing a cyanide moiety in the semisynthesis of the antifungal lipopeptide *echinocandin*. Dehydration of the corresponding amide with **CyCl** afforded the nitrile **1495** in 84 wt-% (92 a-%) yield [1133].

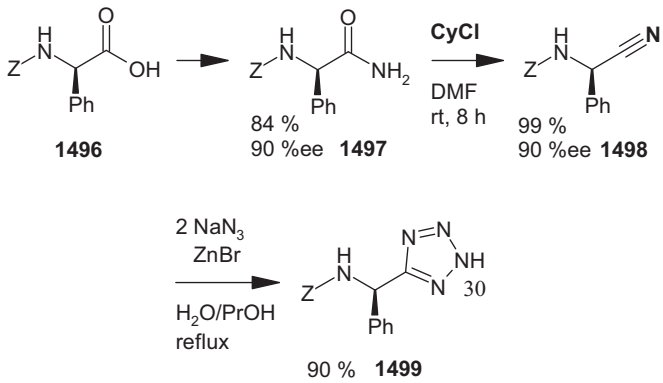
84 %
1495



Typical procedure. *Nitrile* **1495** [1133]: A solution of the amide (87 wt%, 5.97 g assay, 5.45 mmol) in dry DMF (250 mL) was chilled to −30 °C. The water content was measured by Karl-Fischer titration and was adjusted to ca. 1000 μg H_2O/mL (ca. 0.25 g, 13.6 mmol). **CyCl** (2.01 g, 10.9 mmol) was then added in one portion and the resulting pale-yellow solution was stirred at −30 °C. When 98% conversion had been reached (ca. 30 h; HPLC), water (250 mL) was added over a period of 10 min, and the mixture was allowed to warm to room temperature. The crude mixture (DMF/H_2O, 1:1; pH ∼ 2; 500 mL) was loaded onto a column of the C-18 resin IMPAQ RG 10150 (70 g), and the column was washed with water/methanol (9:1; 1.5 L). The nitrile **1495** was eluted with methanol (500 mL). This fraction was concentrated to dryness under reduced pressure to give 6.43 g of **1495** (92 A%, 84 wt%, 5.40 g assay) as a white solid containing 4% of the *epi* isomer and 2% of the unreacted amide.

Sharpless has described the transformation of α-aminonitriles to the tetrazole analogues of α-amino acids. α-Aminonitrile **1498** was prepared from Z-Phg-NH_2 **1497** by dehydration with **cyanuric chloride**/DMF in 99% yield and with 90% *ee*

[1134]. Further reaction of **1498** with sodium azide afforded the tetrazole **1499** in 90% yield.

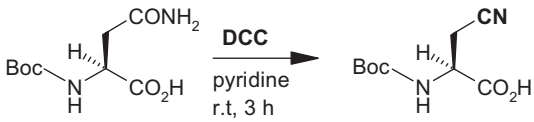


1496 **1497** **1498** **1499**

Typical procedure. *(R)-N-Carboxybenzyloxy phenylglycinonitrile* **1498** [1134]: A 250-mL round-bottomed flask was charged with amide **1497** (2.84 g, 10.0 mmol) and DMF (30 mL) and stoppered. The solution was chilled in an ice bath, **cyanuric chloride** (1.2 g, 6.5 mmol) was added in a single portion, and the reaction mixture was slowly allowed to warm to room temperature and stirred for 8 h. The reaction was then quenched with water (50 mL) and the solution was extracted with ethyl acetate (100 mL). The organic layer was washed with water (5 × 50 mL), dried over $MgSO_4$, and concentrated to dryness. The solid obtained was redissolved in a mixture of ethyl acetate (50 mL) and hexanes (100 mL), this solution was passed through a short plug of silica, and the silica was washed with an equal volume of solvent of the same composition. The eluate was concentrated to give **1498** (2.66 g, 9.9 mmol, 99% yield) as a white powder. The initial product was recrystallized to give enantiomerically pure **1498** with mp 137 °C; HR-MS: (MH^+) 267.1128; found 267.1130. The enantiomeric excess of the crude product was found to be 90%.

Carbodiimides

DCC (**dicyclohexyl carbodiimide**) has been used as a dehydrating agent for converting amide to cyanide in the synthesis of an end-group modified retro-inverso *Bombesin C*-terminal nonapeptide. Using DCC, the amino acid asparagine **1500** was converted into 3-cyanoalanine **1501** in 63% yield [1135].

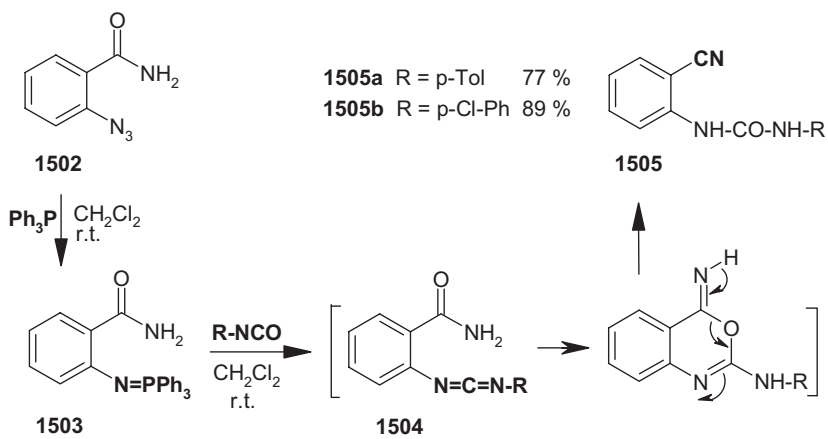


1500 **1501**

Typical procedure. *N-Boc-3-Cyanoalanine* **1501** [1135]: A solution of *N*-Boc-Asn-OH **1500** (100 mg, 0.431 mmol) in redistilled pyridine (2 mL) was cooled in a 16–20 °C

water bath. **DCC** (93.5 mg, 0.454 mmol) was then added, and the mixture was stirred for 3 h. The precipitated dicyclohexylurea was filtered off and washed with pyridine (1 mL). The pyridine was removed at room temperature in vacuo, and the syrupy residue was triturated with water (5 mL). After cooling for 1 h, the mixture was filtered and the filtrate was concentrated to a volume of about 1 mL, acidified to pH 2.1 with 1 N HCl, and extracted with ethyl acetate (2 × 5 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. This oil was stirred with hexane (4 mL) for 20 h, and the solution was cooled in a freezer overnight. The white solid of **1501** (58 mg, 63%) thus obtained was collected by filtration and air-dried; mp 80–81 °C (dec.); $[\alpha]^{rt}_D = -6$ ($c = 0.5$, EtOH).

An intramolecular dehydration of the amide **1502** to cyanide **1505** by a **carbodiimide group** (in **1504**) has been described. The latter was generated from the iminophosphorane **1503** (aza-Wittig) by reaction with an isocyanate (see also Section 4.5.3 "Carbodiimides"). In this way, substituted benzonitriles **1505** were prepared in yields of 77–89% [1136].

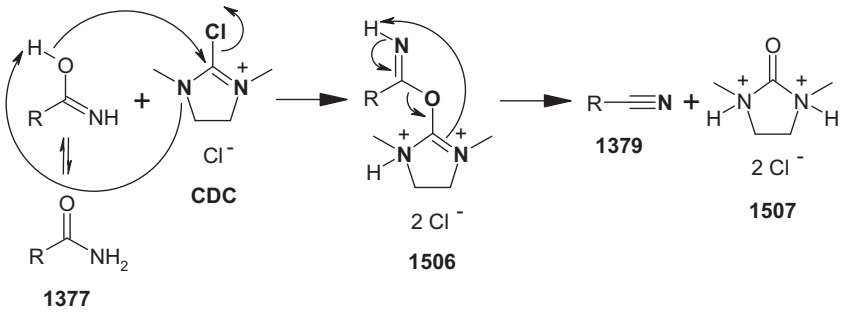


Typical procedure. *N-(o-Cyanophenyl)-N′-(p-chlorophenyl)urea* **1505b** [1136]: To a solution of *o*-carbamoylphenylimino-triphenylphosphorane **1503** (1.0 g, 2.5 mmol) in dry dichloromethane (25 mL) was added *p*-chlorophenylisocyanate (384 mg, 2.5 mmol). The reaction mixture was stirred at room temperature for 24 h. The separated solid was then collected by filtration, washed with diethyl ether (2 × 5 mL), dried, and recrystallized from ethanol to give *N*-(*o*-cyanophenyl)-*N′*-(*p*-chlorophenyl)urea **1505b** (604 mg, 89%); mp 230–231 °C.

2-Chloro-1,3-dimethylimidazolinium chloride (CDC)

A carbodiimide-related reagent is **2-chloro-1,3-dimethylimidazolinium chloride** (**CDC**). It can act as a powerful dehydrating agent, equivalent to DCC. Nitriles **1379** can be prepared from primary amides **1377** or aldoximes **1380** on several structures at room temperature within reaction times of 4–72 h and in yields of 64–99% [1137]. As a strong electrophile, **CDC** reacts with *O*-nucleophiles to form **1506**,

which stabilizes by fragmentation into the low-energy urea **1507** and the desired cyanide **1379**.

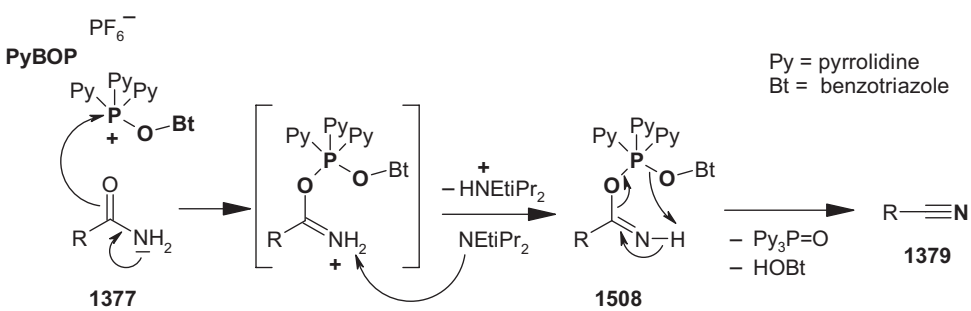


General procedure. *Preparation of cyanides* **1379** [1137]: To a solution of an amide **1377** or aldoxime **1380** (1 equiv.) and **CDC** (1 equiv.) in an appropriate solvent, an amine (2 equiv.) is added dropwise at room temperature. The reaction mixture is stirred at room temperature, poured into water, and extracted with dichloromethane. The organic solution is successively washed with 5% aq. HCl, saturated aq. $NaHCO_3$ solution, and water, then dried ($MgSO_4$) and concentrated to dryness. The residue is purified by short column chromatography (SiO_2) to give the cyanide **1379**.

PyBOP (Benzotriazol-1-yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate)

The well-known and less-toxic peptide coupling reagent **PyBOP** (**benzotriazol-1-yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate**) has been employed in the selective dehydration of aromatic and aliphatic primary carboxamides to the corresponding nitriles. The reaction conditions are mild, the dehydration being performed at 40 °C; reaction times are 5–8 h, and yields are 80–95% [1138].

General procedure. *Nitriles* **1379** *from primary amides* **1377** [1138]: **PyBOP** (1.145 g, 2.2 mmol) was added to a stirred, ice-cooled solution (or suspension) of the amide **1377** (2.0 mmol) in anhydrous dichloromethane (10 mL) and anhydrous *N*,*N*-diisopropylethylamine (569 mg, 4.4 mmol) under N_2. The reaction mixture was



slowly heated to 40 °C and maintained at this temperature for 5–8 h until the amide had been consumed (TLC analysis). The mixture was then quenched with H_2O (2 mL) and extracted with dichloromethane (2 × 15 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and the solvent was removed in vacuo to afford the crude product, which was purified by column chromatography on silica gel (EtOAc/hexane, 1:9, *v*/*v*) to give pure nitriles **1379** in yields of 80–95%.

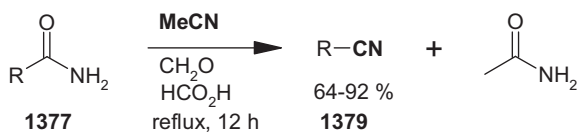
$AlCl_3$/NaI (aluminum chloride/sodium iodide)

A new method has recently been described for the preparation of nitriles from carboxamides or carbaldoximes using a combination of **aluminum chloride** and **sodium iodide** (**$AlCl_3$/NaI**) [1139]. The conversion of 1 equiv. of amide or oxime requires 2 equiv. of **$AlCl_3$** and 6 equiv. of **NaI**. Reactions are performed in refluxing acetonitrile, the reaction time is 2.5 h, and yields are quoted as 80–95%.

Typical procedure. *Benzonitrile from benzaldoxime* [1139]: Anhydrous **aluminum chloride** (0.264 g, 2 mmol) and **sodium iodide** (0.900 g, 6 mmol) were added to dry acetonitrile (25 mL) and the mixture was stirred magnetically for 0.5 h at room temperature under nitrogen. Benzaldoxime (0.121 g, 1 mmol) was added and stirring was continued under reflux for a further 2.5 h. The progress of the reaction was monitored by TLC. The reaction mixture was subsequently poured into ice-cold 10% aq. ammonia solution and extracted with diethyl ether. The combined organic layers were washed with water (2 × 100 mL), dried, and the solvent was distilled off under reduced pressure to give benzonitrile; 0.098 g, 95% yield.

Acetonitrile (MeCN) with an aldehyde

Aldehydes can be used to catalyze water transfer from a primary carboxamide **1377** to **acetonitrile** to furnish the corresponding cyanide **1379** and acetamide as by-product [1140]. The reactions are performed in refluxing **acetonitrile**, the reaction time is 12 h, and yields of 64–92% have been reported for several aromatic and aliphatic nitriles.



In contrast to the common methods described above, no sophisticated or powerful dehydration reagent is needed and the reaction can easily be carried out on a large scale. A reaction mechanism has been suggested, in which the aldehyde serves as a relay for the water transfer from the amide to the acetonitrile solvent. The aldehyde may be varied, but formic acid is essential for the reaction. Alkyne derivatives decompose under the reaction conditions, and both THP ethers and TBDMS groups are unstable.

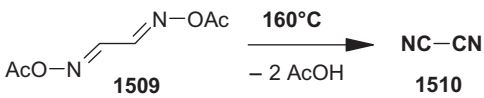
Typical procedure. *3-Phenylpropanonitrile* [1140]: To a stirred solution of 3-phenylpropanamide (50 mg, 0.34 mmol) in **acetonitrile** (0.8 mL) at room temperature were successively added formic acid (0.2 mL) and paraformaldehyde (50 mg, 1.67 mmol). The reaction mixture was then refluxed for 12 h, and the solution obtained was cooled to room temperature.

Work-up A: The crude mixture was concentrated under reduced pressure, and the residue was subjected to flash chromatography on silica gel (230–240 mesh) eluting with hexane/ethyl acetate (7:3) to yield 3-phenylpropanonitrile (37 mg, 85%).

Work-up B: The reaction mixture was diluted with ethyl acetate (10 mL) and washed successively with saturated sodium hydrogen carbonate solution (5 mL) and water (5 mL). The combined aqueous layers were extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude 3-phenylpropanonitrile was purified as described above (Work-up A).

Pyrolysis

Cyanogen, $(CN)_2$ **1510**, can be prepared in 77% yield from diacetylglyoxime **1509** by simply heating it to 160 °C [1141].



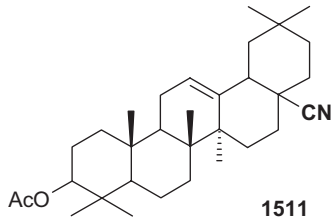
Typical procedure. *Cyanogen* **1510** *from diacetylglyoxime* **1509** [1141]: Diacetylglyoxime **1509** (17.7 g, 0.10 mol) was placed in a 100-mL three-necked, round-bottomed flask equipped with an N_2 inlet, an N_2 outlet with a thermocouple, and a stopper. The N_2 outlet was connected to three traps before exiting to the atmosphere. The first two traps were cooled to 3 °C (iced water), and the third trap was cooled to −77 °C (isopropyl alcohol/dry ice). A slow stream of N_2 was allowed to pass through the system. The flask was heated (oil bath) to 160 °C, whereupon an exothermic reaction occurred. The reaction temperature was allowed to rise and the pyrolysis was complete after the exothermic reaction had subsided (ca. 45 min). The first two traps contained acetic acid, while the third trap contained crude cyanogen **1510** (77% yield).

4.5.1.2 Basic and Neutral Reagents

Dehydration reactions forming cyanides are performed with **sodium hydroxide**/**PTC** [1142, 1143], **silver oxide**/**iodoethane** [1144], and **dibutyltin oxide** [1145, 1146].

Sodium hydroxide and PTC

Aqueous **sodium hydroxide** in conjunction with a **phase-transfer catalyst** (**PTC**) has been employed to prepare the triterpene *Amyrin* derivative 3-acetyloleanolic nitrile **1511** from 3-acetyloleanolic amide in an excellent yield of 98.5% [1142].



1511

Typical procedure. *3-Acetyloleanolic nitrile* **1511** [1142]: 3-Acetyloleanolic amide (497 mg, 1.0 mmol), **benzyl triethylammonium chloride** (PTC; 250 mg), and 40% aq. **NaOH** were refluxed under stirring in chloroform for 20 min. Work-up gave 471 mg (98.5%) of 3-acetyloleanolic nitrile **1511** as needles, mp 299–300 °C (methanol), $[\alpha]^{19}_{D} = +83.40$ ($c = 0.46$).

The above method has been investigated in more detail, e.g. with regard to the influence of **ultrasound** on the reaction of benzamide to give benzonitrile. It was shown that a combination of **PTC** and **ultrasound** could reduce the reaction time by a factor of six compared to the reaction performed without ultrasound; yields were about 80% [1143].

Silver oxide (Ag_2O) and iodoethane

Aryl carboxamides can be converted to the respective nitriles by treatment with **silver oxide** (**Ag_2O**) and **iodoethane** in benzene under non-acidic conditions in good yields of 50–93% [1144].

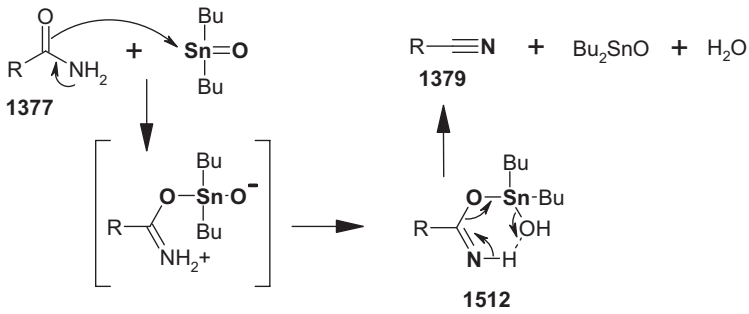
General procedure. *Nitriles from carboxamides* [1144]: A solution of the carboxamide (5 mmol) in dry benzene (50 mL), containing **silver oxide** (1.8 g, 7.7 mmol) and powdered 4 Å molecular sieves (5.0 g) was stirred in the dark at 25 °C for 12 h. **Iodoethane** (0.86 g, 0.44 mL, 5.5 mmol) was then added, and the mixture was heated to reflux under argon for 17 h. The cooled solution was then filtered (Celite) and the filtrate was concentrated under reduced pressure. Purification was accomplished by chromatography on silica gel, eluting with hexane and ethyl acetate in varying proportions.

Dibutyltin oxide

A versatile method for the conversion of aromatic and aliphatic primary amides to nitriles, using **dibutyltin oxide** as a catalytic neutral dehydrating agent, has been applied in various cases. The reaction temperature is about 110 °C, the reaction time is 12–18 h, and product yields are 70–95% [1145]. A reaction mechanism has been proposed.

General procedure. *Nitriles* **1379** from amides **1377** [1145]: A mixture of the amide (2.0 mmol) and **dibutyltin oxide** (0.186 g, 0.373 mmol) was stirred in refluxing anhydrous toluene (5 mL) for a period of 12–18 h until the amide had been consumed (TLC analysis). The mixture was then concentrated in vacuo and the residue was purified by column chromatography (EtOAc/hexane, 1:9, v/v) to afford

pure nitriles **1379** in yields of 70–95%. This procedure has been carried out on a 10–20 mmol scale; some experiments have been carried out on a larger scale in slightly more concentrated solution and using slightly extended overall heating times.



The above **dibutyltin oxide** method has been investigated with heating by **microwave irradiation** instead of conventional heating. In this way, the reaction time can be drastically reduced to 10–15 min (from 12–18 h), and yields are 80–95% [1146]. Experimental investigations have indicated that the greater the polarity of the organic compound, the more microwave energy it absorbs.

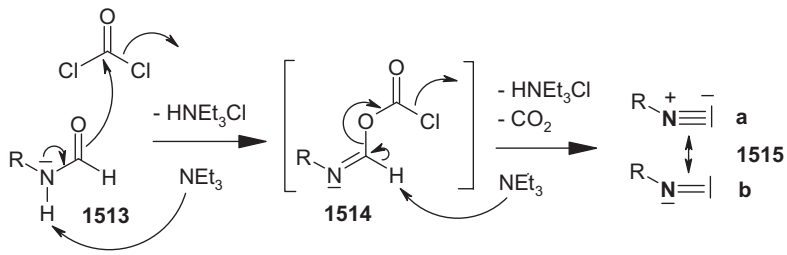
General procedure. *Nitriles* **1379** *from amides* **1377** [1146]: Typically, a heterogeneous mixture of the substrate and 0.25–0.35 mol equiv. of dibutyltin oxide in dry toluene (10–15 mL per mmol of substrate) was placed in a tube. The tube was then sealed (to prevent evaporation of the solvent) and subjected to microwave irradiation in a commercial microwave oven (operating at 2450 MHz) for periods of 2 min. Between each spell of heating, a cooling period of 30 s was allowed to prevent excess heating. This process was repeated 5–8 times (i.e. for a total heating time of 10–16 min). The cooled tube was then opened, and the contents were filtered. The solvent was removed from the filtrate, and the residue was purified by column chromatography (EtOAc/hexane, 1:9, *v*/*v*) to afford pure nitriles **1379** in yields of 80–95%. This procedure has been carried out on a 1–5 mmol scale; some experiments have been carried out on larger scales using slightly more concentrated solutions and slightly extended overall heating times in the microwave oven.

4.5.2 Isocyanides

Isocyanides **1515**, or isonitriles according to an older nomenclature, are a highly interesting species within the system of functional groups, being represented by the mesomeric system **1515a** ↔ **b**. The mesomeric form **a** is isosteric with cyanide and has high nucleophilicity at carbon, whereas in **b** the carbon atom possesses an electron sextet and is thus electron-deficient. The relatively strong contribution from **b** in **1515** is manifested in the considerably lower wavenumber of the ab-

sorption in the IR spectrum of isocyanide **1515** compared with that of the analogous cyanide **1379**, a difference of about 100 cm^{-1} generally being observed. These variations are responsible for the great variety of reactions of isocyanides with several reaction partners and their versatile applications in fascinating syntheses. These properties make isocyanides particularly well-suited for *multicomponent reactions (MCRs)* [1147–1149] and *combinatorial chemistry* [1150, 1151]. Furthermore, isocyanides are applied in syntheses of *heterocycles* [1148, 1152–1154] and *antibiotics* [1155, 1156]. More general reviews on isocyanide organic chemistry are given in [1157–1162]. An outstanding isocyanide of high synthetic value is *p*-tolylsulfonylmethyl isocyanide (TosMIC), a versatile formaldehyde equivalent with reversed polarity [1163, 1164].

The unique versatility of isocyanide chemistry is manifested in the diversity of its reactions.



Among other methods, isocyanides **1515** are mainly prepared by dehydration of the corresponding formamides **1513** [1149, 1157–1159]. In the case of **phosgene** as the dehydrating reagent, the chloroformate **1514** is formed as an intermediate, which stabilizes by decomposition to give hydrogen chloride, carbon dioxide, and the isocyanide **1515**. The reaction has to be performed under neutral or basic conditions because isocyanides react rather easily with acids; the influence of base accelerates the dehydration reaction. Besides **phosgene** [1159–1169], many other dehydration reagents have been used or developed, such as **diphosgene** [1170–1179], **triphosgene** [1180–1189], **phenyl chlorothionoformate** [1130], **phosphoryl chloride** [1131–1221], **phosphorus pentachloride** [1222], **triphenylphosphine/haloalkanes** [1224–1228], **thionyl chloride** [1229], **dipyridyl sulfite** [1230], **sulfuryl chloride** [1231], **mesyl chloride** [1232], ***p*-tosyl chloride** [1233–1236], **triflic anhydride** [1237–1242], the **Burgess reagent** [1243, 1244], and **CDC** [1137, 1245].

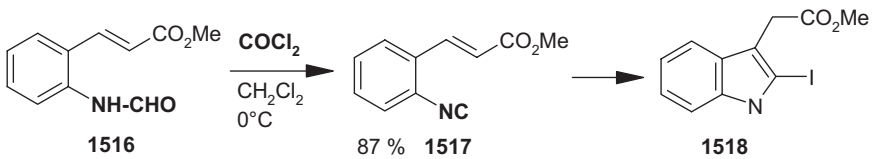
4.5.2.1 Phosgene and Phosgene "Oligomers"

Phosgene

The use of **phosgene** in the presence of triethylamine has become an often applied method since Ugi's extensive works in this field [1157]. As a prelude to preparative isonitrile chemistry, Ugi's 1971 procedure for the production of *tert*-butyl isocyanide is presented [1165]. *tert*-Butyl formamide is dehydrated with **phosgene** to afford *tert*-butyl isocyanide in 82% yield.

Typical procedure. *t-Butyl isocyanide* [1165]: **Phosgene** (for a *safe source* and *safety instructions*, see Chapter 7) (1.0 kg, 10.1 mol) was delivered through a wide tube into a stirred solution of *N-t*-butylformamide (1.01 kg, 10.0 mol) in triethylamine (1.30 kg) and *o*-dichlorobenzene (7.0 L) in a flask fitted with a reflux condenser charged with a freezing mixture of ice and salt (−20 °C). Water was added, the layers were separated, and the non-aqueous layer was dried over anhydrous potassium carbonate or magnesium sulfate and fractionated; bp 90–92 °C/750 mmHg; yield: 681 g (82%).

Isocyanides are very useful tools in the synthesis of *N*-heterocycles such as indoles, imidazoles, tetrazoles, and oxazoles. To form 2,3-disubstituted indoles such as 3-substituted 2-iodo indoles **1518**, *o*-isocyano cinnamates **1517** are important intermediates. They are prepared in high yield (87% for **1517**) by dehydration of *o*-(*N*-formylamino)cinnamate **1516** with **phosgene** [1153, 1166].

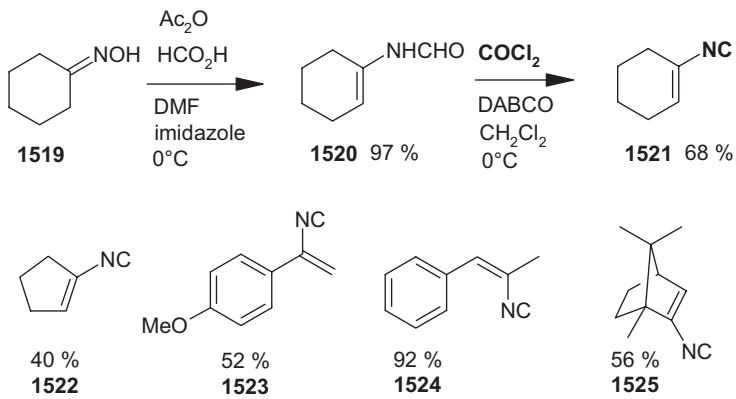


1516 87 % **1517** **1518**

Typical procedure. *Methyl o-isocyanocinnamate* **1517** [1166]: To a solution of methyl *o*-(*N*-formylamino)cinnamate **1516** (141 mg, 0.68 mmol) and triethylamine (287 µL, 2.06 mmol) in dichloromethane at 0 °C, a solution of **phosgene** (for a *safe source*, see Chapter 7) in dichloromethane was added dropwise. The reaction was closely monitored by TLC until completion. The mixture was then partitioned between Et_2O and satd. aq. $NaHCO_3$, and then brine. The combined extracts were dried (Na_2SO_4), filtered, and concentrated to dryness in vacuo. The crude product was purified by flash column chromatography on silica gel eluting with Et_2O/hexane (1:4) to give methyl *o*-isocyanocinnamate (106 mg, 87%) as a white solid; mp 57–59 °C.

Various *vinyl isocyanides* **1521–1525** are prepared from oximes (for example, **1519**) by reductive formylation and dehydration of the resulting vinyl formamides (for example, **1520**) with **phosgene** in 40–97% yield [1167]. For the dehydration step, DABCO proved to be the most effective base among acid scavengers (Et_3N, pyridine, and quinoline were also used).

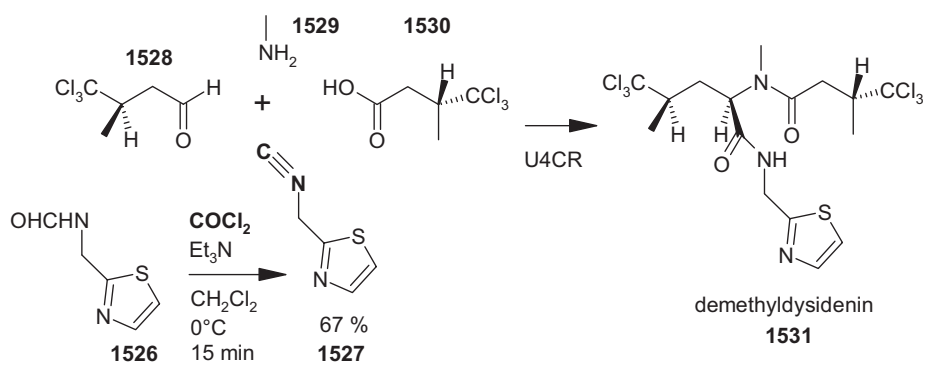
General procedure. *Vinyl isocyanides* [1167]: The *N*-formyl enamine (1 g) and DABCO (3 equiv.) were dissolved in dry dichloromethane (20 mL) and the solution was cooled to 0 °C. **Phosgene** (for a *safe source*, see Chapter 7) (2 equiv., 10% *w*/*v* in dichloromethane) was added dropwise with stirring at 0 °C and the resulting solution was stirred until TLC indicated that no starting material remained. The cold solution was filtered, and the filtrate was concentrated to a volume of 10 mL, filtered once more, and concentrated to dryness in a flask containing glass wool. The residue was flash distilled at 8 Torr using a kugelrohr apparatus with a preset oven temperature of 100 °C.



Cyclohexen-1-yl isocyanide **1521**, *rac*-4-*tert*-butyl-cyclohexen-1-yl isocyanide, and *rac*-4-phenyl-cyclohexen-1-yl isocyanide were likewise prepared by a similar method using **gaseous phosgene** to furnish the vinyl isocyanides in yields of 71–80% [1168]. These were applied in a multicomponent approach to novel totally protected precursors of PNA monomers through an *Ugi 4CR*.

General procedure. *Vinyl isocyanides* [1168]: The appropriate formamide (0.2 mol) and abs. triethylamine (64 mL) were dissolved in dichloromethane (500 mL). The solution was cooled to 0 °C and **phosgene** (20 g, 0.202 mol) was introduced over a period of about 2 min. After stirring for 1 h at 0 °C, water (140 mL) was added and the layers were separated. The organic layer was washed with water (2 × 140 mL) and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was subjected to flash chromatography on silica gel to furnish **1521** in 71% yield.

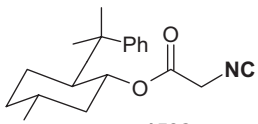
Multicomponent reactions (MCRs) have, as a matter of principle, an enormous synthetic value in saving several reaction steps compared with a sequence of one- or two-component reactions. This is demonstrated in the total synthesis of the marine hexachlorinated amino acids *(+)-demethyldysidenin* **1531** and *(−)-demethyl-isodysidenin* [1169]. The key step of the synthesis is a U4CR (Ugi four-component reaction) using an amine **1529**, an aldehyde **1528**, a carboxylic acid **1530**, and thiazol-2-ylmethyl isocyanide **1527**, which is prepared from the corresponding formamide **1526** by dehydration with **phosgene** under mild conditions in 67% yield.



Typical procedure. *Thiazol-2-ylmethyl isocyanide* **1527** [1169]: In a dry 25-mL round-bottomed flask was placed *N*-(thiazol-2-yl)methylformamide (0.5 g, 3.52 mmol) and to this was added dichloromethane (2 mL) and dry triethylamine (1.15 mL, 8.22 mmol). The mixture was cooled in a ice bath under a positive N_2 pressure. **Phosgene** (for a *safe source*, see Chapter 7) (3.52 mL of a 1 M solution in dichloromethane; 3.52 mmol) was added dropwise. An exothermic reaction was observed; a precipitate of triethylammonium chloride formed and the mixture turned brown. After 15 min, saturated Na_2CO_3 solution (10 mL) was added and a thick glutinous precipitate formed. The dichloromethane solution was decanted off and the solid was washed further with dichloromethane (3×10 mL). The combined extracts were dried over $MgSO_4$, concentrated in vacuo, and distilled at 100 °C (30 mmHg) to give thiazol-2-ylmethyl isocyanide **1527** as a pale-brown oil; yield 0.293 g (67%).

Diphosgene

An interesting chiral building block for the synthesis of optically active unusual amino-hydroxy acids is (+)-8-phenylmenthyl isocyanoacetate **1532** [1170]. It is prepared in optically pure form in 95% yield by dehydration of the corresponding formamide with **diphosgene** within ca. 10 h at room temperature.

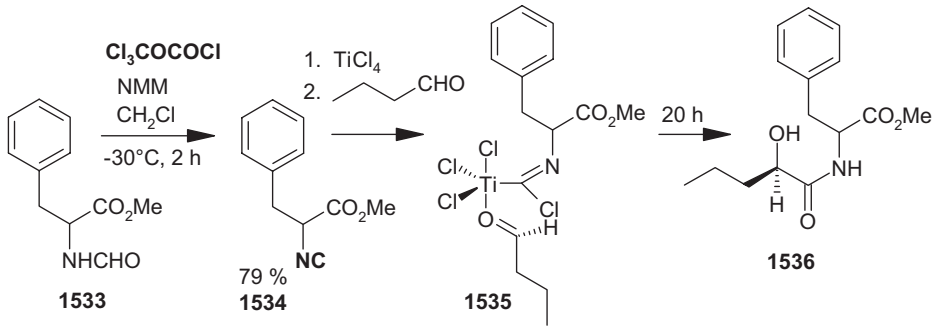


1532

Typical procedure. *(+)-8-Phenylmenthyl isocyanoacetate* **1532** [1170]: To 8-phenylmenthyl formamidoacetate (480 mg, 1.51 mmol) in anhydrous dichloromethane (15 mL) was added anhydrous triethylamine (0.45 mL, 3.16 mmol, 2 equiv.). The mixture was cooled to 0 °C in an ice-bath and a solution of **diphosgene** (0.096 mL, 0.8 mmol, 1.1 equiv.) in anhydrous dichloromethane (2 mL) was added dropwise. After stirring at 25 °C overnight, the mixture was washed with 10% aq. $NaHCO_3$ solution (2×5 mL) and then with water until the washings were of pH 6–7. The organic phase was dried over $MgSO_4$ and the solvent was evaporated in vacuo. The crude product, which consisted of a mixture of the desired isocyanoacetate **1532** (55%) and the starting material (45%), as determined by ^1H NMR, was then recycled under the same conditions (with 2 equiv. of Et_3N and 0.5 equiv. of **diphosgene**). After the same work-up, the crude compound, a yellowish viscous liquid, was obtained. Yield: 411 mg (95%) of **1532**; $R_f = 0.6$ (Et_2O/hexane, 1:1); $[\alpha]_D^{21} = +20.5$ ($c = 4.4$, CCl_4).

In the recent patent literature, an application on *"Preparation of alkyl isocyanoacetates"* from amino acids by dehydration of the corresponding formamides has been filed [1171].

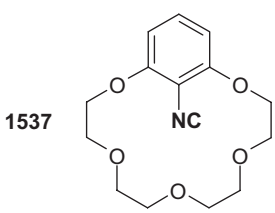
α-Hydroxycarboxylic acid amides **1536** are formed by $TiCl_4$-mediated addition of isocyanides to aldehydes and ketones **1535** in a Passerini-type reaction [1172]. The yields of **1536** range from 14% to in excess of 95%. The isocyanides are obtained by dehydration of the corresponding formylated amino acid esters with **diphosgene**; yields 42–91%.



Typical procedure. *Methyl (S)-2-isocyano-3-phenylpropionate* **1534** [1172]: In a 250-mL three-necked flask equipped with a dry-ice reflux condenser, a dropping funnel, and a rubber septum, *N*-formyl-(*R*)-phenylalanine methyl ester (10.0 g, 48.3 mmol) $\{[\alpha]_D = -31.7$ ($c = 1.0$ in ethanol)$\}$ was dissolved in dichloromethane (60 mL) under an argon atmosphere. The solution was initially cooled to -10 °C and *N*-methylmorpholine (10.4 mL, 94 mmol) was added by means of a syringe; then, at a temperature of -30 °C, a solution of **diphosgene** (2.9 mL, 24 mmol) in dichloromethane (10 mL) was added from the dropping funnel at such a rate that the internal temperature did not exceed -30 °C. The orange suspension was stirred for 2 h at this temperature and then allowed to warm slowly to -15 °C. The mixture was then hydrolyzed with ice/water (40 mL) and the aqueous layer was extracted with dichloromethane (3×40 mL). The combined organic layers were washed twice with 7.5% aq. $NaHCO_3$ solution and once with water, and dried over 4 Å molecular sieves at -30 °C for 10 h. The crude product was purified by flash chromatography on silica gel, eluting with pentane/ethyl acetate (7:3). The product **1534** was obtained as red-orange crystals: 7.2 g (79%), mp 57–58 °C, $[\alpha]_D = -13.2$ ($c = 1.3$ in benzene).

Methyl (*R*)-2-isocyano-3-phenylpropionate was prepared in the same way as above: yield 4.8 g (53%); mp 58–59 °C, $[\alpha]_D = +18.6$ ($c = 1.0$ in methanol).

3,3,3-Trifluoro-2-isocyano propionates, versatile building blocks for the introduction of trifluoromethyl groups into organic molecules, are synthesized using **diphosgene** to dehydrate the corresponding formamides to give the desired isocyanides in yields of 60–88% [1173].

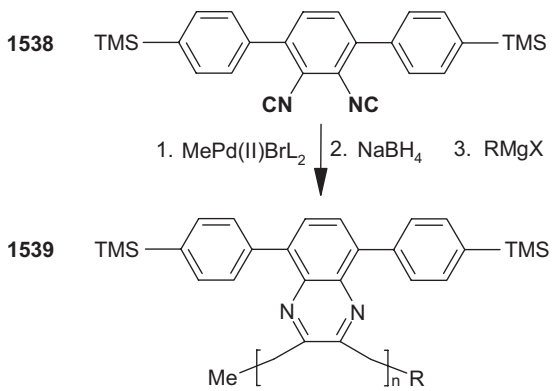


A crown ether containing an isocyanide group, **1537**, a π-acceptor macrocycle, has been prepared by dehydration of the corresponding formamide with **diphosgene**,

chromatography on alumina, and crystallization from hexane; yield 83%; mp 107–108 °C [1174].

In preparative pharmaceutical chemistry, particularly for multicomponent reactions (MCRs), there is a need for multifunctional isocyanides that are useful as building blocks in the preparation of drugs, which contain a high density of organic functional groups.

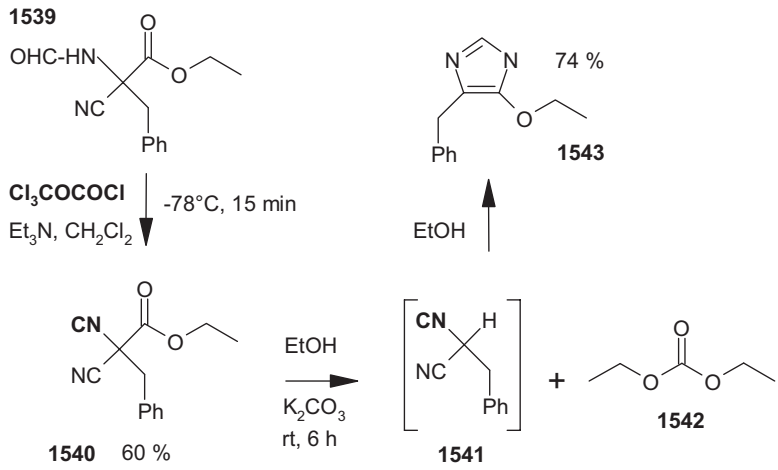
Various 2,3-disubstituted quinoxaline derivatives **1539** are synthesized by palladium-catalyzed oligomerization of 1,2-diisocyanoarenes **1538** [1175, 1176]. Isocyanides **1538** are obtained by dehydration of the corresponding 1,2-diformamidoarenes with **diphosgene**.



Typical procedure. *3,6-Bis(4-trimethylsilylphenyl)-1,2-diisocyanobenzene* **1538** [1176]: A suspension of 3,6-bis(4-trimethylsilylphenyl)-1,2-diformamidobenzene (600.0 mg, 1.30 mmol) and triethylamine (2.7 mL, 19.5 mmol) in dichloromethane (10 mL) was cooled to −78 °C. To this mixture, a solution of **diphosgene** (0.78 mL, 19.5 mmol) in dichloromethane (10 mL) was added dropwise at −78 °C. The mixture was stirred at this temperature for 8 h, then gradually warmed to −20 °C, whereupon 10% aq. K_2CO_3 solution (20 mL) was added dropwise. The mixture was extracted several times with dichloromethane. The combined extracts were washed with water, dried over magnesium sulfate, and the solvent was evaporated. The residue was subjected to column chromatography on silica gel (eluent: *n*-hexane/CH_2Cl_2, 1:1) to give 253.9 mg (46%) of 3,6-bis(4-trimethylsilylphenyl)-1,2-diisocyanobenzene **1538**.

In the 1,2-difunctions series, a patent application has been filed entitled *"High-yield method for the preparation of multi-functional isonitriles from diamines"* [1177]. Here, the diamines are 1,2-diamines, and the functions are 1-isocyanides and 2-alkoxycarbonylamines.

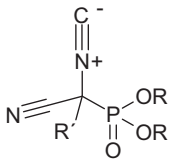
An even higher density of functional groups can be achieved with 1,1-difunctionalized isocyanides. α-Cyano-α-isocyanoalkanoates **1540** are synthesized as versatile synthons for the assembly of imidazoles **1543** by the loss of carbonate **1542** from intermediate **1541** [1178]. Dehydration of the corresponding formamides **1539** with **diphosgene** affords the 1-cyano-1-isocyanides **1540**.



Typical procedure. *Ethyl 2-cyano-2-isocyano-3-phenylpropanoate* **1540** [1178]: To a stirred solution of 2-cyano-2-formamido-3-phenylpropanoate (0.615 g, 2.5 mmol) in dichloromethane (7.5 mL) at −78 °C, triethylamine (1.75 mL) was added in a single portion and then **diphosgene** (0.3 g, 0.183 mL) was added dropwise over a period of 10 min. The solution turned slightly brown, and a white precipitate was formed. After stirring for 15 min at −78 °C, the mixture was allowed to warm to room temperature and water (25 mL) was added. The organic layer was separated, washed with water, and dried with Na_2SO_4. The resulting solution was filtered through silica (15 × 1 cm), and the pure product ethyl 2-cyano-2-isocyano-3-phenylpropanoate **1540** was obtained as a solution in dichloromethane. It could be stored at −25 °C for a few months. Yield: 342 mg (60%); R_f (hexane/EtOAc, 3:1) = 0.49.

The highest functional group density is established in a 1,1,1-trifunctionalized carbon atom. The same author as above has described syntheses and reactions of 1-cyano-1-isocyanoalkyl-phosphonic acid esters **1544** [1179, 1287].

General procedure. *1-Cyano-1-isocyanoalkylphosphonic acid esters* **1544** [1179]: To a stirred solution of the 1-cyano-1-(formylamido)alkyl-1-phosphonic acid ester (4.54 mmol) and triethylamine (3.2 mL) in dichloromethane (25 mL) at −78 °C, **diphosgene** (0.33 mL, 0.54 g, 2.72 mmol) was added dropwise over a period of 10 min. The mixture was stirred at this temperature for a further 15 min, and then the cooling bath was removed and water (25 mL, pH 7) was added. The organic layer was separated, washed with water (30 mL), dried over Na_2SO_4, and the solvent was evaporated in vacuo at a temperature below 20 °C. Chromatography of the resulting solution on silica gel (15 × 2 cm) eluting with diethyl ether/acetone (9:1) afforded 1-cyano-1-isocyanoalkyl-phosphonic acid esters as colorless to yellow solutions. Yields: 24–98%.



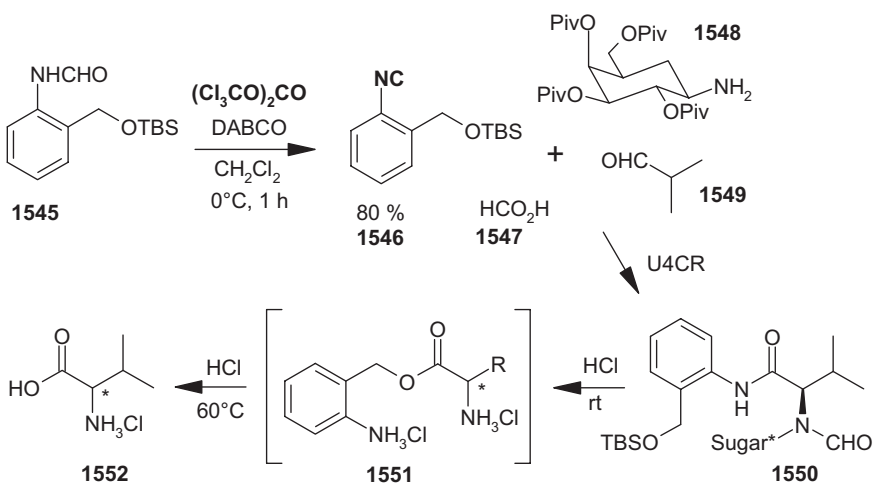
R = Et, *i*-Pr
R´= Bn, 4-MeBn

1544

Triphosgene

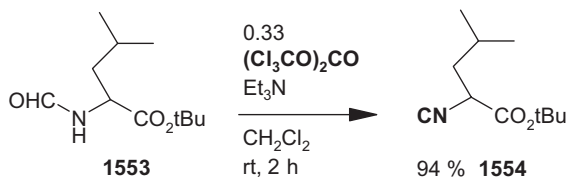
As *multicomponent reactions (MCRs)* are pairs of reversible reaction steps, the final step should be irreversible to afford good yields. Known reactions of isocyanides are irreversible, and this peculiarity, coupled with their high reactivity and versatility, makes isocyanides the ideal cornerstones of efficient MCRs. The function that results from the isocyanide moiety in MCRs is primary amide. Amide groups are rather inert and can only be transformed into other functional groups under forcing conditions. An approach is to use *cyclohexenyl isocyanide* **1521**, which, in a U4CR, forms cyclohexenyl primary amide; this can easily be transformed into carboxylic acids, esters, and thioesters, and thus gives the desired variety of functional groups [1180]. **Triphosgene** is the preferred reagent for the dehydration reaction affording cyclohexenyl isocyanide **1521**.

Another approach is to use a *"convertible" isocyanide* **1546**, which reacts with formic acid **1547**, amino sugar **1548**, and isobutyraldehyde **1549** to form the U4CR product **1550**. The TBS residue is removed by acid, and an intramolecular substitution takes place forming a benzyl ester of the generated amino acid **1551**. **1551** can be cleaved under somewhat stronger conditions to afford the amino acid **1552** [1181]. The isocyanide **1546** is obtained in 80% yield by dehydrating the formamide **1545** with **triphosgene**.



General procedure. *2-Isocyanobenzyl-trialkylsilyl ether* (*e.g.* **1546**) [1181]: The formamide (e.g. **1545**) (1.66 mmol) and DABCO (559 mg, 4.9 mmol) were dissolved in dichloromethane (10 mL). To the cooled solution (0 °C), a solution of **triphosgene** (328 mg, 1.1 mmol) in dichloromethane was added dropwise. The clear solution soon became cloudy and whitish-yellow. After stirring for 30 min, the reaction was quenched with aq. sodium carbonate solution (0.5 M, 15 mL) and the biphasic solution was stirred for a further 5 min to ensure that all the phosgene was destroyed. The mixture was then poured into 0.5 M aq. sodium carbonate solution. The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate, the solvent was removed under reduced pressure, and the crude material was rapidly chromatographed on neutral alumina (hexane/ethyl acetate, 9:1) (to give, e.g., 80% of 2-isocyanobenzyl-*tert*-butyl-dimethylsilyl ether **1546**).

Isocyanides from *N*-formylated amino acid *tert*-butyl esters, such as For–Gly–O*t*Bu, For–Leu–O*t*Bu **1554**, and For–Phe–O*t*Bu, are obtained in good yields (79–94%) by their dehydration with **triphosgene** at room temperature within 1.5–3 h [53, 1182].

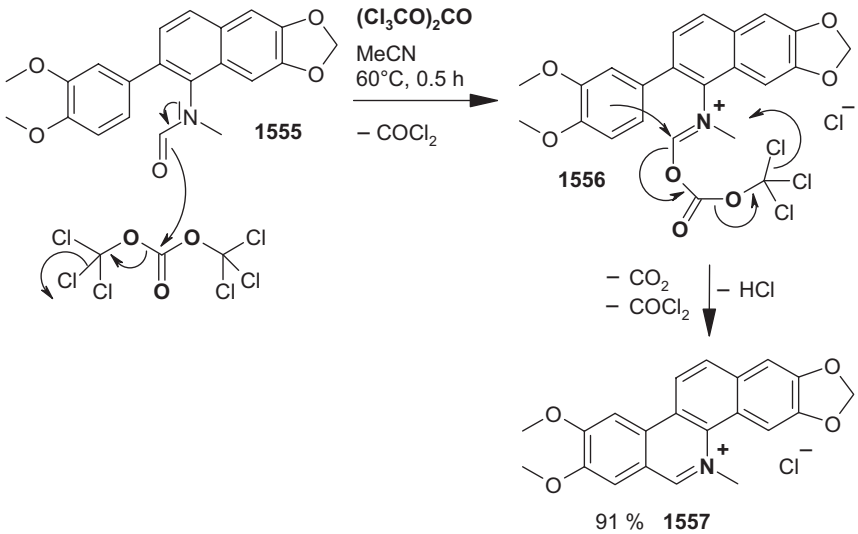


Typical procedure. *tert-Butyl 2-isocyano-4-methyl pentanoate* **1554** [1182]: *N*-Formyl-leucine *tert*-butyl ester **1553** (5.00 g, 23.2 mmol) and triethylamine (7.13 g, 69.7 mmol) were dissolved in dichloromethane (36 mL) and the solution was cooled to 0 °C. At this temperature, a solution of **triphosgene** (2.30 g, 7.74 mmol) in dichloromethane (25 mL) was added dropwise. The mixture was stirred for 2 h at room temperature, water (5 mL) was then poured into it, and the phases were separated. The organic layer was washed with 5% aq. sodium hydrogen carbonate solution, dried over sodium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel eluting with ethyl acetate to furnish *tert*-butyl 2-isocyano-4-methyl pentanoate **1554** (4.29 g, 94%) as a colorless oil.

In a facile synthesis of 6-hydroxyindole-3-acetic acid, the *o*-isocyanocinnamate route was also chosen [1183], as in a similar synthesis carried out with **phosgene** [1168; see above]. The **isocyanide** was obtained in 92% yield by using **triphosgene** as dehydration reagent [1183].

Isoquinolines can be prepared by a Bischler–Napieralski reaction involving a tertiary formamide **1555**, which reacts with the dehydration reagent **triphosgene** to form the anti-tumor active *nitidine chloride* **1557** [1184]. As regards the reaction mechanism, it can be suggested that the first step affords the same intermediate chloroformate **1556** as the isocyanide-generating process. Then, a Friedel–Crafts acylation-like attack of the iminium cation at the benzene moiety affords the isoquinoline *nitidine chloride* **1557** in 91% yield.

Typical procedure. *Nitidine chloride* [1184]: A solution of **1555** (0.102 g, 0.278 mmol) and **triphosgene** (0.179 g, 0.602 mmol) in acetonitrile (2.5 mL) was stirred at 60 °C (bath temperature) for 0.5 h. After the addition of ice/water, a yellow precipitate was collected by filtration and recrystallized from ethanol/diethyl ether to directly afford *nitidine chloride* (0.098 g, 91%); mp 285–292 °C.

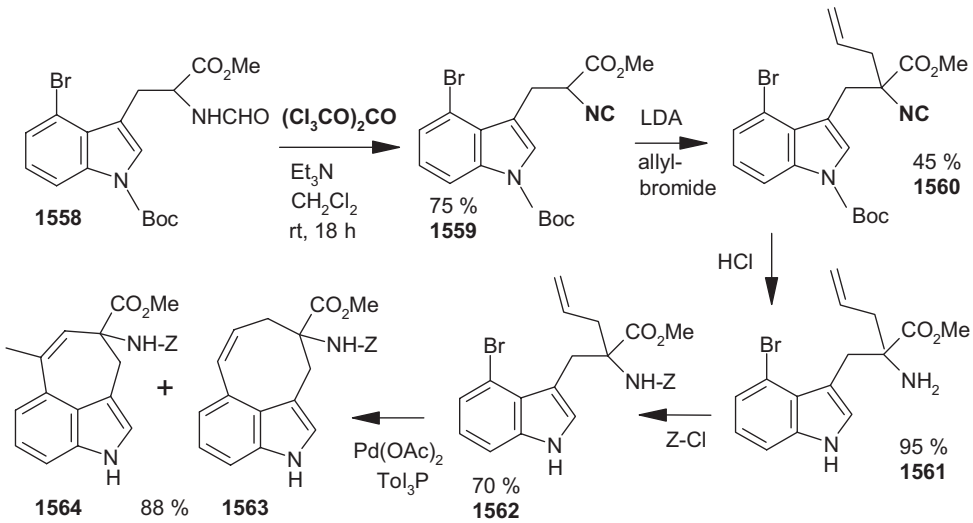


An isocyano group can serve as both a protecting group for the amino function, and, due to its electronic effect, as an activating group as well. These two functionalities are employed in a synthetic route whereby an amino function has to be protected and a condensation reaction is performed at the α-carbon atom, for which activation is required [1185–1187].

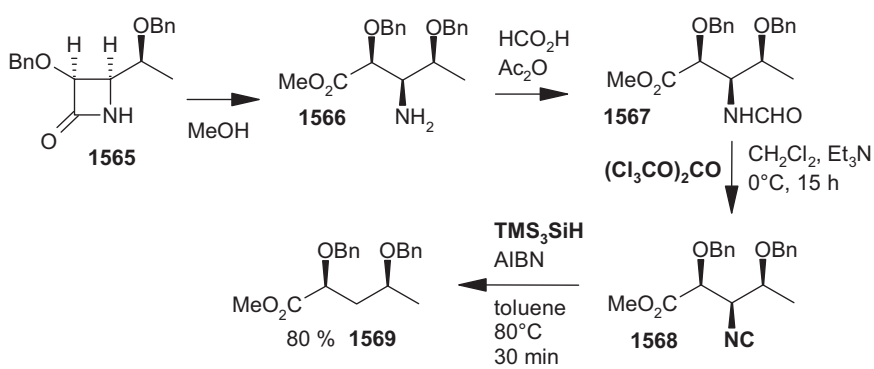
3,4-Fused tryptophan analogues **1563** and **1564** contain a ring that bridges the α-carbon and the 4-position of the indole ring, thus limiting the conformational flexibility of the side chain. The synthesis proceeds from *N*-formylated 4′-bromotryptophan **1558** via isocyanide **1559**, 2-propenoate **1560**, and Pd-catalyzed cyclization of the α-2-propenyl DL-tryptophan derivatives **1561** and **1562** to give both the seven- and eight-membered constrained ring analogues **1564** and **1563**. Dehydration of the formamide **1558** with **triphosgene** affords the isocyanide **1559** in 75% (87%) yield [1187].

Typical procedure. *4-Bromo-3-[2-isocyano-2-(methoxycarbonyl)ethyl]indole-1-carboxylic acid tert-butyl ester* **1559** [1187]: The *N*-formyl-*N*′-Boc-4′-bromo-tryptophan methyl ester **1558** (0.05 g, 0.14 mmol) was suspended in dry dichloromethane (3 mL) under argon and the solution was cooled to below 0 °C using an ice/salt bath. Triethylamine (0.09 g, 0.86 mmol) was added through a septum, and then a solution of **triphosgene** (0.014 g, 0.05 mmol) in dichloromethane (1 mL) was added dropwise. The solution was allowed to warm to room temperature and stirred for a further

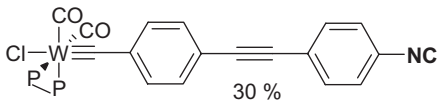
18 h. The solvent was then removed in vacuo and the residue was taken up in Et_2O (50 mL). The remaining precipitate was removed by filtration and the filtrate was concentrated to dryness in vacuo. Flash chromatography, eluting with 30% Et_2O in *n*-hexane yielded 4-bromo-3-[2-isocyano-2-(methoxycarbonyl)ethyl]indole-1-carboxylic acid *tert*-butyl ester **1559** as a white gum (0.05 g, 75%).



A further valuable tool in organic chemistry is facilitated by isocyanides: the *de-amination* reaction. When the standard deamination reaction via a diazonium salt is undesirable (due to a need to avoid acidic conditions), primary amines can be converted by well-known methods into isocyanides, which are reduced using tributyltin hydride under Barton's conditions (heating for 5 h at 80 °C in toluene). This reaction sequence has been applied as a new route to 1,3-polyols using azetidinone frameworks **1565** as chiral templates [1188]. Dehydration of the formamide **1567** was accomplished with **triphosgene** to afford the isocyanide **1568**, which was reduced efficiently with tris(trimethylsilyl)silane to afford the desired *α,γ-dialkoxy ester* **1569** in 80% yield [1188].



In unsaturated alkylidyne metal complexes, the metal–carbon triple bond establishes a strong electronic connection between transition metal centers and organic π-systems. It is of great interest to attach additional metal centers to unsaturated alkylidyne ligands in a π-conjugated manner via the isocyanide functionality. Such isocyanides are prepared by dehydration of the corresponding formamides with **triphosgene** affording, for example, **1570** in 30% yield [1189].



30 %
1570

Typical procedure. *[W(CC$_6$H$_4$(C≡CC$_6$H$_4$NC-4)-4)Cl(CO)$_2$(dppe)]* **1570** [1189]: Formamide [W(CC$_6$H$_4$(C≡CC$_6$H$_4$NHCHO-4)-4)Cl(CO)$_2$(dppe)] (0.908 g, 1 mmol) was dissolved in dichloromethane (50 mL) and triethylamine (0.56 mL) was added. After cooling to −78 °C, a solution of **triphosgene** (0.2 g) in dichloromethane (10 mL) was added. The resulting mixture was allowed to warm to 0 °C and was stirred at this temperature for 30 min. The solvent was then removed in vacuo. The residue was washed with hexane, redissolved in THF (30 mL), and this solution was filtered. The solvent was again removed in vacuo, and the residue was redissolved in dichloromethane. After filtration, hexane was added to the solution to afford yellow-orange crystals of [W(CC$_6$H$_4$(C≡CC$_6$H$_4$NC-4)-4)Cl(CO)$_2$(dppe)] **1570** (0.266 g, 30%), mp 135–138 °C (dec.).

4.5.2.2 Chloroformates

Phenyl chlorothionoformate

Phenyl chlorothionoformate is presented as a versatile reagent for the preparation of nitriles and isonitriles under mild conditions [1130]. A general procedure is given for cyanides (see Section 4.5.1). Benzyl isocyanide and trimethoxybenzyl isocyanide have also been prepared according to this procedure within 7.5–10 h at room temperature in yields of 82 and 85% [1130].

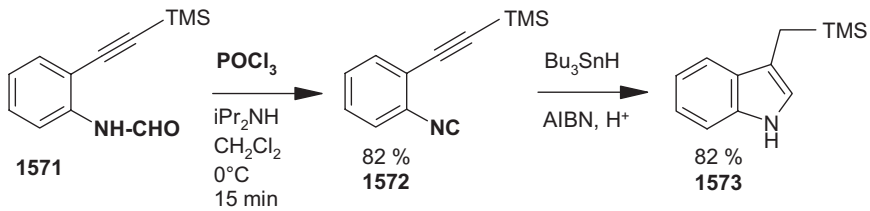
4.5.2.3 Phosphorus Chlorides

Phosphoryl chloride

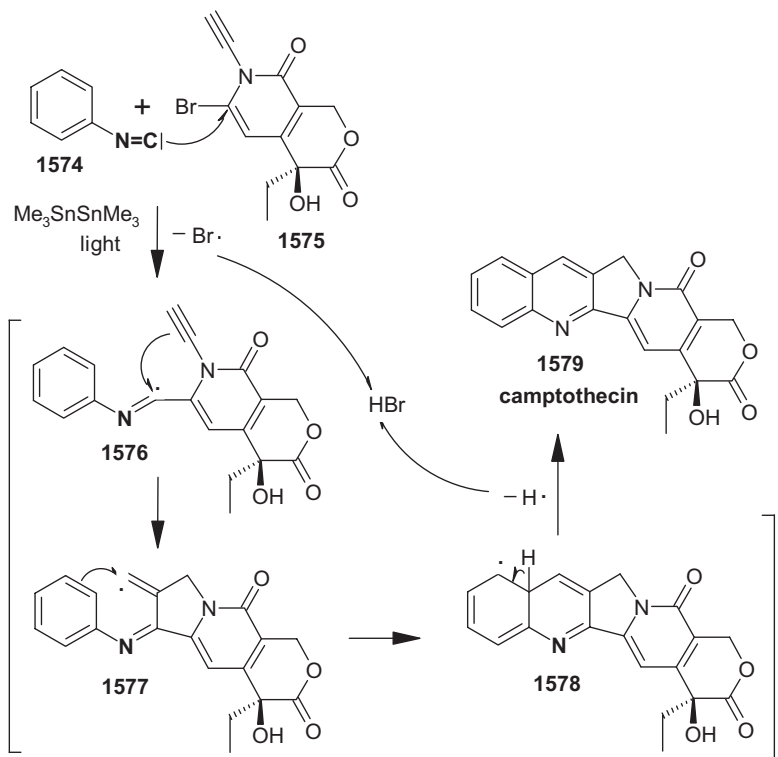
Nowadays, it seems that **phosphoryl chloride** is the most used reagent for the dehydration of formamides to prepare isocyanides, even though some authors have critical remarks about it, particularly with regard to very sensitive isocyanides (see Chapter 6).

An approach to the synthesis of indoles **1573** employing a free-radical cyclization of aryl isocyanides bearing pendant alkynes **1572** in a cascade-type reaction has recently been described [1190]. Isocyanide **1572** is prepared in 82% yield from formamide **1571** by dehydration with **phosphoryl chloride** at 0 °C within 15 min.

Typical procedure. *Trimethylsilylethynyl-2-phenyl isocyanide* **1572** [1190]: To a solution of the formamide **1571** (0.34 g, 1.6 mmol) in dichloromethane (10 mL) at 0 °C was added $i\mathrm{Pr_2NH}$ (1.3 mL, 9.3 mmol) and then **phosphoryl chloride** (0.32 mL, 3.4 mmol) was slowly added. The reaction mixture was quenched after 0.25 h with 20% aq. Na_2CO_3 (1 mL) at 0 °C and then diluted with dichloromethane (25 mL). The organic phase was washed with 20% aq. Na_2CO_3 (25 mL) and brine (50 mL), dried (K_2CO_3), and concentrated. Bulb-to-bulb vacuum distillation (50–65 °C, 5 mmHg) provided 0.26 g (82%) of isocyanide **1572** as a green liquid. Alternatively, isocyanide **1572** can be chromatographed on a short alumina column (hexanes/ethyl acetate, 50:1).

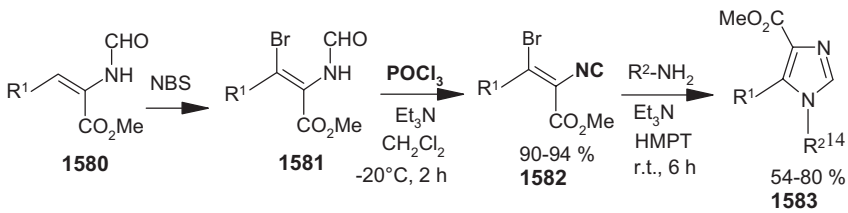


Another example of a free radical driven reaction cascade is given by the following reaction sequence, which clearly demonstrates the versatility and originality of isocyanide chemistry.



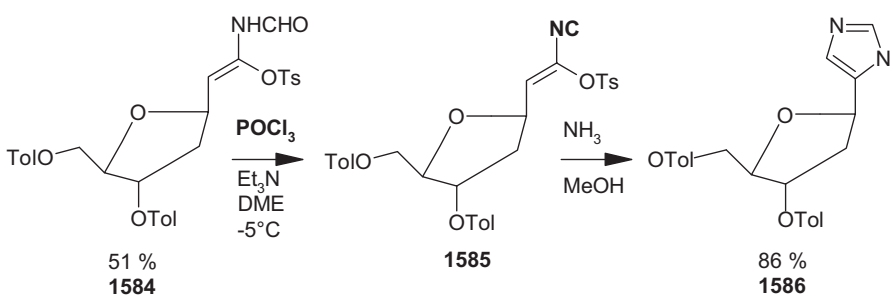
In a total synthesis of (±)-*camptothecin* **1579**, which shows high potential in terms of anti-tumor and anti-retroviral activity, a new [4+1] radical annulation has been established, facilitated by the use of phenyl isocyanide **1574**. With **1575**, **1574** effects a cascade of free radical reactions via **1576–1578** forming *two* new ring systems, a quinoline and a pyrrolidine, in a one-pot-synthesis [1191, 1192]. An improved synthesis of *camptothecin analogues*, in which the alkyne moiety is protected by a TMS group, has been filed for a patent application [1193].

A facile synthesis of various methyl 1,5-disubstituted imidazole-4-carboxylates can be realized by the reaction of methyl 3-bromo-2-isocyanoacrylates with a variety of primary amines [1194]. Dehydration of formamide **1581** with **phosphoryl chloride** at −20 °C for 2 h affords the isocyanide **1582** in 90–94% yield.



Typical procedure. *Methyl (E)- and (Z)-3-bromo-2-isocyanocinnamate* **1582** [1194]: **$POCl_3$** (5.1 g, 33 mmol) was added dropwise to a mixture of methyl (*E*)- and (*Z*)-3-bromo-2-formylamino-cinnamate **1581** (8.52 g, 30 mmol) and triethylamine (8.41 g, 83 mmol) in dichloromethane (30 mL) at −20 to −10 °C under vigorous stirring. The mixture was stirred at room temperature for 2 h and then poured into 20% aq. K_2CO_3 (30 mL). The organic layer was washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The resultant oil was chromatographed on a silica gel column using $CHCl_3$ as eluent to give a mixture of methyl (*E*)- and (*Z*)-3-bromo-2-isocyanocinnamate **1582** as a colorless oil; yield 7.2 g (90%).

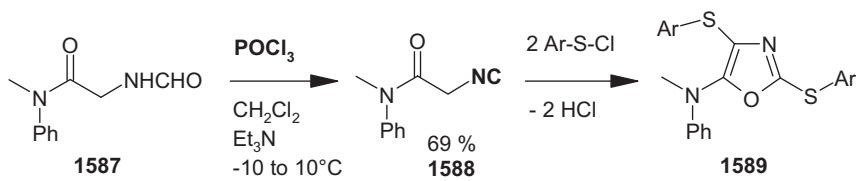
The synthesis of an imidazole C-nucleoside linked through C-4, namely 2-carbamoyl-4-(2′-deoxy-β-D-ribofuranosyl)imidazole **1586**, was achieved by way of a nine-step reaction sequence starting from 2-deoxy-3,5-di-O-*p*-tolyl-D-*erythro*-pentofuranosyl chloride. The isocyanide intermediate **1585** was obtained by dehydration of the corresponding formamide **1584** with **phosphoryl chloride**, affording the imidazole **1586** in a good yield of 86% based on formamide **1584**. Substituted imidazole nucleotides play a vital role in purine biosynthesis, and some of them



are found in the pathway leading from 1,6-ribosyldiphosphate to inosinic acid [1195].

Alkyl isocyanoacetates are important building blocks in the synthesis of oxazoles. Marcaccini [1196] employed *N*-methylisocyanoacetanilide **1588** as an isocyanoacetate derivative to prepare 2,4-diarylthio-5-*N*-alkyl-*N*-phenylaminooxazoles **1589**. **1588** was prepared in 69% yield from its formamide **1587** [1196].

Typical procedure. *N-Methylisocyanoacetanilide* **1588** [1196]: A solution of **$POCl_3$** (18.4 g, 120 mmol) in dichloromethane (20 mL) was slowly dropped into a well-stirred solution of formamido-*N*-methylacetanilide **1587** (19.2 g, 100 mmol) and triethylamine (40.35 g, 400 mmol) in dichloromethane (280 mL) maintaining the temperature at −10 °C. The reaction mixture was allowed to stand until the temperature rose to 10 °C and then stirred with a solution of Na_2CO_3 (33.9 g, 308 mmol) in water (180 mL). The resulting mixture was filtered and the phases were separated. The organic layer was washed with water (200 mL), the resulting emulsion was filtered through Celite 545 (Fluka), and the phases were separated. The organic phase was dried over $MgSO_4$ and then concentrated to dryness. The residue was redissolved in ethanol and this solution was refluxed with charcoal and then filtered. The filtrate was concentrated to dryness and the residue was recrystallized from isopropyl ether to give *N*-methylisocyanoacetanilide (12 g, 69%), mp 85–86 °C. An analytical sample was obtained from hexane; mp 86–87 °C.

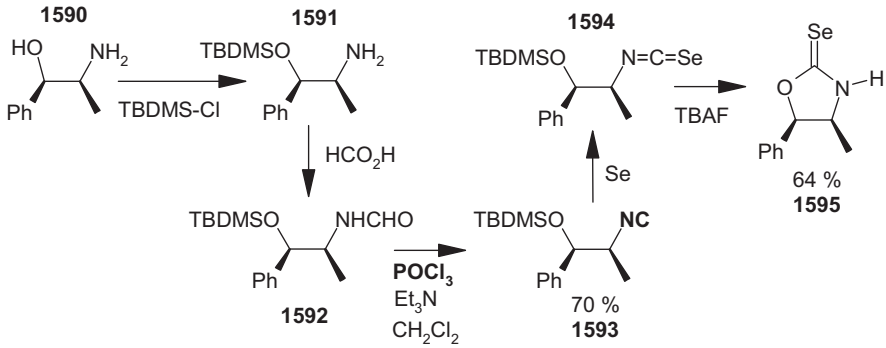


Asymmetric aldol reactions of α-keto esters (R–CO–COOMe; R = Me, *i*Bu, Ph) with methyl isocyanoacetate or *N*,*N*-dimethyl-α-isocyanoacetamide in the presence of 1 mol% of a chiral ferrocenylphosphine-gold(I) catalyst proceed enantioselectively (up to 90% *ee*) to give the corresponding oxazolines, which can be converted into optically active *β*-alkyl-*β*-hydroxyaspartic acid derivatives [1197]. Dehydration of the intermediate formamide to the corresponding isocyanide is accomplished in 97% yield with **phosphoryl chloride** at room temperature within 2 h.

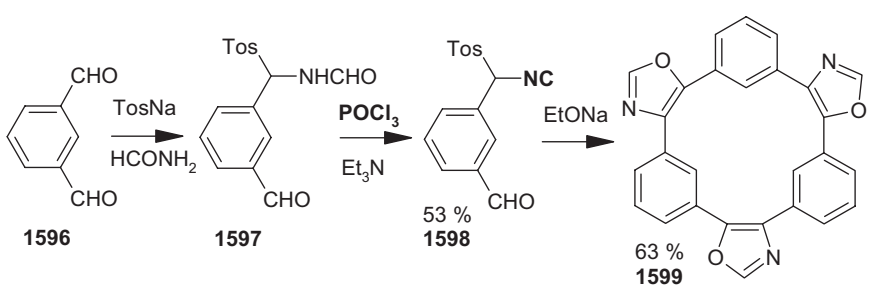
^{77}Se NMR spectroscopy needs chiral auxiliary reagents. One such reagent is (4*S*,5*R*)-(−)-4-methyl-5-phenyloxazolidine-2-selone **1595**, which reacts with (*R*,*S*)-lipoic acid and permits the detection of enantiomers [1198, 1199]. This reagent is constructed from norephedrine **1590** via its formamide **1592**, the isocyanide **1593**, and the selene **1594**; ring-closure of **1594** furnishes the oxazolidine-2-selone **1595** in 64% yield.

Typical procedure. *(1S,2R)-2-(tert-Butyldimethylsiloxy)-1-methyl-2-phenylethyl isocyanide* **1593** [1198]: In a 250-mL single-necked, round-bottomed flask fitted with a sep-

tum and a stirrer bar was placed a solution of (1*S*,2*R*)-*N*-[2-(*tert*-butyldimethylsiloxy)-1-methyl-2-phenylethyl] formamide **1592** (15.3 g, 52 mmol) in freshly distilled dichloromethane (100 mL). At 0 °C, while stirring under nitrogen, the solution was treated with **$POCl_3$** (4.86 mL, 52 mmol) and triethylamine (22 mL, 158 mmol, 3.04 mol equiv.) by means of a syringe. The mixture was stirred for 5 min, and then filtered through silica gel. The silica gel was rinsed with several portions of diethyl ether. The combined filtrate and washings were concentrated under reduced pressure and the residue was purified by flash column chromatography (diethyl ether/hexane, 1:9, *v*/*v*). Evaporation of the solvents gave (1*S*,2*R*)-2-(*tert*-butyldimethylsiloxy)-1-methyl-2-phenylethyl isocyanide **1593** as a pale-yellow oil (9.7 g, 68%); MS: $m/z = 218.1008$.

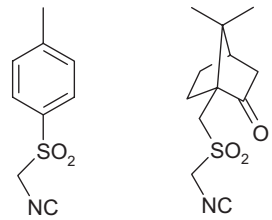


Trioxazolo[2]metacyclophane **1599** can be obtained by a smart synthesis from a cyclization reaction of 1-(3′-formylphenyl)-1-(4′-toluenesulfonyl)-methylisocyanide **1598** (3-formylphenyl-TosMIC). **1598** is obtained in 53% yield by dehydration of the corresponding formamide **1597** with **phosphoryl chloride** [1200].



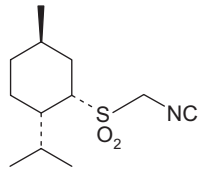
The above synthesis gives an example of the high synthetic value of 1-substituted TosMICs (*p*-toluenesulfonyl methylisocyanides). TosMIC **1600** has been created by van Leusen, who describes syntheses of some chiral sulfonylmethyl isocyanides as TosMIC analogues [1201]. Most of the isocyanides **1600–1605** are prepared by dehydration of the corresponding formamides with **phosphoryl chloride**, whereby yields of 60–85% are obtained. The chiral isocyanides are compared in terms of their ability to achieve asymmetric induction in base-mediated reactions with

acetophenone and trifluoroacetophenone. Acid hydrolysis of the intermediate 2-oxazolines gives optically active α-hydroxy aldehydes. The best asymmetric induction of the isocyanides is seen with (−)-*S*-phenyl-*N*-tosylsulfonimidoylmethyl isocyanide **1605**.

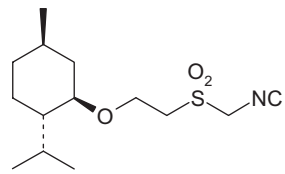


TosMIC
1600

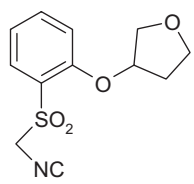
1601



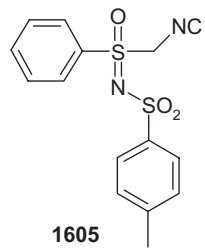
1602



1603



1604



1605

Typical procedure. *p-Toluenesulfonylmethyl isocyanide (TosMIC)* **1600** [1202]: *N-(p-Tolylsulfonylmethyl)formamide* **1609**:

$$\underset{\mathbf{1606}}{\text{Tol-SO}_2\text{Na}} + \underset{\mathbf{1607}}{\text{CH}_2\text{O}} + \underset{\mathbf{1608}}{\text{H}_2\text{NCHO}} \rightarrow \underset{\mathbf{1609}}{\text{Tol-SO}_2\text{NHCHO}} + \text{H}_2\text{O}$$

A 3-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer, a condenser, and a thermometer, was charged with sodium *p*-toluenesulfinate **1606** (267 g, 1.5 mol). After the addition of water (750 mL), a 34–37% solution of formaldehyde **1607** (350 mL, 378 g, ca. 4.4 mol), formamide **1608** (600 mL, 680 g, 15 mol), and formic acid (200 mL, 244 g, 5.3 mol), the stirred reaction mixture was heated at 90 °C. The sodium *p*-toluenesulfinate dissolved during the heating, and the clear solution was kept at 90–95 °C for 2 h. It was then cooled in an ice/salt bath with continued stirring and further cooled overnight in a freezer at −20 °C. The white solid produced was collected by suction filtration. It was washed thoroughly in a beaker by stirring with three 250 mL portions of iced water. The product was dried under reduced pressure over phosphorus pentoxide at 70 °C to provide 134–150 g (42–47%) of crude *N*-(*p*-tolylsulfonylmethyl)formamide **1609**; mp 106–110 °C. This product was sufficiently pure to be used directly in the following reaction.

p-Toluenesulfonylmethyl isocyanide (TosMIC) **1600**:

$$\underset{\mathbf{1609}}{\text{Tol-SO}_2\text{NHCHO}} + \mathbf{POCl_3} \rightarrow \underset{\mathbf{1600}}{\text{Tol-SO}_2\text{CH}_2\text{N=C}} + \text{HPO}_2\text{Cl}_2 + \text{HCl}$$

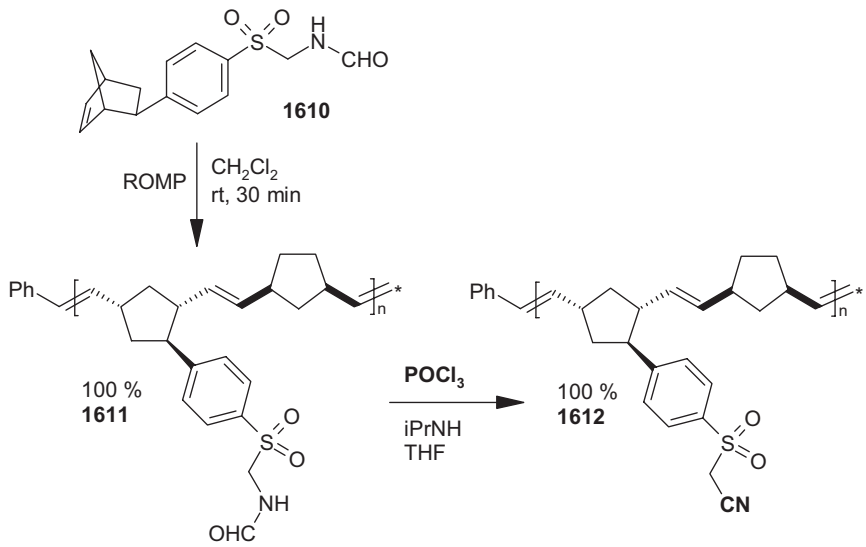
A 3-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, a thermometer, a 250-mL dropping funnel, and a drying tube, was charged with crude *N*-(*p*-tolylsulfonylmethyl)formamide **1609** (107 g, 0.50 mol), 1,2-dimethoxyethane (250 mL), anhydrous diethyl ether (100 mL), and triethylamine (350 mL, 255 g, 2.5 mol). The stirred suspension was cooled in an ice/salt bath to −5 °C. A solution of **phosphoryl chloride** (50 mL, 84 g, 0.55 mol) in 1,2-dimethoxyethane (60 mL) was then added from the dropping funnel at such a rate that the temperature remained between −5 and 0 °C. During the reaction, **1609** gradually dissolved and triethylamine salts were precipitated. On nearing completion of the reaction, the white suspension slowly turned brown. After stirring for a further 30 min at 0 °C, iced water (1.5 L) was added with continued stirring. The solid material dissolved to give a clear, dark-brown solution, and then the product began to separate as a fine, brown crystalline solid. After stirring for 30 min, the precipitate was collected by suction filtration and washed with cold water (250 mL). The wet product was dissolved in warm (40–60 °C) benzene (400 mL), the aqueous layer was removed with a separatory funnel, and the dark-brown benzene solution was dried over anhydrous magnesium sulfate. After removal of the magnesium sulfate, 2 g of activated charcoal was added, and the mixture was heated at about 60 °C for 5 min and then filtered. Petroleum ether (bp 40–60 °C) (1 L) was added to the filtrate with thorough swirling. After 30 min, the precipitate was collected by suction filtration and dried in vacuum desiccator to give 74–82 g (76–84%) of crude TosMIC **1600** as a light-brown odorless solid; mp 111–114 °C (dec.). This material could be used for synthetic purposes without further purification.

Completely white material was obtained by rapid chromatography through alumina. An analytically pure product, mp 116–117 °C (dec.), was obtained after one crystallization from methanol.

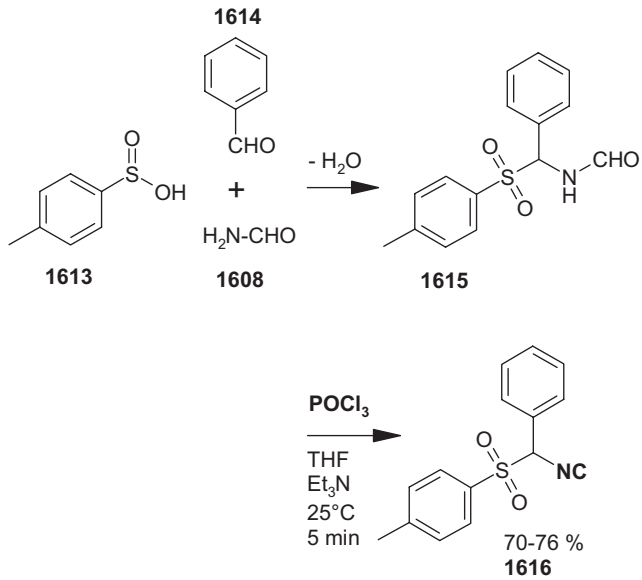
Typical procedure. *(+)-(10-Camphorsulfonyl)methyl isocyanide* **1601** [1201]: (+)-*N*-(10-Camphorsulfonylmethyl) formamide (27.3 g, 0.10 mol) was dehydrated with **$POCl_3$** according to the above procedure for the synthesis of TosMIC **1600** [1202]. After the addition of **$POCl_3$** was complete, the reaction mixture was stirred for 0.5 h at −5 °C, poured into ice/water, and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with cold 5% aqueous $NaHCO_3$ solution and cold water, dried ($MgSO_4$), and concentrated. The resulting oil was rapidly chromatographed (neutral Al_2O_3, $CHCl_3$) to provide 15.3 g (60%) of (+)-(10-camphorsulfonyl)methyl isocyanide **1601** as a light-brown viscous oil; $[\alpha]^{25}_D = +20.5$ ($c = 0.82$, $CHCl_3$).

Polymer-supported TosMIC reagent **1612** has been described and employed in an oxazole synthesis involving minimal purification [1203]. ROMPgel TosMIC reagent **1612** was prepared from the corresponding polymeric formamide **1611** by dehydration with **phosphoryl chloride** in 100% yield. **1611** was obtained by ROM polymerization of **1610** in 100% yield [1203].

Many 5-aryl-1,3-oxazoles, bearing various functions at the aryl group, can be prepared in good yields of 68–90% and with high purities from aldehydes and ROMPgel TosMIC reagent **1612**; they are purified only by filtration without any need for chromatography [1203]. This makes the method particularly well-suited for use in *combinatorial chemistry*.

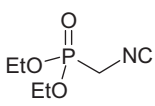


α-Substituted TosMICs are obtained by dehydration of the corresponding formamides with **phosphoryl chloride** [1204]. A detailed procedure for the preparation of α-tosyl benzyl isocyanide **1616** is given by the same authors [1205]. Tolylsulfinic acid **1613** is condensed with benzaldehyde **1614** and formamide **1608** to afford the α-tosylbenzyl formamide **1615**, which is dehydrated with **phosphoryl chloride** to afford α-tosylbenzyl isocyanide **1616** in 70–76% yield [1205].

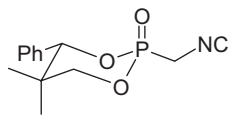


Typical procedure. *α-Tosylbenzyl isocyanide* **1616** [1205]: A 1-L, three-necked, round-bottomed flask fitted with an overhead stirrer, a 100 mL addition funnel, and a temperature probe was charged with THF (200 mL) and **1615** (27.6 g, 94.8 mmol). **Phosphoryl chloride** (17.7 mL, 190 mmol) was added and the resulting solution was stirred for 5 min at 25 °C. After cooling the solution to 0 °C, triethylamine (79.3 mL, 569 mmol) was added slowly over 30–45 min while keeping the internal reaction temperature below 10 °C. After the addition of triethylamine was complete, the reaction mixture was warmed to 5–10 °C and maintained at this temperature for 30–45 min. Ethyl acetate (140 mL) and water (140 mL) were added sequentially to the reaction mixture, stirring was continued for 5 min, and then the mixture was transferred to a separatory funnel and the aqueous layer was removed. The organic layer was washed with water (2 × 140 mL), saturated sodium hydrogen carbonate solution (140 mL), and brine (70 mL). The organic layer was transferred to a 500-mL, round-bottomed flask and concentrated on a rotary evaporator. The residue was diluted with 1-propanol (140 mL) and this solution was concentrated on a rotary evaporator to half of its original volume. The residue was cooled to 5–10 °C for 30 min and the beige solid that crystallized was collected by filtration through a Büchner funnel. The filter cake was rinsed with 1-propanol (2 × 75 mL). The beige solid was dried in vacuo for 3–4 h to give 18.1–19.7 g (70–76%) of α-tosylbenzyl isocyanide **1616**.

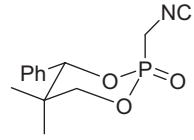
Structurally analogous to TosMIC **1600** is PhosMIC **1617**, which has a phosphonate residue instead of a sulfonate residue. Some representatives have been described by Bartlett [1206].



PhosMIC
1617



1618



1619

Van Leusen [1207] has introduced chiral isocyanomethylphosphonates into this field. Both *cis*-2-(isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane **1618** and the *trans* epimer **1619** have been prepared as potentially useful *chiral* isocyanomethylphosphonate *synthons*.

Typical procedure. *(±)-cis-2-(Isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane* **1618** [1207]: A solution of **$POCl_3$** (2.4 mL, 26.0 mmol) in dichloromethane (10 mL) was added dropwise to a stirred solution of (±)-*cis*-2-(formamidomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane (6.38 g, 22.5 mmol) and $i\mathrm{Pr_2NH}$ (9.5 mL, 67.5 mmol) in dichloromethane (130 mL) at −20 °C and the reaction mixture was stirred for 2.5 h at 0 °C. Aqueous $NaHCO_3$ (20 g in 150 mL of water) was added carefully (evolution of CO_2) and the mixture was stirred for 20 min. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were dried

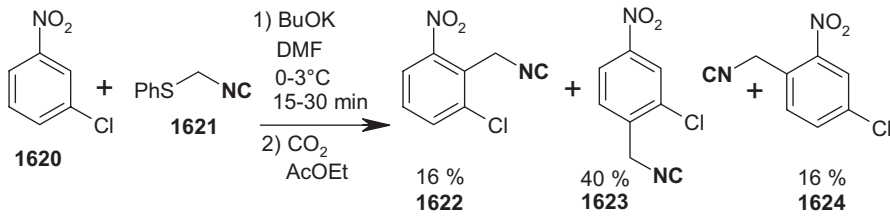
($MgSO_4$) and concentrated under reduced pressure to give 5.8 g of crude (±)-*cis*-isocyanide as a yellow solid. Column chromatography (SiO_2; EtOAc/hexane, 2:1) gave 4.52 g (17.0 mmol, 69%) of analytically pure (±)-*cis*-2-(isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane **1618** as transparent needles; mp 145 °C.

(2S,4S)-(−)-cis-2-(Isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane was prepared as described above from (2*S*,4*S*)-(+)-*cis*-2-(formamidomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane (3.5 g, 12.4 mmol) in 31% yield (1.0 g, 4.0 mmol); mp 133 °C; $[\alpha]^{20}_{578} = -46.4$ ($c = 0.5$, $CHCl_3$) [1207].

Typical procedure. *(2R,4S)-(−)-trans-2-(Isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane* **1619** [1207]: A solution of (2*S*,4*S*)-(−)-*cis*-2-(isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane (265 mg, 1.00 mol) and KF (25 mg, 0.4 mmol) in DMSO (4 mL) was heated at 100 °C for 4 h. After cooling to room temperature, water (20 mL) was added and the mixture was cooled in ice. The solid formed was collected and dried to give 250 mg (94%) of a solid mixture of (2*S*,4*S*)-(−)- and (2*R*,4*S*)-(−)-isomers (1:3). The mixture was separated by column chromatography (SiO_2; EtOAc/hexane, 2:1) and the first fraction ($R_f = 0.6$) gave, after three crystallizations from hexane/Et_2O (2:1), solid (2*R*,4*S*)-(−)-*trans*-2-(isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane **1619** (160 mg, 60%), mp 155 °C, which was pure according to NMR; $[\alpha]^{20}_{578} = -38.2$ ($c = 0.5$, $CHCl_3$).

Formamidines are interesting and important compounds that feature in the biosyntheses of imidazoles and purines. For the preparation of unsymmetrical formamidines, benzotriazol-1-ylalkyl isocyanides are versatile synthons [1208]. They are prepared from the corresponding formamides by dehydration with **phosphoryl chloride** in yields of 64–77%.

A useful tool in the direct isocyanomethylation of nitroarenes **1620** at the *ortho*- or *para*-positions to the nitro group, thereby yielding **1622–1624**, is phenylthiomethyl isocyanide **1621** [1209]. The isocyanomethyl group can be readily converted into the aminomethyl group, which is otherwise not easily accessible in the vicinity of a nitro group.



Typical procedure. *Phenylthiomethyl isocyanide* **1621** [1209]: To a stirred solution of *N*-(phenylthiomethyl)formamide (10.9 g, 0.065 mol) and triethylamine (55 g, 0.54 mol) in dichloromethane (200 mL), **$POCl_3$** (10.7 g, 0.07 mol) was slowly added dropwise while the temperature was kept at 20–30 °C. After the addition was

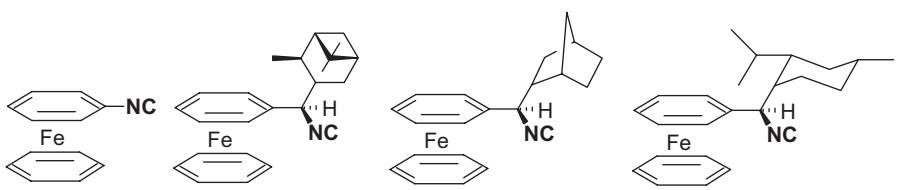
complete, the mixture was washed with 10% aq. Na_2CO_3 (3 × 50 mL), the organic phase was dried (Na_2SO_4), the solvent was evaporated, and the product was purified by fast distillation under reduced pressure. The fraction boiling at 65–73 °C/0.3 Torr was collected; yield 4.8 g (50%). The crude product could also be purified by flash chromatography (silica gel, 200–300 mesh; $CHCl_3$ as eluent). From *N*-(phenylthiomethyl)formamide (3.30 g, 0.02 mol), 1.62 g (55%) of the pure phenylthiomethyl isocyanide **1621** was obtained.

In the field of medicinal chemistry, the isocyano analogue of AZT (3′-azido-3′-deoxythymidine) has been shown to have anti-retrovirus effects. Syntheses of 3′-isocyano-3′-deoxythymidine and 3′-isocyano-2′,3′-dideoxyuridine employing **phosphoryl chloride** have been described [1210].

(*E*)-4-Alkoxy-2-amino-3-butenoic acid derivatives are of substantial interest, for they are potentially useful as inhibitors of important enzymes. During their syntheses, some isocyanides, such as 1-benzyloxy-3-isocyano-2-methoxypropane, 1-isocyano-2-methoxy-3-phenoxypropane, 1-benzyloxy-3-isocyano-2-methoxy-2-methylpropane, and 2-benzyloxymethyl-1-isocyano-2-methoxybutane are necessary, which are prepared by dehydration of the corresponding formamides with **phosphoryl chloride** [1211].

α-Amino isocyanides and α-alkylthio isocyanides are prepared from the corresponding formamides by dehydration with **phosphoryl chloride** in good yields of 81–96% [1212].

Typical procedure. *α-Morpholinobenzyl isocyanide* [1212]: *i*Pr_2NH (0.303 g, 3 mmol) was added to α-morpholinobenzyl formamide (0.22 g, 1 mmol) in dichloromethane (40 mL). **$POCl_3$** (0.20 g, 1.3 mmol) in dichloromethane was added dropwise at 0 °C with stirring. The solution was stirred for 4 h at 0 °C and then 20% aq. Na_2CO_3 (8 mL) was added slowly. After stirring at 20 °C for 1 h, dichloromethane (20 mL) and water (20 mL) were added. The organic layer was washed with water (3 × 15 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography (silica gel; CH_2Cl_2) to give a yellowish solid (0.19 g, 96%); mp 66–67 °C; IR (KBr) $\nu_{max} = 2250\ cm^{-1}$ (NC).



90 %
1625

1626

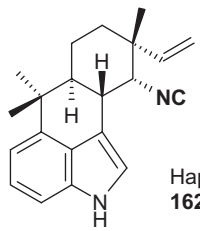
1627

1628

The ferrocenyl and ferrocenyl-1-alkyl residues continue to find various applications in organic chemistry, due to the peculiar properties of such residues. Syntheses of isocyano ferrocene **1625** [1213] and of 1-isocyano-1-alkyl ferrocene compounds **1626–1628** [1214] have been described, all of which involve the standard procedure of dehydration of the corresponding formamide with **phosphoryl chloride**.

A high-yield access to cyanides from isocyanides is given by the *isocyanide–cyanide rearrangement* [1215, 1216]. Isocyanides are converted to cyanides by flash thermolysis in excellent yields (often near 100%) under strict retention of configuration. The employed isocyanides were prepared by standard procedures from the corresponding formamides by the use of **phosphoryl chloride**. A 1-homocubyl isocyanide was synthesized in 51% yield [1216].

A total synthesis of the marine indole alkaloids (±)-hapalindoles, e.g. **1629**, has been described, in which the isocyanide function is formed in the last step by dehydration of a formamide precursor with **phosphoryl chloride**; yields are 73–85% [1217, 1218].

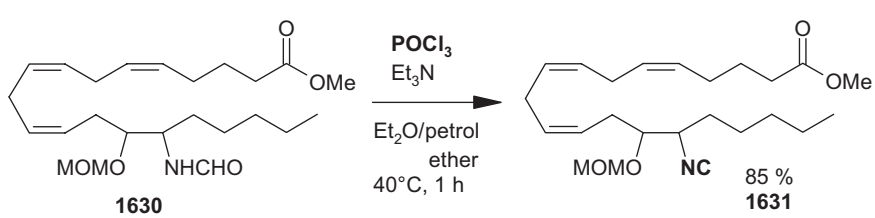


Hapalindole U
1629

Typical procedure. *(±)-Hapalindole U* **1629** [1218]: To a cooled (−20 °C) solution of the formamide (6.5 mg) in pyridine (0.4 mL) under Ar atmosphere was added **phosphoryl chloride** (11 μL) and the mixture was stirred at the same temperature for 40 min. Addition of saturated aq. $NaHCO_3$, extraction with 10% MeOH/CH_2Cl_2, standard work-up, and PTLC (hexane/EtOAc, 4:1) afforded (±)-hapalindole U **1629** (4.5 mg, 73%) as colorless needles; mp 240–242 °C (CH_2Cl_2/hexane).

During the synthesis and evaluation of a series of arachidonate epoxy inhibitors, **1631** was prepared in 85% yield by dehydration of the formamide **1630** with **phosphoryl chloride** [1219].

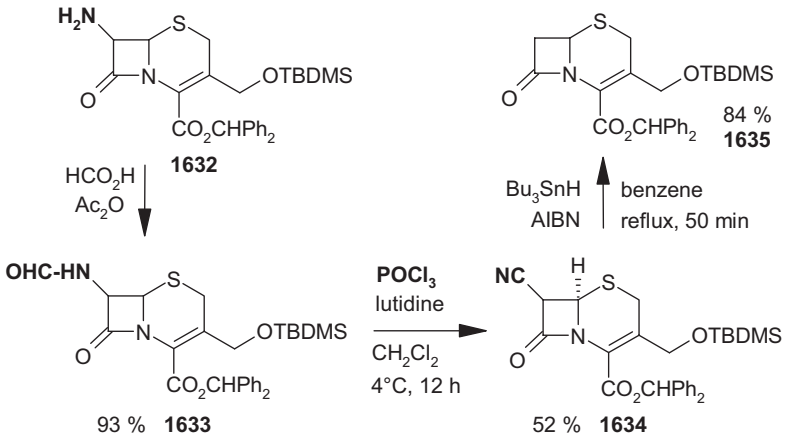
The synthesis of 1,6-di-*O*-(2-isocyano-3-methylcrotonyl)-D-mannit (*antibiotic A 32390 A*) required diisocyano compounds as intermediates, which were prepared from the corresponding formamides by dehydration with **phosphoryl chloride** in yields of 54–74% [1220].



1630 **1631**

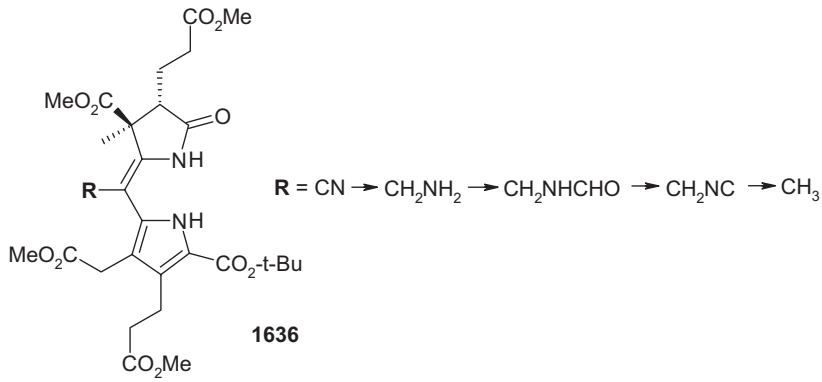
Another type of isocyanide reaction is the facile reductive removal of the amino group in **1632**, via the formamide and the isocyanide. It is exploited in a synthesis

of 3-cyano-3-cephem derivatives from readily available 7β-aminocephalosporanic acid. The 7β-isocyanide **1634** is prepared by dehydration of the formylated 7β-amino cephalosporanic acid derivative **1633** with **phosphoryl chloride**. Removal of the 7β-isocyano group is carried out with tributyltin hydride and affords the deaminated cephem derivative **1635** [1093].



Typical procedure. *Diphenylmethyl 7β-isocyano-3-tert-butyldimethylsilyloxymethyl-3-cephem-4-carboxylate* **1634** [1093]: To a solution of diphenylmethyl 7β-formamido-3-*tert*-butyldimethylsiloxymethyl-3-cephem-4-carboxylate (1.0 g, 1.9 mmol) in dichloromethane (15 mL), 2,6-lutidine (0.81 mL, 7 mmol) and **phosphoryl chloride** (0.22 mL, 2.3 mmol) were added at 0 °C. After being kept at 4 °C for 12 h, the mixture was washed successively with 5% aqueous citric acid (15 mL), 5% aqueous sodium hydrogen carbonate solution (15 mL), and saturated brine (15 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on Florisil (100–200 mesh, 20 g) eluting with dichloromethane to give a yellow oil. This was triturated with petroleum ether and filtered to give diphenylmethyl 7β-isocyano-3-*tert*-butyldimethylsilyloxymethyl-3-cephem-4-carboxylate **1634** as a yellow powder (450 mg, 52%); mp 93–95 °C (dec.); $[\alpha]^{25}{}_D = +29.5$ ($c = 1$, $CHCl_3$).

Typical procedure. *Diphenylmethyl 3-tert-butyldimethylsilyloxymethyl-3-cephem-4-carboxylate* **1635** *(removal of the isocyano group)* [1093]: To a solution of diphenylmethyl 7β-isocyano-3-butyldimethylsilyloxymethyl-3-cephem-4-carboxylate **1634** (100 mg, 0.19 mmol) in benzene (1.0 mL), azobisisobutyronitrile (1.0 mg) and tributyltin hydride (0.21 mL, 0.21 mmol) were added at room temperature. The mixture was refluxed for 50 min and then the volatiles were evaporated in vacuo. The residue was chromatographed on a silica gel column (4.5 g) eluting with dichloromethane to give an oil, which on crystallization from hexane gave colorless crystals of diphenylmethyl 3-*tert*-butyldimethylsilyloxymethyl-3-cephem-4-carboxylate **1635** (79 mg, 84%); mp 105–110 °C (dec.); $[\alpha]^{25}{}_D = +55.8$ ($c = 1$, $CHCl_3$).

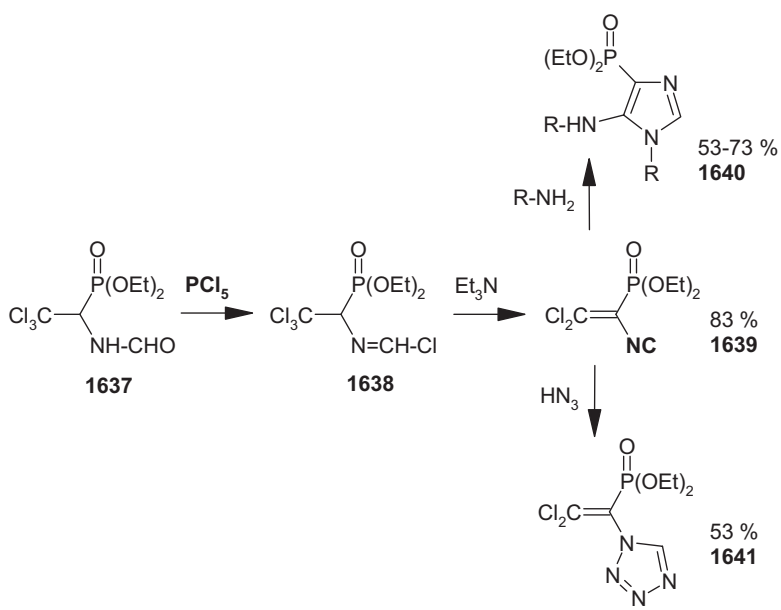


1636

The same method has been applied in the synthesis of the western building block **1636** of *vitamin* B_{12}, relevant to *vitamin* B_{12} biosynthesis. The original cyano group is reduced to an amino group, this is formylated, the resulting formamide is dehydrated with phosphoryl chloride forming the isocyanide, which is reductively cleaved [1221]. For the dehydration of the formamide with **phosphoryl chloride**, 1,8-bis(dimethylamino)naphthalene was chosen as an auxiliary base.

Phosphorus pentachloride

Also interesting in the field of physiologically active substances are phosphorylated imidazoles **1640**. These can be prepared from an isocyanide intermediate **1639** with primary amines, while reaction of the isocyanide with hydrazonic acid yields phosphorylated tetrazole **1641**. The phosphorylated isocyanide **1639** is obtained by dehydration of the corresponding formamide **1637** with **phosphorus pentachloride** via an imine intermediate **1638** [1222].



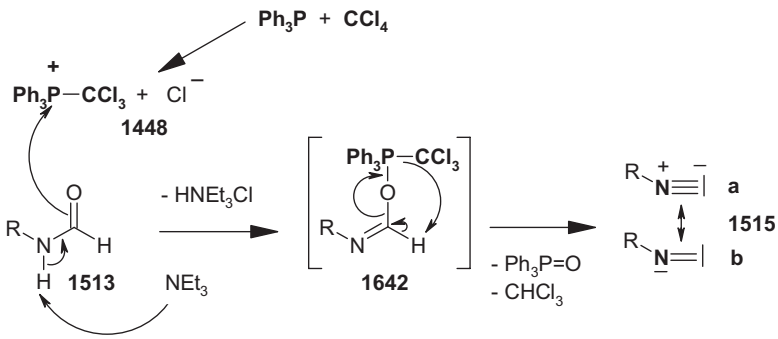
1637 **1638**

Typical procedure. *Diethyl [(2,2-dichloro-1-isocyano)ethenyl]-phosphonate* **1639** [1222]: A mixture of the formamide **1637** (7.81 g, 25 mmol) and **phosphorus pentachloride** (5.21 g, 25 mmol) in anhydrous tetrachloromethane (50 mL) was stirred at 50 °C for 30 min. The solvent was then evaporated under reduced pressure and the residue was redissolved in absolute Et_2O (200 mL). The solution was stirred at 0–5 °C, and triethylamine (6.07 g, 60 mmol) was very slowly added dropwise. After standing overnight in a refrigerator, the $Et_3N{\cdot}HCl$ deposited was filtered off, the solvent was evaporated from the filtrate, and the residue was chromatographed on a silica gel column (EtOAc); yield 83%.

Similar results were achieved by the same research group by using **triphenylphosphine** instead of phosphorus pentachloride; the reaction proceeds via a formimide intermediate [1223]. The yield of the diethyl [(2,2-dichloro-1-isocyano)-ethenyl] phosphonate was 85%.

4.5.2.4 Triphenylphosphine/Haloalkanes

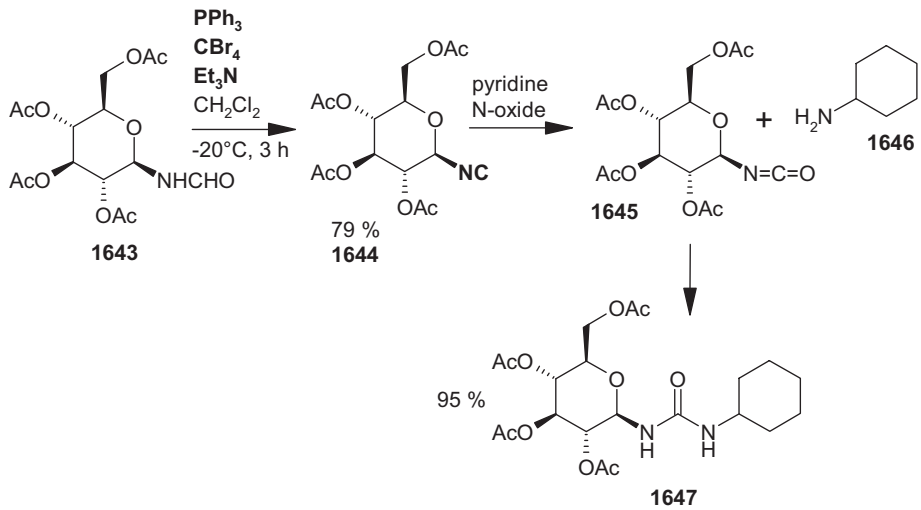
Appel's dehydration reagent can be successfully applied to the synthesis of isocyanides **1515** from formamides **1513** [987, 1224]. The dehydration reaction with **triphenylphosphine**/**tetrachloromethane** proceeds smoothly and furnishes generally good yields of 89–91% for alkyl, benzylic, and aryl isocyanides **1515** [1224].



General procedure. *Isocyanides* **1515** [1224]: Equimolar amounts of monosubstituted formamide **1513**, **tetrachloromethane**, triethylamine, and **triphenylphosphine** (20% excess) are dissolved in 1,2-dichloroethane, dichloromethane, or chloroform (0.1 mol in 100 mL solvent) and warmed at 60 °C for 2.5 h. The solvent is then distilled off at slightly reduced pressure and the residue is extracted with petroleum ether (5×). After distilling off the petroleum ether, the residue is fractionated (yields of isocyanides **1515** are 89–91%).

Systematic investigations have been performed in which the haloalkane was varied in order to optimize the method [1103, and refs. cited therein]. It was found that TosMIC **1600** could be prepared in 60% yield from formamide with **triphenylphosphine**/**1,2-dibromotetrachloroethane** at a significantly lower temperature of −10 °C within a drastically reduced reaction time of <1 min [1103]. This is in contrast to the reaction with tetrachloromethane at 85 °C, which affords a complex reaction mixture after 50 h [1103]. Usually, TosMIC is prepared with phosphoryl chloride (see the relevant section).

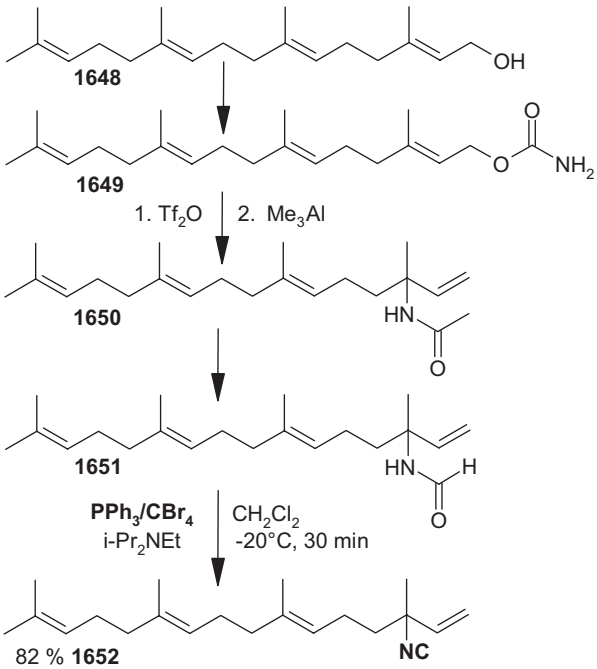
The α- and β-glycosyl isocyanates **1645** can be obtained by oxidation of glycosyl isocyanide **1644**, which, in turn, is produced by stereospecific dehydration with **triphenylphosphane**/**tetrabromomethane** of the corresponding glycosyl formamide **1643** [1225]. The reaction of α- and β-glycosyl isocyanates with amines proceeds smoothly to provide α- and β-glycosyl ureas with retention of the stereochemistry at the anomeric position. This method allows the synthesis of a building block that can be used for the construction of glycopeptide mimics with urea-glycosyl linkages **1647**.



Typical procedure. *2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl isocyanide* **1644** [1225]: To a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl formamide **1643** (2.80 g, 7.47 mmol), triethylamine (4.48 mL, 32.2 mmol), and **tetrabromomethane** (8.00 g, 24.1 mmol) in dichloromethane (85 mL) cooled to −20 °C under nitrogen atmosphere was added a solution of **triphenylphosphine** (6.30 g, 24.1 mmol) in dichloromethane (5 mL). After stirring at −20 °C for 3 h, the solution was diluted with diethyl ether, washed with aqueous ammonium chloride solution, water, and brine, and dried over anhydrous sodium sulfate. Concentration and purification by chromatography on silica gel (diethyl ether/hexane, 2:1) gave 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl isocyanide **1644** (0.86 g, 79%).

A synthesis of the marine diterpene *geranyllinaloisocyanide* **1652** has been successfully accomplished by a novel regioselective allylamine construction, which is achieved by an allyl cyanate-to-isocyanate rearrangement **1649** → **1650**. The resulting formamide **1651** is dehydrated with **triphenylphosphane**/**tetrabromomethane** to give the *geranyllinaloisocyanide* **1652** in 82% yield [1226].

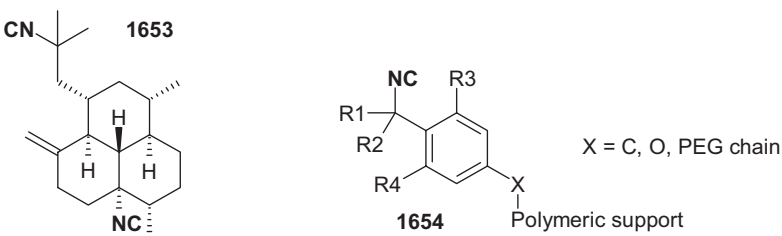
Typical procedure. *Geranyllinaloisocyanide* **1652** [1226]: A solution of the formamide **1651** (204 mg, 0.64 mmol), **tetrabromomethane** (594 mg, 1.79 mmol), and diisopropylethylamine (0.60 mL, 3.45 mmol) in dichloromethane (7 mL) was cooled to −20 °C. To this solution was added dropwise a solution of **triphenylphosphine**



(423 mg, 1.33 mmol) in dichloromethane (ca. 1.5 mL). After stirring at −20 °C for 30 min, the reaction mixture was diluted with water. The aqueous layer was extracted with diethyl ether and the combined organic phases were washed with 0.5 M HCl, saturated aq. sodium hydrogen carbonate solution, and brine, dried, and concentrated under reduced pressure to afford the crude product (844 mg), which was purified by chromatography on silica gel eluting with diethyl ether/hexane (1:50, *v*/*v*) to provide the isocyanide, geranyllinaloisocyanide **1652** (156 mg, 82% yield).

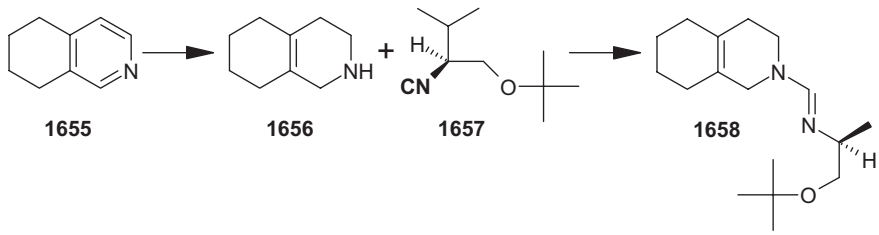
A total synthesis of the natural product *(±)-8,15-diisocyano-11(20)-amphilectene* **1653** has been accomplished. In the last step, the two isocyano functions were formed from the corresponding formamides by dehydration with **triphenylphosphine**/**tetrachloromethane** [1227].

Polymeric reagents bearing an isocyanide group **1654** cannot be prepared easily. A patent application *"New functionalized polymeric reagents with an isonitrile moiety for solution and solid-phase synthesis"* details syntheses of such isocyanides **1654** from the corresponding formamides according to an Appel reaction with **triphenylphosphane**/**tetrachloromethane** and triethylamine [1228].



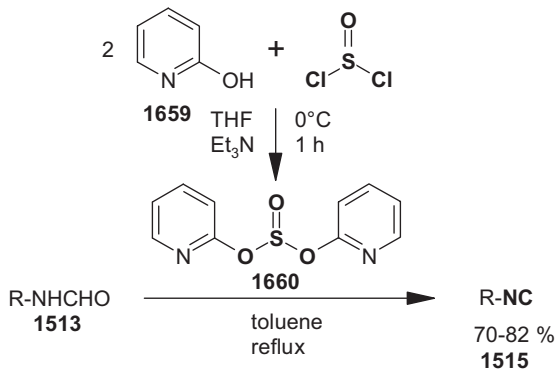
4.5.2.5 Sulfurous Chlorides and Derivatives

The formation of the chiral formamidine **1658** from octahydroisoquinoline **1656** and the isocyanide **1657** derived from valinol *tert*-butyl ester gives an intermediate with high chirality-inducing potential, which, through further reaction steps, allows an asymmetric synthesis of *(+)-morphinane* with high enantiomeric purity (>98% *ee* in the decisive asymmetric reaction step) [1229]. The isocyanide **1657** is obtained in 85% yield by dehydration of the corresponding formamide with **thionyl chloride**.



Typical procedure. *Isocyanide of (S)-valinol tert-butyl ether* **1657** [1229]: *N*-Formylvalinol *tert*-butyl ether (8.52 g) was dissolved in dry DMF (50 mL), the solution was cooled to −50 °C, and then a solution of **thionyl chloride** (5.4 g) in DMF (20 mL) was added. After the addition was complete, the solution was warmed to −30 °C and then cooled to −50 °C once more. While stirring the solution at −50 °C, solid K_2CO_3 (9.6 g) was added. The colorless mixture was allowed to warm to room temperature overnight. The crude material was extracted by partitioning it between water and diethyl ether and drying the combined organic layers with $MgSO_4$. The crude product was bulb-to-bulb distilled at 78 °C (3 Torr), yielding 6.5 g (85%) of the isonitrile **1657**; $[\alpha]^{24}_D = +1.76$ ($c = 1.19$, $CHCl_3$).

Di-2-pyridyl sulfite 1660 is presented as a useful reagent for the preparation of isocyanides under mild conditions [1230]. Yields given in the table therein are good (70–82% for ''test'' alkyl, benzylic, and aryl isocyanides). The reagent (prepared from 2-hydroxypyridine **1659** and thionyl chloride) is rather unstable, but ''can be stored in a refrigerator for a week without decomposition'', according to the authors.



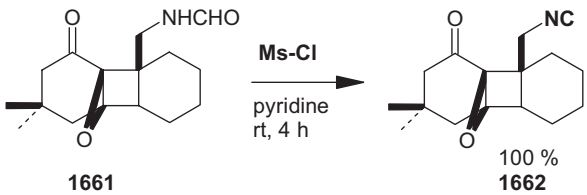
A patent application in this field *"Process for preparing 2-(2,6-dichloroanilino)-imidazole"* has been filed [1231], using **sulfuryl chloride** as the dehydration reagent for the formamide.

4.5.2.6 Sulfonyl Chlorides and Anhydrides

Methanesulfonyl chloride (MsCl)

A stereoselective construction of the *taxane BC* substructure requires an intermediate isocyano function in **1662**, which is obtained in 100% yield from the formamide **1661** by dehydration with **mesyl chloride** [1232].

Typical procedure. *Isocyanide* **1662** [1232]: To a solution of **1661** (227 mg, 1 mmol) in pyridine at 0 °C under argon, **mesyl chloride** (0.155 mL, 2 mmol) was added dropwise. After stirring at the same temperature for 1 h and then at room temperature for 4 h, the reaction mixture was diluted with dichloromethane, washed with aqueous 0.5 N hydrochloric acid and water, dried (Na_2SO_4), and passed through a short column of silica gel. Removal of the solvent left 258 mg (100%) of **1662** as a waxy solid; mp 85–89 °C; IR (neat): $\nu_{max} = 2150, 1710\ cm^{-1}$.

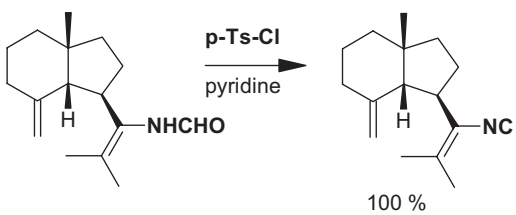


1661 **1662**

p-Tolylsulfonyl chloride (TsCl)

A total synthesis of the sesquiterpenoids *(−)-axamide-4* **1663** and *(−)-axisonitrile-4* **1664**, affording both natural products, has been accomplished in eleven steps [1233]. From the view of a chemist, it is remarkable that both the isocyanide and its chemical precursor molecule formamide are naturally occurring. The transformation of *(−)-axamide-4* into *(−)-axisonitrile-4* is carried out with ***p*-tosyl chloride** in 94% yield.

dl-Axisonitrile-4 **1664** can also be synthesized in 100% yield from *dl-axamide-4* **1663** by dehydration with ***p*-tosyl chloride** [1234]. *(±)-Axisonitrile-4* is prepared in the same way from *(±)-axamide* in 87% yield as a white solid [1235].



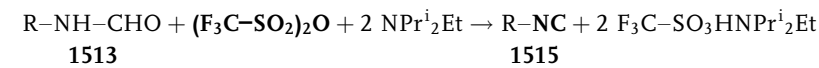
axamide-4 **1663** axisonitrile-4 **1664**

Typical procedure. *dl-Axisonitrile-4* **1664** [1234]: To a solution of dl-axamide-4 **1663** (344 mg, 1.39 mmol) in dry pyridine (5 mL), ***p*-tosyl chloride** (535 mg, 2.8 mmol) was added at room temperature. The mixture was stirred at room temperature for 15 h, then cooled to 0 °C and crushed ice (3 g) was added. The resulting mixture was stirred at 0 °C for 30 min, diluted with petroleum ether/diethyl ether, (1:1; 50 mL), and washed with brine (3 × 10 mL). The combined aqueous layers were extracted with petroleum ether (3 × 15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on 30 g of silica gel (eluting with petroleum ether, bp 35–60 °C) to give 0.32 g (100%) of dl-axisonitrile-4 **1664** as a pale-yellow solid; mp 61–63 °C.

A synthesis of *17β-amino-5α-androstan-3α-ol* from *epiandrosterone* has been performed [1236]. The intermediate 17*β*-isocyano-5*α*-androstan-3*β*-ol was formed from the corresponding formamide by dehydration with ***p*-tosyl chloride** [1236].

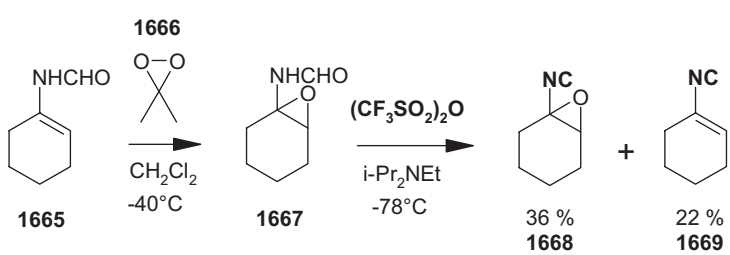
Trifluoromethanesulfonic anhydride (triflic anhydride)

A communication from Baldwin on **triflic anhydride** (trifluoromethanesulfonic anhydride) describes this reagent as being superior for the conversion of formamides and vinyl formamides to isocyanides and vinyl isocyanides in yields of about 80% [1237]. Dehydration with **triflic anhydride** seems to be the method of choice for preparing epoxy isocyanides (see below).



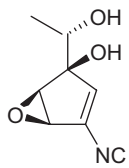
General procedure. *Isocyanides* **1515** [1237]: To a stirred solution of the formamide **1513** (0.055 mmol) in dry dichloromethane (5 mL) under argon at −78 °C is added dry diisopropylethylamine (0.058 mL, 0.33 mmol) followed by **triflic anhydride** (0.014 mL, 0.082 mmol). The pale-yellow solution is stirred at −78 °C for 20 min and then quenched by the addition of 5% aq. $NaHCO_3$ solution. The solution is allowed to warm to room temperature, and the organic layer is separated, washed with 5% aq. $NaHCO_3$ solution, and dried (Na_2SO_4). Removal of the solvent followed by flash chromatography (appropriate solvent) gives the product **1515**.

Using the **triflic anhydride** method, the biomimetic *theonellin isocyanide* has been synthesized from its formamide in 89% yield [1238]. *Theonellin* is a marine sesquiterpene.

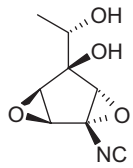


The **triflic anhydride** method is particularly well-suited for the synthesis of epoxy isocyanides (isocyano oxiranes) [1239]; yields vary between 30% and 68%. Epoxy isocyanide **1668** was prepared by Baldwin from vinyl formamide **1665** using an epoxidation/dehydration sequence. Attempted direct epoxidation of vinyl isocyanide **1669** (formation of epoxy isocyanides is always accompanied by the formation of vinyl isocyanides) failed to give any of the desired product. The epoxidation step could be achieved with dimethyldioxirane **1666** [Note: magnesium sulfate induces decomposition of dioxirane]. The use of **triflic anhydride** for the dehydration of the intermediate epoxy formamide **1667** proved essential to the success of this reaction; attempted use of *phosgene-based reagents* in this step failed to give any of the target product [1239]. Further experimental data relating to this method are described in a synthesis of *(−)-isonitrin B* [1240].

The first enantioselective synthesis of *(−)-isonitrin B* **1670**, the parent of a small family of isonitrile antibiotics having compact but highly functionalized (and highly reactive) cyclopentane rings, has been described [1240]. In the penultimate reaction step, the corresponding formamide is dehydrated with **triflic anhydride** forming the *O*-protected isocyanide in 52% yield; deprotection affords *(−)-isonitrin B* **1670** in 68% yield.



Isonitrin B
Deoxytrichoviridin
1670



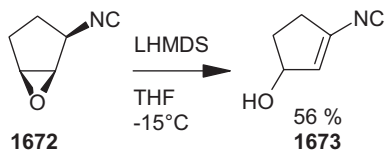
Isonitrin C
Trichoviridin
1671

Typical procedure. *O,O′-Di(TBS)-(−)-isonitrin B* (*derivative of* **1670**) [1240]: To a stirred solution of the dry formamide (38 mg, 0.092 mmol) in dichloromethane (6 mL) under nitrogen at −78 °C was added dry diisopropylethylamine (0.096 mL, 0.55 mmol) followed by a solution of **triflic anhydride** (39 mg, 0.14 mmol) in dichloromethane (1 mL). The solution was stirred at −78 °C for 40 min, and then the reaction was quenched by the addition of saturated aq. $NaHCO_3$ solution (4 mL) at −78 °C. The mixture was allowed to warm to room temperature, the layers were separated, and the organic phase was washed with further dichloromethane and saturated aqueous $NaHCO_3$ solution. The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was chromatographed to provide the isonitrile *O,O′*-di(TBS)-(−)-isonitrin B (19 mg, 0.048 mmol, 52% yield) as a white solid. TLC: R_f (5% MTBE/petroleum ether) = 0.53; $[\alpha]_D = -18.1$ ($c = 0.5$, $CHCl_3$); IR: $\nu_{max} = 2115\ cm^{-1}$ (NC).

A total synthesis of the related *(±)-trichoviridin* **1671**, a naturally occurring epoxy-isonitrile, has also been described [1241]. The dehydration step to afford the *O*-protected *trichoviridin* was accomplished with **triflic anhydride**.

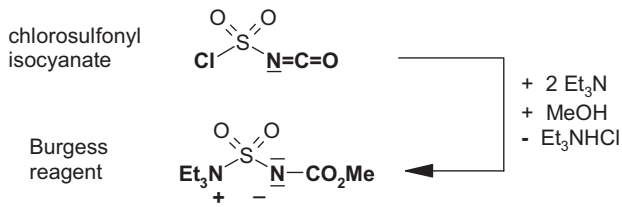
The isomerization of epoxy isocyanide **1672** to hydroxy-vinyl isocyanide **1673** has been described [1242]. This isomerization is base-mediated and the stereochemistry can be reversed by switching from lithium diisopropylamide (LDA) to lithium bis(trimethylsilyl)amide (LHMDS). The **triflic anhydride** method was applied to prepare **1672** [1242].

4.5.2.7 Tailored Reagents



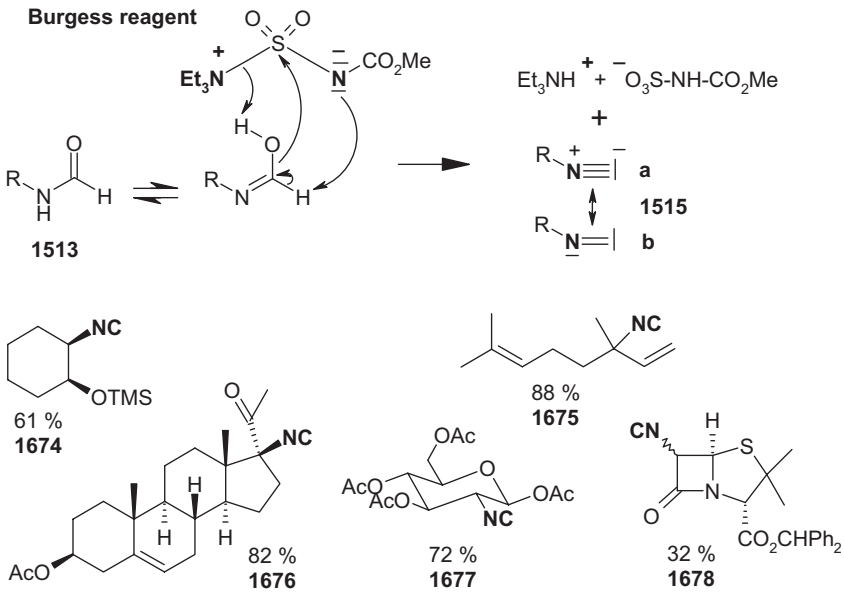
While the dehydration reagents discussed thus far in this Section are all well known, or at least are existing compounds, some reagents have been specifically developed for dehydration reactions.

Burgess reagent (methyl carboxysulfamoyl triethylammonium hydroxide inner salt)
The **Burgess reagent** is a chlorine-free advancement of **chlorosulfonyl isocyanate** (see also Section 4.5.1), in which the two active sites are reacted with triethylamine and methanol, respectively, forming appropriate residues. This achieves the required level of reactivity and the right degree of selectivity, and thus enables consistent reaction mechanisms.



A wide range of isocyanides can be synthesized in generally good yields from the corresponding formamides using the **Burgess reagent** [1243]. A further advantage is that β-trialkylsilyl residues are not attacked during the dehydration reaction. Halides often desilylate such residues, but the **Burgess reagent** is halide-free. It is worth mentioning that the isocyanide function can even be formed at the extremely sensitive penicillanic ester; thus **1678** is obtained in a remarkable yield of 32%.

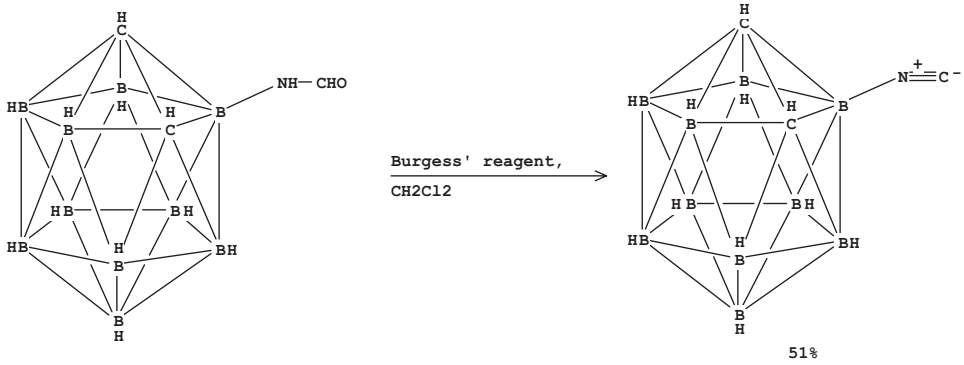
Typical procedure. *3-Isocyano-3,7-dimethylocta-1,6-diene* **1675** [1243]: **Burgess reagent** (0.35 g, 1.5 mmol) was added in a single portion to a solution of the formamide (0.18 g, 1 mmol) in dry dichloromethane (25 mL). The solution was heated at reflux under a nitrogen atmosphere until TLC analysis indicated that the formamide



had been consumed (80 min). The resulting mixture was then cooled, diluted with dichloromethane (20 mL), washed with water (2 × 20 mL), and dried ($MgSO_4$). Evaporation of the solvent in vacuo and dry flash chromatography of the residue on silica gel 60, eluting with 5% dichloromethane in hexane, gave 3-isocyano-3,7-dimethyl-octa-1,6-diene **1675** (0.14 g, 88%) as a clear oil, which darkened rapidly on standing.

The **Burgess reagent** has been applied to the synthesis of isonitrile carborane derivatives. This approach involved the dehydration of both boron- and carbon-derived formamides. The products could be used as ligands for the synthesis of transition metal based boron neutron capture therapy and synovectomy agents (BNCS) and targeted radiopharmaceuticals. Isonitrile carborane **1680** has been prepared in 51% yield by dehydration of the formamide **1679** with the Burgess reagent under mild conditions (5 h reaction time at room temperature) [1244].

Typical procedure. *3-Isonitrile-1,2-dicarba-closo-dodecaborane* **1680** [1244]: The formamide **1679** (0.422 g, 2.25 mmol) was added to dry dichloromethane (30 mL) with stirring. The **Burgess reagent** (1.07 g, 4.50 mmol) was added to the solution as a solid under argon atmosphere. The homogeneous reaction mixture was maintained at ambient temperature under dry nitrogen for 5 h, at which time TLC indicated the complete consumption of the starting material. The solvent was removed by rotary evaporation leaving a white solid, which was redissolved in dichloromethane (25 mL) and extracted with distilled water (2 × 25 mL). The aqueous layers were combined and further extracted with dichloromethane (25 mL) and diethyl ether (25 mL). All the organic phases were pooled, dried over

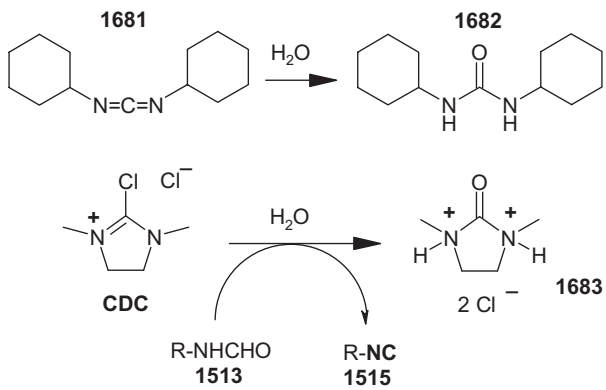


1679 **1680**

sodium sulfate, and gravity filtered. The clear, colorless filtrate was concentrated in vacuo and the crude product was purified by chromatography on silica gel (gradient: 100% hexanes to 25% CH_2Cl_2 in hexanes). A by-product (24%; $R_f = 0.79$, 5% MeOH in CH_2Cl_2) eluted prior to the isonitrile. Single crystals of the isonitrile **1680** were obtained by slow evaporation of an ethanolic solution at −10 °C. Yield 0.191 g (51%); TLC: $R_f = 0.51$ (5% MeOH in CH_2Cl_2); mp 136 °C; IR (NaCl): $\nu_{max} = 2622$, 2606 (BH), 2139 cm^{-1} (NC).

2-Chloro-1,3-dimethylimidazolinium chloride (CDC)

2-Chloro-1,3-dimethylimidazolinium chloride (**CDC**) [1137, 1245] represents an alternative reagent to carbodiimides such as dicyclohexylcarbodiimide **1681**, which, although inexpensive and usable under mild conditions, is less reactive and the dicyclohexylurea **1682** it produces presents difficulties in the purification of products. The reagent **CDC** is a solid, mp 95–100 °C, is stable to oxygen, but unstable in the presence of moisture, producing hydrochloric acid. It is stable at room temperature for over a year when kept desiccated. **CDC** represents a powerful dehy-



drating equivalent to DCC under nearly neutral conditions [1137, 1245]. Dehydration reactions of formamides **1513** forming isocyanides **1515** have been described for four model compounds; yields were 25–78%. For mechanistic aspects, see Section 4.5.1.

General procedure. *Isocyanides* **1515** [1137]: To a solution of the formamide **1513** (1 equiv.) and **CDC** (1 equiv.) in an appropriate solvent, the amine (2 equiv.) was added dropwise at room temperature. The reaction mixture was stirred at room temperature (under reflux in some cases), then poured into water and extracted with dichloromethane. The organic solution was successively washed with 5% HCl, saturated aq. $NaHCO_3$, and water. It was dried ($MgSO_4$) and concentrated to dryness. The residue was purified by short column chromatography (SiO_2) to give the isocyanide **1515**.

For another application **CDC** has been employed in specific dehydrosulfurization reactions to synthesize modified guanidines as potential *chiral superbases* [1100].

4.5.3 Carbodiimides

In World War II, penicillins proved their worth as antibiotics, curing infections in a hitherto unprecedented manner. There was a great need for penicillins, which could by no means be met by isolation from cultures of the fungus *penicillium notatum*. It was a challenge for organic chemists to synthesize penicillins, but due to the extreme sensitivity of the molecules under nearly all conditions (even in distilled water at pH 7!) they proved very elusive. The key step was forming the *β*-lactam moiety, for which all known common coupling methods failed (attempts to prepare penicillin G provided isolated product yields of just 0.008%). In 1959, Sheehan succeeded in achieving the total synthesis of penicillin V **1687**; the key step of *β*-lactam formation was performed with **dicyclohexylcarbodiimide** (**DCC**) in a yield of 5% [1246]. Three years later, the same group were able to increase the yield of the key intermediate **1686** to 67% in an improved synthesis using **1684** and **diisopropylcarbodiimide 1685** for the key step, but applied another synthetic strategy to obtain penicillin V **1687** [1247].

Because of the convincing results even in penicillin chemistry, due to the smooth reaction conditions, carbodiimides and particularly **DCC** became common coupling reagents in natural compound and peptide chemistry. In combination with binucleophiles, such as *N*-hydroxysuccinimide or *N*-hydroxybenzotriazole, the method is racemization-free [1248]. Other frequent applications are in esterifications and general dehydration reactions, and, more recently, in carbodiimide-mediated *multicomponent reactions* [1251] (see Section 4.5.3.5). All these reactions proceed through activated intermediates **1689**. Thus, compounds with a carboxylic function **1688** can be coupled with a nucleophilic compound **1690** to afford the coupled product **1691** under extremely mild conditions. The resulting by-product dicyclohexylurea **1693**, however, is difficult to separate because of its ambivalent solubility properties, which usually complicate the whole work-up procedure.

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4.5.3
Carbodiimides

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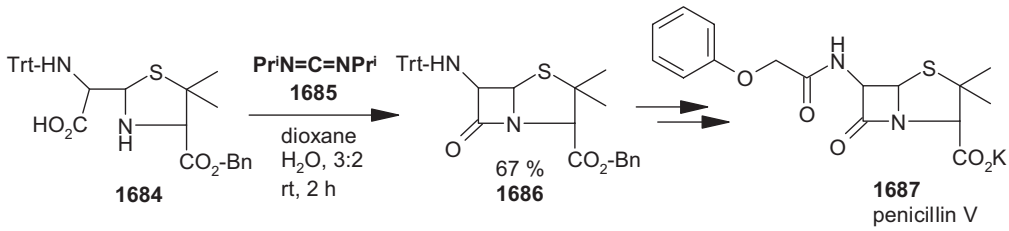
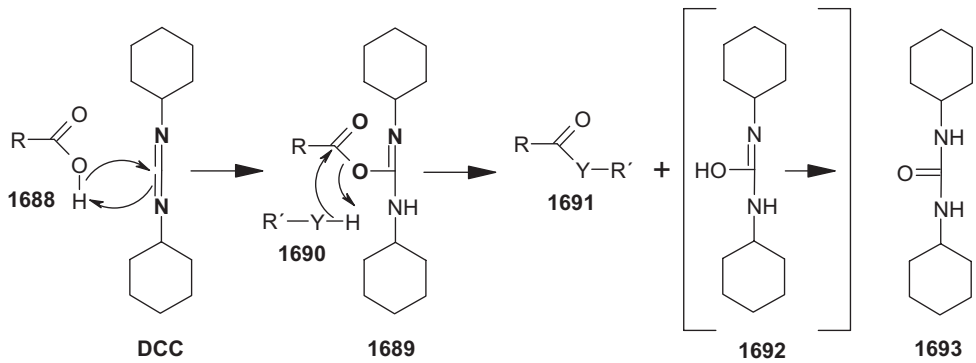




1688: carboxylic acid, amino acid, peptide acid

1690: alcohol, amine, amino acid ester, peptide ester

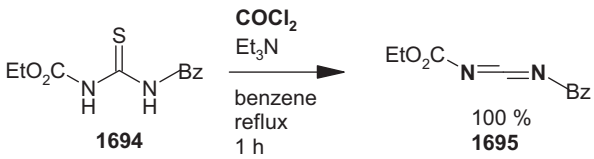
1691: ester, amide, peptide ester

Reviews on the synthesis and chemistry of carbodiimides are given in [1248–1250]. Carbodiimides are mainly synthesized in one of three ways: from ureas or thioureas, from isocyanates, or from isocyanides. Several reagents have been employed in carbodiimide synthesis: **phosgene** [1252, 1253], **dimethylphosgeniminium chloride** [1254], **triphosgene** [561, 562], **phosphorus pentoxide** [1255], **phosphoryl chloride** [1256], **triphenylphosphine dibromide** [758, 1257–1261], **triphenylphosphine/tetrahalomethanes** [1262, 1263], **iminophosphoranes** [1264–1277], **Mitsunobu reagent** [1278, 1279], ***p*-tosyl chloride** [1280, 1281], and **CDC** [1137]; **oxidative additions** have also been used [1282–1284].

4.5.3.1 Phosgene and Equivalents

Phosgene

In a new and efficient synthesis of *guanosine*, 1-alkoxycarbonyl-3-arylmethylcarbodiimides serve as essential reagents. They can be synthesized in excellent yields from thioureas using **phosgene** [1252]. 1-Ethoxycarbonyl-3-benzylcarbodiimide **1695** has been prepared quantitatively from the corresponding thiourea **1694** within 1 h at 80 °C.

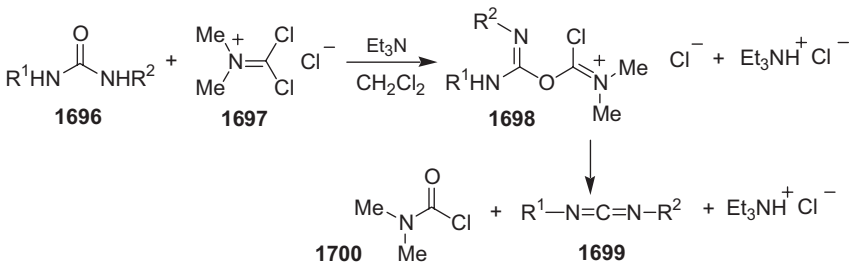


Typical procedure. *1-Benzyl-3-ethoxycarbonylcarbodiimide* **1695** [1252]: A solution of **1694** (7.16 g, 30 mmol) in anhydrous benzene (80 mL) under nitrogen was treated with dry triethylamine (10.5 mL, 75 mmol), and then **phosgene** (for a *safe source*, see Chapter 7) (28.5 mL of a 12.5% solution in anhydrous benzene, 33 mmol) was added dropwise. The resulting thick mixture was heated at reflux under nitrogen for 1 h, allowed to cool to room temperature, and then rotary evaporated to dryness in a hood. The residue was treated with anhydrous diethyl ether (200 mL) and filtered through Celite, and the Celite was washed with an additional 100 mL of anhydrous diethyl ether. The combined ether solutions were rotary evaporated in vacuo, and the resulting yellowish oil was pumped free of residual benzene at room temperature to afford 6.1 g (quantitative) of **1695** as a pale-yellow oil. IR (neat): $\nu_{max} = 1720$, 2180 cm^{-1}. Freshly prepared **1695** was employed undistilled (substantial decomposition takes place during attempted distillation) in subsequent reactions.

DCC has been prepared in high yield (98%) and with high purity by a two-step process involving dehydration of dicyclohexylurea with **phosgene** in MTBE and addition of NH_3 (g) with removal of NH_4Cl by filtration, as presented in a patent application [1253] (see also Section 4.5.3.5, Table 4.48).

Dimethylphosgeniminium chloride (Viehe's salt)

A variety of substituted ureas **1696** (Table 4.47) react with **dimethylphosgeniminium salts 1697** in the presence of triethylamine to directly afford the corresponding carbodiimides **1699** in good yields. The only side product of the reaction is *N,N*-dimethylcarbamoyl chloride **1700**, and this can be easily removed by evaporation under reduced pressure [1254].



General procedure. *Carbodiimides* **1699** *from ureas* **1696** [1254]: To a suspension of the urea **1696** (1 equiv.) and **dimethylphosgeniminium salt 1697** (1 equiv.) in dichloromethane (0.3 M) at 0 °C under argon atmosphere was added a solution of

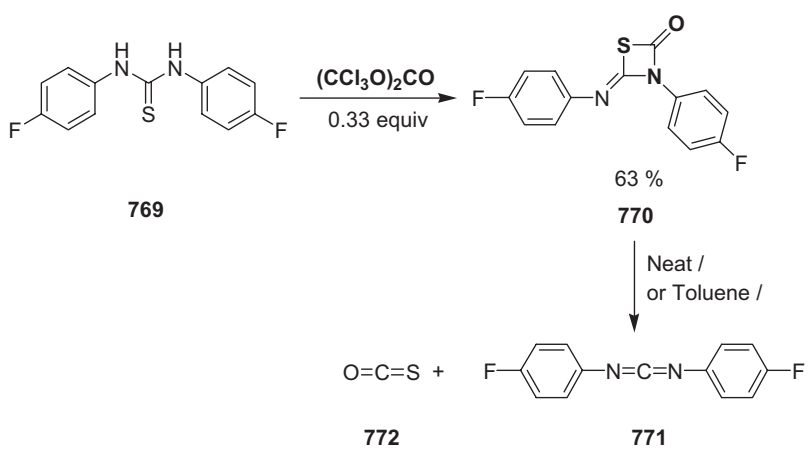
Tab. 4.47. Preparation of carbodiimides **1699** [1254].

Entry	R^1	R^2	*Isolated yields (%)*
1	*t*-butyl	1-naphthyl	90
2	cyclohexyl	1-naphthyl	75
3	cyclohexyl	phenyl	95
4	cyclohexyl	cyclohexyl	100
5	*t*-butyl	*t*-butyl	85
6	1-naphthyl	-(*R*)-(*i*Pr)CHCOOEt	100

triethylamine (0.3 M, 2 equiv.) in dichloromethane. The reaction was followed by TLC (disappearance of the starting urea). After removal of the solvent, hexane was added to the reaction mixture and the resulting suspension was triturated for 30 min. The precipitated triethylammonium chloride formed was filtered off and the filtrate was concentrated under reduced pressure. The resulting carbodiimides **1699** were sufficiently pure to be used directly, but could be made analytically pure by column chromatography or short-path distillation.

Triphosgene

As already presented in Section 4.3.2.4, it has been found that thiazetidinones (such as **770**) are highly versatile intermediates allowing the facile conversion of thioureas into carbodiimides in good yields [561]. 3-(4-Fluorophenyl)-1,3-thiazetidin-4-one-2-(4-fluorophenyl)imine **770** was obtained in 63% yield as the main product from the reaction of *N*,*N*′-bis(4-fluorophenyl)thiourea **769** with one-third of an equivalent of **triphosgene**.



Heating **770** either neat or in refluxing toluene affords *N*,*N*′-di-4-fluorophenylcarbodiimide **771** as the sole product (presumably with evolution of O=C=S **772**) [562].

4.5.3.2 Phosphorus-Based Reagents

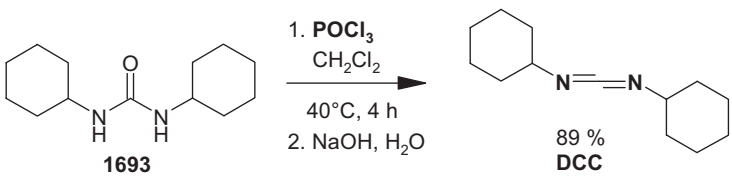
Phosphorus pentoxide

Dialkyl- and diarylcarbodiimides bearing cyclohexyl, phenyl, *p*-chlorophenyl, and *p*-ethoxyphenyl residues have been synthesized from the corresponding ureas with **phosphorus pentoxide** in pyridine, charged with sand, under reflux [1255]. DCC has been prepared this way within 2.25 h in 76% yield (see also Section 4.5.3.5, Table 4.48).

Typical procedure. *Dicyclohexylcarbodiimide* **DCC** [1255]: A stirred mixture of *N*,*N*′-dicyclohexylurea (19.7 g), **phosphorus pentoxide** (100 g), sand (175 g), and pyridine (700 mL) was refluxed for 2.25 h. Stirring was no longer possible after about 30 min. The mixture was filtered and the residue was extracted with pyridine (100 mL). Pyridine was removed from the combined solutions on a flash evaporator, and the residual oil was extracted with boiling petroleum ether (bp 60–80 °C) (2 × 100 mL), and then with diethyl ether (100 mL). The combined extracts were washed with iced water (3 × 80 mL), dried over calcium chloride, and filtered. The solvents were removed from the filtrate under reduced pressure to give 17.4 g of an oil, which on distillation yielded 13.7 g (76%) of a clear liquid; bp 143 °C (3.5 mmHg), which solidified in the receiver; mp 34–35 °C.

Phosphoryl chloride

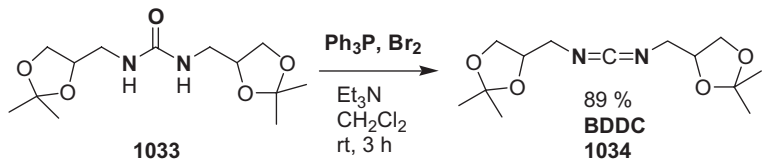
Another method for producing DCC from dicyclohexylurea is a two-step process using **phosphoryl chloride** in dichloromethane at 40 °C for 4 h under non-basic conditions followed by removal of acidic components with aq. sodium hydroxide. This method, which gives an 89% yield of DCC, has been presented in a patent application [1256] (see Section 4.5.3.5, Table 4.48).



Triphenylphosphine dibromide

A general method for the synthesis of carbodiimides, isonitriles, ketimines, and aldehydes using **triphenylphosphine dibromide** has been developed. Diphenyl and dicyclohexyl carbodiimides are formed from *N*,*N*′-disubstituted ureas in the presence of triethylamine at 80 °C in 90 min in yields of 66–75% [1257].

As already mentioned in Section 4.3.4.1, bis-4-(2,2-dimethyl-1,3-dioxolyl)methyl carbodiimide (BDDC) **1034**, a useful reagent for residue-free esterifications, racemization-free peptide couplings, and dehydrations, has been prepared in 89% yield from the symmetrical urea **1033** by dehydration with **triphenylphosphine dibromide** at room temperature [758].



Typical procedure. *Bis-4-(2,2-dimethyl-1,3-dioxolyl)methyl carbodiimide* (**BDDC**) **1034** [758]: **Triphenylphosphine** (131 g, 110 mol%) was dissolved in dry dichloromethane (1.1 L), and the resulting solution was cooled to 0 °C. **Bromine** (25.7 mL, 80 g, 110 mol%) was added dropwise over a period of 15 min, and then triethylamine (157 mL, 114 g, 250 mol%) was added in one portion. Solid urea **1033** (131 g, 0.45 mol) (for the preparation of **1033**, see Section 4.3.4.1) was added to the yellow suspension in small portions over a period of 50 min. The resulting brown slurry was stirred at room temperature for an additional 3 h, then diluted with hexane (500 mL), and the solids were filtered off and washed with diethyl ether. The solvents were evaporated from the combined filtrate and washings to leave a brown slurry, which was resuspended in fresh diethyl ether and again diluted with hexane. The solids were filtered off and washed with diethyl ether as before. This procedure of evaporation, suspension, and filtration was repeated until no further solids precipitated (usually four cycles). The final viscous, clear brown oil, crude **1034**, was bulb-to-bulb distilled at reduced pressure to give pure **BDDC 1034** (107 g, 89%) as a pale-yellow oil. It could be stored indefinitely at 0 °C under argon; bp 115–125 °C, 0.3 mmHg; IR: $\nu_{max} = 2130\ cm^{-1}$.

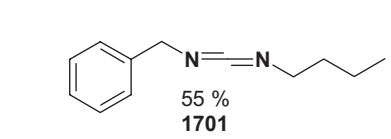
This procedure also gives a good example of the purification of carbodiimides.

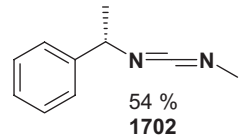
Carbodiimides **1701**–**1703** and **1707** were each prepared in 52–56% yield by dehydrating the appropriate urea with **triphenylphosphine dibromide**. **1701** is used as a peptide coupling reagent in an inverse Merrifield approach to peptide synthesis [1258]. **1702** is applied in forming guanidines for enantiomerically pure guanidine-catalyzed asymmetric nitroaldol reaction [1259]. **1703** is employed as an efficient sulfur-transfer agent based on *N*-acetylcysteine methyl ester **1704**, forming a thiazole **1706** via intermediate **1705** [1260]. **1707** is an intermediate in a new synthesis of *ranitidine*, in which a nitromethenylation at the carbodiimide carbon affords **1708** [1261].

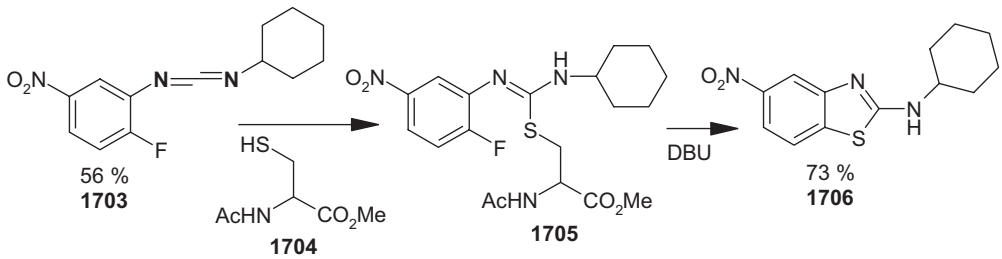
Triphenylphosphine/tetrahalomethanes

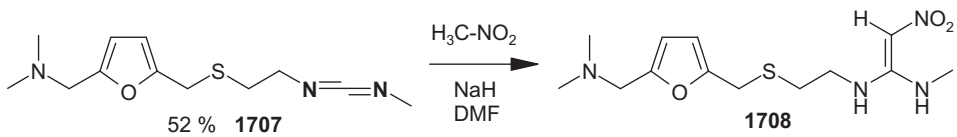
Appel applied the dehydration reagent **triphenylphosphine**/**tetrachloromethane** to the synthesis of carbodiimides from ureas under extremely mild conditions, and obtained yields of 87–92% [1262].

General procedure. *Carbodiimides from ureas or thioureas* [1262]: Equimolar amounts of urea or thiourea, **tetrachloromethane**, triethylamine, and **triphenylphosphine** (in 20% excess) are warmed to 40 °C under stirring in dry dichloromethane. Within 1 h, the initial suspension (ureas are only sparingly soluble in dichloromethane) is transformed into a clear, yellow-brown solution. After a further 1.5 h, most of the resulting triethylammonium chloride has crystallized. The solvent is evaporated at

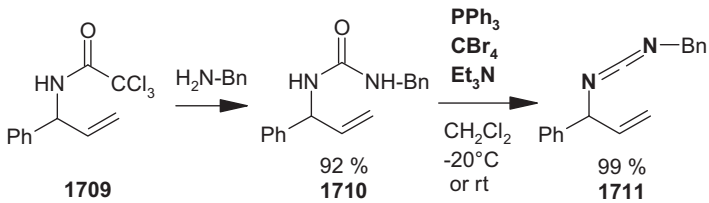


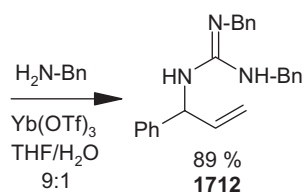






room temperature and the residue is extracted four times with petroleum ether (40–60 °C). After evaporation of the solvent, the residue is fractionated. Carbodiimides are identified by their ^{1}H NMR spectra and boiling points.





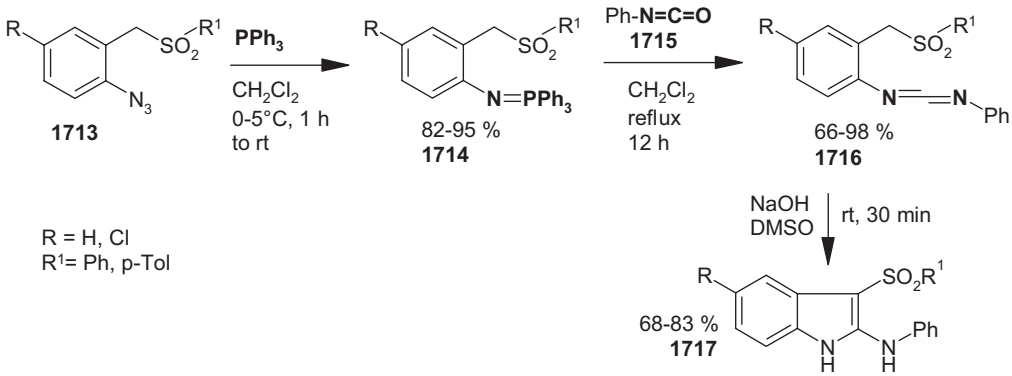
Among many naturally occurring compounds, such as *tetrodotoxin*, the guanidinium group plays an important role in expressing biological activity due to its cationic nature. It can be directly prepared from trichloroacetamide **1709** via allyl benzyl urea **1710** by dehydration with **triphenylphosphine**/**tetrabromomethane** and triethylamine at room temperature or −20 °C affording carbodiimide **1711** in 99%

yield. Reaction of **1711** with benzylamine in the presence of $Yb(OTf)_3$ (10%) in THF/water gives the guanidine **1712** in 89% yield [1263].

Iminophosphoranes

An often used method for the preparation of carbodiimides is the aza-Wittig reaction of an isocyanate with an **iminophosphorane**. The latter can be formed either from an amine and **triphenylphosphine dibromide** or from an azide and **triphenylphosphine**.

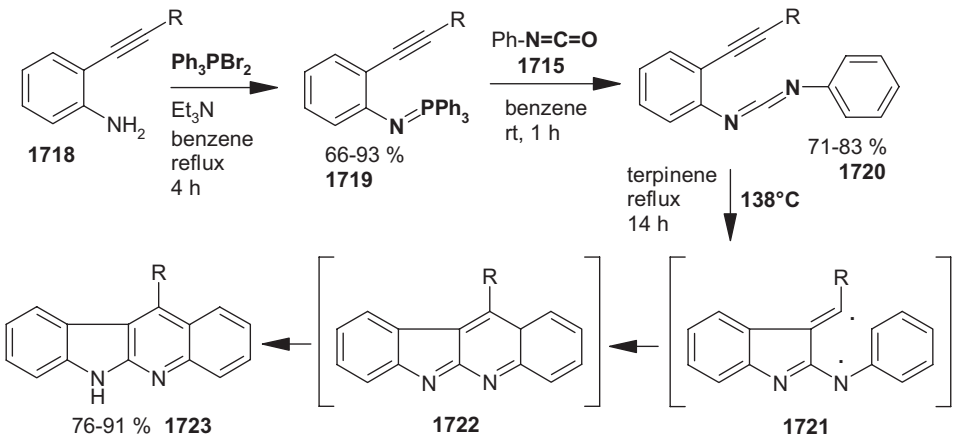
Syntheses of 2-anilino-3-arylsulfonylindoles from 2-arylsulfonylmethylanilines have been accomplished by reaction of **iminophosphoranes** with phenyl isocyanate [1264]. **Iminophosphoranes 1714** are obtained in 82–95% yield by treating the azides **1713** with **triphenylphosphine**. Carbodiimides **1716** are formed in 66–98% yield by the aza-Wittig reaction of **iminophosphoranes 1714** and phenyl isocyanate **1715**. The ring closure of carbodiimides **1716** under strongly basic conditions to afford 2-anilinoindoles **1717** proceeds in 68–83% yield.



General procedure. *N-[2-(Arylsulfonylmethyl)phenyl]-N′-phenylcarbodiimides* **1716** [1264]. *2-(Arylsulfonyl)methyl-N-(triphenylphosphoranylidene)anilines* **1714** *from azide*: To a cooled (0–5 °C) and stirred solution of **triphenylphosphine** (7.86 g, 30 mmol) in dichloromethane (150 mL) was added a solution of azide **1713** (30 mmol) in dichloromethane (150 mL) under N_2. The mixture was stirred at 0–5 °C for 1 h and then slowly warmed to room temperature. The solvent was removed in vacuo and the residue was treated with benzene to precipitate the product, which was collected by filtration and recrystallized from benzene/hexane to give a white powder or from chloroform/hexane to give white needles of **1714**.

N-[2-(Arylsulfonylmethyl)phenyl]-N′-phenylcarbodiimides **1716**: To a stirred solution of **iminophosphorane 1714** (4.0 mmol) in dichloromethane (50 mL), phenyl isocyanate **1715** (480 mg, 4.0 mmol) was added at room temperature under N_2. After the mixture had been refluxed for 12 h, the solvent was removed in vacuo. The residue was washed with hexane and then recrystallized from dichloromethane/hexane to give **1716** as white needles or as a white powder.

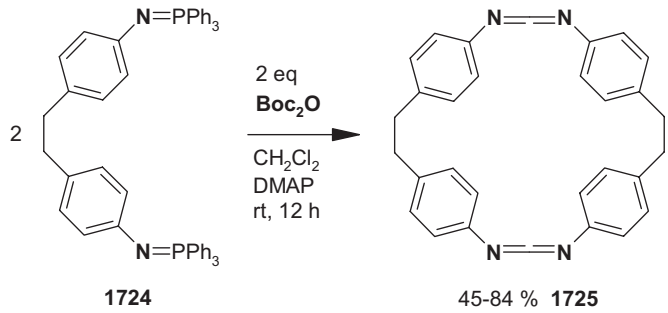
The construction of tetracyclic 6*H*-indolo[2,3-*b*]quinolines **1723** by generating two annulated rings via biradicals **1721** is achieved using an yne-carbodiimide **1720** [1265]. This is obtained in 71–83% yield by aza-Wittig reaction of phenyl isocyanate **1715** with an **iminophosphorane 1719**, which is formed in 66–93% yield by the reaction of an amine **1718** and **triphenylphosphine dibromide**. An annulation reaction of the yne-carbodiimide **1720** by thermolysis at 138 °C creating biradical **1721** and proceeding via **1722** affords the 6*H*-indolo[2,3-*b*]quinolines **1723** in yields of 77–91% [1265].



Typical procedure. *N-(2-Ethynylphenyl)-N′-phenylcarbodiimide* **1720** (R = H) [1265]. *2-(1-Propynyl)-N-(triphenylphosphoranylidene)benzenamine* **1719** (R = H): To **Ph_3PBr_2** (4.22 g, 10.0 mmol) were added amine **1718** (R = H) (1.31 g, 10.0 mmol), anhydrous triethylamine (2.78 mL), and anhydrous benzene (100 mL) under nitrogen atmosphere. The reaction mixture was heated under reflux for 4 h. The white triethylammonium bromide that precipitated was removed by filtration, and the filtrate was concentrated. The residue was purified by column chromatography (silica gel; 40–60% diethyl ether in hexanes) to furnish 2.776 g (7.10 mmol, 71%) of **1719** (R = H) as colorless crystals.

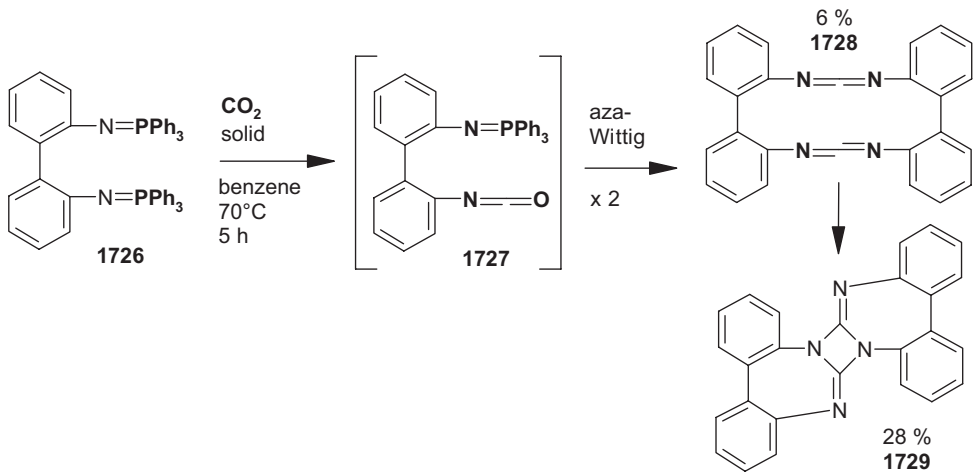
N-(2-Ethynylphenyl)-N′-phenylcarbodiimide **1720** (R = H): To **1719** (R = H) (0.377 g, 1.00 mmol) under nitrogen atmosphere, a solution of phenyl isocyanate **1715** (0.119 g, 1.00 mmol) in anhydrous benzene (15 mL) was added via a cannula at room temperature. After 1 h, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (silica gel; 5% diethyl ether in hexanes) to furnish 0.181 g (0.83 mmol, 83%) of **1720** (R = H) as a yellow oil; IR (neat): ν_{max} = 2258, 2139, 2103 cm^{-1}.

A method for preparing cyclic bis(carbodiimide)s **1725** in up to 84% yield by reacting **iminophosphoranes 1724** with **Boc_2O** in the presence of DMAP at room temperature for 12 h has been developed [1266].



Typical procedure. *Bis(carbodiimide)* **1725** [1266]: To a suspension of the **bis(iminophosphorane) 1724** (0.69 mmol) in dry dichloromethane (20 mL) was added **Boc_2O** (0.30 g, 1.39 mmol) and DMAP (0.083 g, 0.69 mmol). The resultant mixture was stirred under nitrogen at room temperature for 12 h. The solvent was then removed under reduced pressure, the resulting material was suspended in anhydrous ethanol (10 mL), and the solid was collected by filtration, air-dried, and recrystallized from dichloromethane to give the bis(carbodiimide) **1725** in 84% yield; mp 104–106 °C; pale-yellow crystals; IR (Nujol): $\nu_{max} = 2139\ cm^{-1}$.

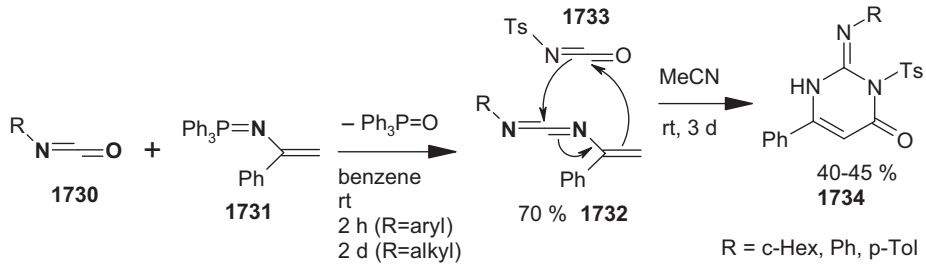
The preparation and intramolecular cyclization of other bis(carbodiimide)s has been described. Treatment of 2,2′-bis[(triphenylphosphoranylidene)amino]-biphenyl **1726** with **carbon dioxide** provides, through an intermolecular aza-Wittig reaction, the bis(carbodiimide) **1728** (6% yield), which reacts further in an intramolecular cyclization to form diazetidine **1729** (28% yield) [1267].



Typical procedure. *Bis(1,1′-biphenyl-2,2′-diyl)bis(carbodiimide)* **1728** *and diazetidine* **1729** [1267]: To a solution of 2,2′-bis[(triphenylphosphoranylidene)amino]biphenyl **1726** (1.0 g, 1.4 mmol) in dry benzene (40 mL) cooled to −78 °C was added an ex-

cess of solid **carbon dioxide**. The resulting mixture was transferred to a sealed glass tube, which was heated at 70 °C for 5 h. The solvent was subsequently removed under reduced pressure, and the remaining material was chromatographed on a column of silica gel (*n*-hexane/dichloromethane, 1:1) to give bis(1,1′-biphenyl-2,2′-diyl)bis(carbodiimide) **1728** (6% yield; white prisms from dichloromethane; mp 205–207 °C; IR (Nujol): $\nu_{max} = 2158\ cm^{-1}$) and the diazetidine **1729** (28% yield).

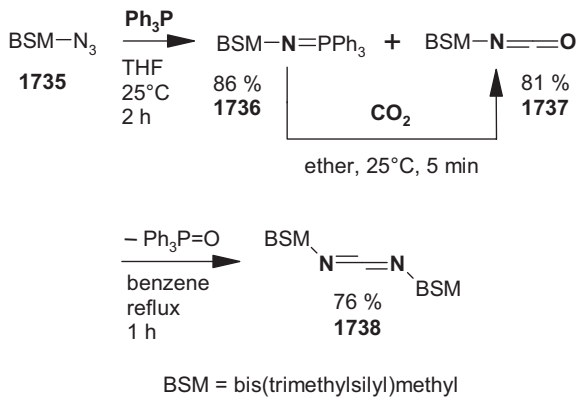
N-Vinylcarbodiimides **1732**, useful building blocks for the synthesis of *N*-heterocycles, are prepared from isocyanates **1730** and **vinyl-iminophosphoranes 1731** in yields of about 70% [1268]. *N*-Vinylcarbodiimides **1732** react with tosyl isocyanate **1733** in a hetero-Diels–Alder reaction to form pyrimidines **1734** in 40–45% yield.



General procedure. *N-Vinylcarbodiimides* **1732** [1268]: To a solution of **iminophosphorane 1731** (5.27 mmol) in dry benzene (50 mL) was added dropwise a solution of the isocyanate **1730** (5.83 mmol) in benzene (50 mL). The reaction mixture was stirred at room temperature for 1–2 h (R = aryl, *β*-styryl) or for 1–2 d (R = alkyl). Evaporation of the solvent and trituration of the residue with hexane afforded triphenylphosphine oxide as colorless crystals, which were filtered off. Removal of the solvent from the filtrate and short column chromatography of the residue (silica gel; benzene/hexane, 1:5) gave the carbodiimides **1732** as viscous oils or solids in yields of around 70%, which were immediately used in the next reaction. Attempts to purify them by distillation under reduced pressure failed.

The functional group $(Me_3Si)_2CH–N=$ (BSM-N=) is a versatile group in organic synthesis with three potential active sites at C and N. Particularly interesting are BSM-*N*-heterocumulenes such as BSM-carbodiimides. These are prepared from **BSM iminotriphenylphosphorane 1736** and BSM isocyanate **1737** by an aza-Wittig reaction, affording the *N*,*N*′-bis-(BSM-carbodiimide) **1738** in 76% yield.

Typical procedure. *N,N′-Bis[bis(trimethylsilyl)methyl]carbodiimide* **1738** [1269]. *Bis-(trimethylsilyl)methyliminotriphenylphosphorane* **1736**: Bis(trimethylsilyl)methyl azide **1735** (10.00 g, 49.65 mmol) and **triphenylphosphine** (13.00 g, 49.56 mmol) were stirred in THF (50 mL) at 25 °C for 2 h. The solvent was then removed under reduced pressure, and the crude reaction mixture was treated with *n*-pentane. Filtration gave **1736** (18.65 g, 86%).



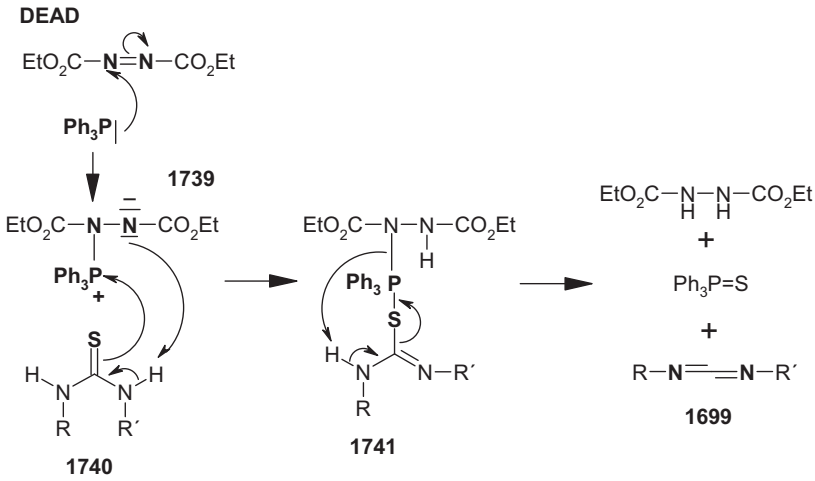
Bis(trimethylsilyl)methyl isocyanate **1737**: **Carbon dioxide** was bubbled into a solution of **1736** (6.00 g, 13.77 mmol) in diethyl ether (25 mL) at 25 °C for 5 min. The Ph_3PO produced was filtered off, and the solvent was removed from the filtrate. Fractional distillation of the oily residue (63–65 °C, 20 Torr) gave 2.25 g (81%) of **1737**.

N,N′-Bis[bis(trimethylsilyl)methyl]carbodiimide **1738**: Iminophosphorane **1736** (0.85 g, 1.95 mmol) and isocyanate **1737** (0.39 g, 1.94 mmol) were reacted in refluxing benzene (25 mL) for 1 h. The solvent was then removed in vacuo, and the crude reaction mixture was treated with *n*-pentane (50 mL). After filtration of the Ph_3PO produced and evaporation of the solvent, flash chromatography of the residue (SiO_2; *n*-pentane/Et_2O, 14:1) gave 0.53 g (76%) of carbodiimide **1738** as an oil.

By aza-Wittig reactions of **iminophosphoranes** with isocyanates, carbodiimide-mediated syntheses of pyrrole and indole derivatives [1270], pentasubstituted pyridines [1271], pyrimidine derivatives [1272–1274], bis(*β*-ferrocenylvinyl)carbodiimide [1274], amino-tetrazolyl-deoxythymidines [1275], the marine alkaloid *leucettamine B* [1276], and aza-analogues of *aplysinopsins* [1277] have also been accomplished.

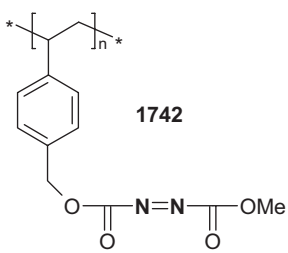
Mitsunobu reagent (diethyl azodicarboxylate/triphenylphosphine)

Alkyl- and aryl carbodiimides can be prepared under mild conditions from thioureas with **diethyl azodicarboxylate**/**triphenylphosphine** (**Mitsunobu reagent**), typically in yields of around 80%; the by-products are triphenylphosphine sulfide and diethyl hydrazodicarboxylate [1278]. The active intermediate in this system is the betaine **1739**, which is formed from **diethyl azodicarboxylate** (**DEAD**) and **triphenylphosphine**. Driven by its charge distribution and its chalcogenophilicity, **1739** reacts with the thiourea **1740** to form the P,S bond in **1741**. This energy-rich molecule stabilizes by decomposition into three molecules, namely the two by-products, triphenylphosphine sulfide and diethyl hydrazodicarboxylate, and the desired carbodiimide **1699**. Diphenylcarbodiimide **1699** (R = R′ = Ph) was prepared from *N,N′*-diphenylthiourea **1740** (R = R′ = Ph) with **DEAD** and **triphenylphosphine** in 65% yield [1278].



Typical procedure. *Diphenylcarbodiimide* **1699** (R = R′ = Ph) [1278]: **Triphenylphosphine** (2.62 g, 0.01 mol) in THF (10 mL) was added dropwise to *N*,*N*′-diphenylthiourea (2.28 g, 0.01 mol) and **diethyl azodicarboxylate** (1.74 g, 0.01 mol) in THF (20 mL) at room temperature. After standing overnight, the solvent was removed under reduced pressure and the residue was extracted with light petroleum (bp 30–60 °C) to separate soluble material from the remainder. The light petroleum extract was concentrated and distilled to give diphenylcarbodiimide; bp 85–90 °C/0.2 mmHg, 1.27 g, 65%.

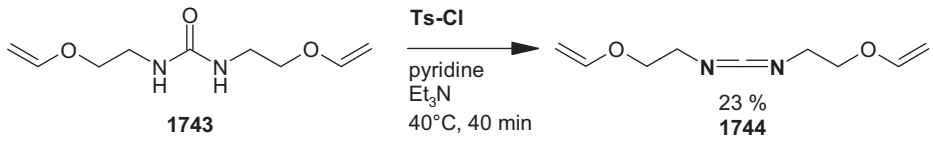
A further development of the method by immobilization of **DEAD** effects an easily separable (insoluble) and non-explosive reagent in Mitsunobu reactions. The **methyl azodicarboxylate** reagent immobilized on polystyrene **1742** functions well in Mitsunobu reactions and gives yields comparable to those obtained with soluble **DEAD** [1279]. Diphenylcarbodiimide was obtained in 41% yield.



4.5.3.3 Other Reagents

p-Toluenesulfonyl chloride (TsCl)

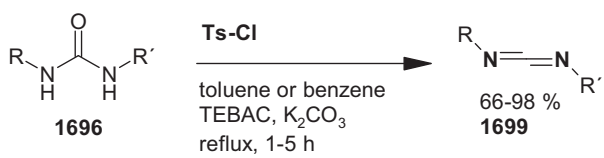
Dehydration of *N*,*N*′-bis(2-vinyloxyethyl)urea **1743** with ***p*-toluenesulfonyl chloride** (**TsCl**) gives bis(2-vinyloxyethyl)carbodiimide **1744** in 23% yield. The compound is a prospective cross-linking agent [1280].



Typical procedure. *Bis(2-vinyloxyethyl)carbodiimide* **1744** [1280]: To a vigorously stirred solution of the urea **1743** (4.99 g) in pyridine (50 mL) and triethylamine (14 mL), ***p*-toluenesulfonyl chloride** (9.52 g) was added in small portions. (Spontaneous heating of the reaction mixture to 41 °C was observed.) Stirring was continued for a further 40 min. The precipitated salts, i.e. triethylammonium tosylate and triethylammonium chloride, were filtered off, the solvent was removed from the filtrate, and the residue was distilled in vacuo to give 1.02 g (23%) of the carbodiimide **1744**; bp 82 °C (0.5 mmHg); IR: $\nu_{max} = 2130\ cm^{-1}$. On storage under normal conditions, carbodiimide **1744** is stable for several months.

A method has been described for the preparation of carbodiimides **1699** by dehydration of ureas **1696** with ***p*-tosyl chloride** under solid–liquid phase-transfer catalytic (PTC) conditions using solid potassium carbonate as a base and a lipophilic quaternary ammonium salt as a catalyst. The method is generally applicable for the synthesis of disubstituted carbodiimides, but is especially useful for unsymmetrically substituted carbodiimides. Yields of the resulting carbodiimides **1699** vary depending on the solvent (usually used at reflux temperature); in benzene or toluene yields of 66–98% are achieved, while in chloroform they are only 30–50% [1281].

General procedure. *Carbodiimides* **1699** *from ureas* [1281]: A solution of disubstituted urea **1696** (10 mmol) and ***p*-toluenesulfonyl chloride** (10 mmol) in benzene or toluene (70 mL) is stirred at reflux temperature for 1–5 h in the presence of potassium carbonate (3.53 g, 40 mmol) and benzyltriethylammonium chloride (TEBAC) (0.23 g, 1 mmol).

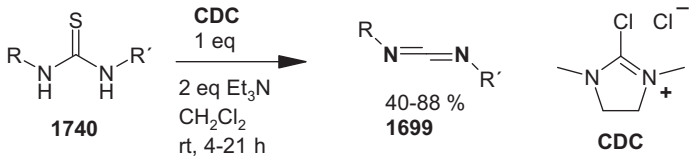


The reaction is monitored by TLC. The resultant precipitate is filtered off, and the filtrate is washed with water (2 × 10 mL). The organic layer is dried with magnesium sulfate and concentrated to give the carbodiimide **1699** as an oily residue (66–98% yield), which is generally pure or can be distilled in vacuo.

CDC (2-Chloro-1,3-dimethylimidazolinium chloride)

The versatile dehydration reagent **CDC** has also been employed to prepare carbodiimides **1699** from the corresponding thioureas **1740** in yields of 40–88% [1137].

For a description and mechanistic aspects regarding **CDC**, see Sections 4.5.1.1 and 4.5.2.7.



General procedure. *Carbodiimides* **1699** *from thioureas* [1137]: To a solution of a thiourea **1740** (1 equiv.) and **CDC** (1 equiv.) in dichloromethane, triethylamine (2 equiv.) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 4–21 h, then poured into water, and extracted with dichloromethane. The combined organic phases were successively washed with 5% aq. HCl, saturated aq. $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated to dryness. The residue was purified by short column chromatography (SiO_2) to give the carbodiimide **1699** (yields 40–88%).

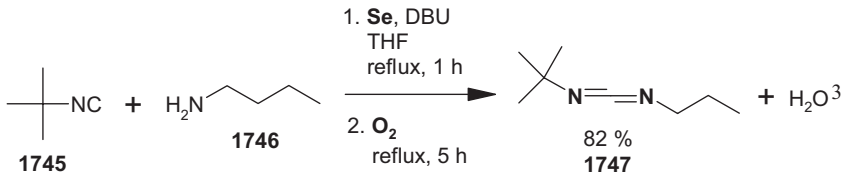
4.5.3.4 Oxidative Addition Reactions of Primary Amines with Isocyanides

Formally, carbodiimides may be generated by the addition of a (nucleophilic) primary amine to an isocyanide (with an electron deficiency; see constitutional formula **1515b** and considerations on isocyanides in the introduction to Section 4.5.2) under release of a reduction equivalent (two electrons) and two protons. The required oxidation equivalent can be provided most easily with an **oxygen** atom.

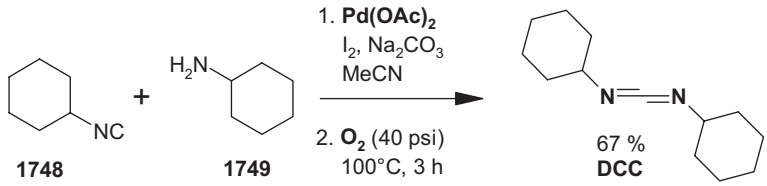
Dioxygen

Reaction of isocyanides with primary amines in the presence of **selenium** and DBU, followed by the introduction of molecular **oxygen** in refluxing THF, affords unsymmetrical and symmetrical carbodiimides in isolated yields of 58–87% [1282] (see also Section 4.5.3.5, Table 4.48). The oxidation reaction is mediated by **selenium** with the assistance of base DBU.

Typical procedure. *N-tert-Butyl-N′-n-butylcarbodiimide* **1747** [1282]: A mixture of *tert*-butyl isocyanide **1745** (2 mmol), *n*-butylamine **1746** (2 mmol), **selenium** (2 mmol), and DBU (8 mmol) was stirred for 1 h in refluxing THF (5 mL). Then, molecular **oxygen** was introduced by means of a peristaltic pump at 20 mL min^{-1} for 5 h while maintaining reflux. After deposited selenium had been filtered off, the filtrate was diluted with Et_2O (50 mL), washed with brine (3×50 mL), dried over $MgSO_4$, and concentrated in vacuo to give essentially pure **1747** in 82% yield.



Another variation of the oxidation reaction with **dioxygen** can be efficiently accomplished by a catalytic condensation of amines and isonitriles using a palladium complex catalyst and iodine at 100 °C to give dialkylcarbodiimides in yields of 35–86% [1283]. Dicyclohexylcarbodiimide was obtained in 67% yield from cyclohexylisonitrile **1748** and cyclohexylamine **1749** (see Section 4.5.3.5, Table 4.48).



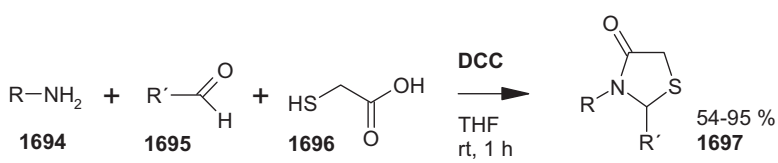
Typical procedure. *Dicyclohexylcarbodiimide* **DCC** [1283]: **Palladium acetate** (22 mg, 0.1 mmol), iodine (50 mg, 0.2 mmol), and anhydrous sodium carbonate (320 mg, 3.0 mmol) were placed in a pressure vessel. Cyclohexylamine (0.11 mL, 1.0 mmol) and cyclohexyl isocyanide (0.1 mL, 0.8 mmol) were dissolved in acetonitrile (10 mL) and this solution was added to the reaction vessel, which was then pressurized with **oxygen** (40 psi) and heated to 100 °C for 3 h. The initially deep-red reaction mixture turned yellow-orange; no Pd black precipitation was observed. There was no obvious reaction rate dependence on **oxygen** pressure. The mixture was cooled to ambient temperature, depressurized, filtered, and analyzed by GC. **DCC** was isolated by evaporating the solvent and residual amine, followed by vacuum distillation.

Palladium(II) complexes with a carbodiimide ligand, in which a nitrogen of the linear N=C=N moiety is bonded to the metal center, and bis(carbodiimido)palladium(II) complexes, both derived from isocyanides, have been described [1284].

4.5.3.5 Dicyclohexylcarbodiimide (DCC)

Dicyclohexylcarbodiimide (DCC) is the most widely used carbodiimide and many efforts have been made to produce it efficiently. Recent publications and patents are presented in Table 4.48.

A new field of application for **DCC** has been entered with carbodiimide-mediated *multicomponent reactions (MCRs)*. 4-Thiazolidinones **1697** have been assembled by a 3CR of amine **1694**, aldehyde **1695**, and mercaptoacetic acid **1696**, mediated by **DCC**, in yields of 54–95% within 1 h at room temperature [1251].



R = benzyl, phenyl, cyclohexyl, n-butyl, n-octyl, i-propyl, $CH(CH_2Ph)CO_2Me$
R´= phenyl, 4-chlorophenyl, 2-methoxyphenyl, 1-naphthyl, 4-cyanophenyl

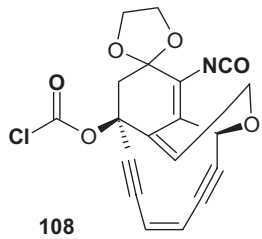
Tab. 4.48. A comparison of various methods for producing DCC.

Entry	*Method*		*Yield (%) DCC*	*Ref.*
	Starting material	*Reagent, reaction conditions*		
1	dicyclohexylurea	1. **$COCl_2$**, *t*BuOMe (MTBE) 2. NH_3	98	1253
2	dicyclohexylurea	1. **P_2O_5**, pyridine, sand 2. petroleum ether, water	76	1255
3	dicyclohexylurea	1. **$POCl_3$**, CH_2Cl_2 2. NaOH, H_2O	89	1257
4	cyclohexylisocyanate (2 mol)	1. **$Ti(OBu)_4$** 2. acetone, H_2O	98	1285
5	cyclohexylisocyanide cyclohexylamine	1. **Se**, DBU, THF 2. **O_2**	87	1282
6	cyclohexylisocyanide	1. **$Pd(OAc)_2$**, I_2, Na_2CO_3, MeCN	67	1283
	cyclohexylamine	2. **O_2**		

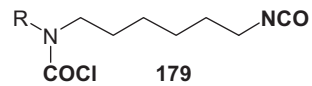
General procedure. *4-Thiazolidinones* **1697** *by a 3CR* [1251]: The appropriate amine or amino acid ester **1694** (1.0 mmol) and aldehyde **1695** (2.0 mmol) were stirred in THF at around 0 °C for 5 min, and then mercaptoacetic acid **1696** (3.0 mmol) was added. After a further 5 min, **DCC** (1.2 mmol) was added to the reaction mixture at 0 °C, and stirring was continued for a further 50 min at room temperature. DCU (dicyclohexylurea) was removed by filtration, the filtrate was concentrated to dryness under reduced pressure, and the residue was taken up in ethyl acetate. The organic phase was successively washed with 5% aq. citric acid, water, 5% aq. sodium hydrogen carbonate, and brine. It was then dried over sodium sulfate and the solvent was removed under reduced pressure to leave the crude **1697**, which was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent.

4.6 Divalent Compounds

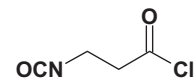
All of the synthesized compounds described thus far in this chapter have been of *monovalent* reactivity, i.e. the compounds consist of *one or more active* functional groups of the *same selectivity* and, where appropriate, one or more further *non-active* functions. Difunctional compounds such as *isocyanato-chloroformate* **108** [60] (Section 4.2.1), **446** [300] (Section 4.3.1.4), *isocyanato-carbamoyl chloride* **179** [111, 112] (Section 4.2.2.2), *isocyanato acid chloride* **1231** [447] (Section 4.3.5.4), and **1343** [1016] (Section 4.4.2.3), also fall into this category because all of their functions are of the same selectivity, in these examples electrophiles.



108



179

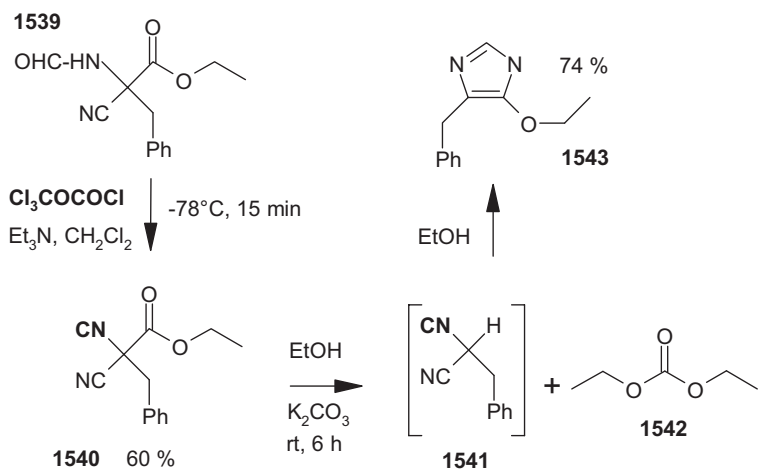


1343

In this Section, we consider those rare cases where functional groups on the same molecule are of orthogonal selectivity, such as a nucleophilic group alongside an electrophilic one, such that spontaneous reactions would seem to be inevitable.

4.6.1
1-Cyano-1-isocyanides

Whereas cyano groups are generally rather *inert* alongside other functional groups, they become *highly reactive* when in a 1,1-arrangement with isocyanides. As versatile synthons, *α-cyano-α-isocyanoalkanoates* **1540** can react intramolecularly as electrophiles with the nucleophilic partner isocyanide to form imidazoles **1543**, as already presented in Section 4.5.1.1 [1178].



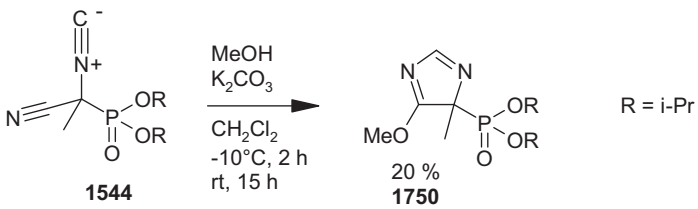
Typical procedure. *5-Benzyl-4-ethoxyimidazole* **1543** [1178]: In the presence of K_2CO_3, **1540** (for a preparation, see Section 4.5.1.1) (228 mg, 1 mmol) in ethanol (room temperature, 6 h) yielded 150 mg (74%) of **1543**; mp 121–123 °C (EtOAc; sublimation at 105 °C).

In 1979, Schollkopf synthesized 5-alkoxy-4-alkylimidazoles in a similar manner as above [1286].

Similarly, *1-cyano-1-isocyanoalkylphosphonic acid esters* **1544** [1179] (see Section

4.5.1.1) react intramolecularly at their cyano and isocyano functions to form the corresponding imidazoles **1750** [1287].

Typical procedure. *Diisopropyl 5-methoxy-4-methyl-4H-imidazole-4-phosphonate* **1750** [1287]: To **1544** (2.216 g, 9.08 mmol) were added anhydrous K_2CO_3 (0.4 g) and methanol (15 mL) at −10 °C, and the solution obtained was stirred for 2 h at −10 °C and for 15 h at 20 °C. After concentration, the residue was dissolved in CH_2Cl_2/MeOH (20:1) and chromatographed on a silica gel column (13 × 2 cm). Fractions were obtained as follows: with CH_2Cl_2/MeOH (20:1) decomposition products and with MeOH the substituted imidazole. Evaporation of the solvent from the latter fraction yielded 519 mg (20%) of **1750** as an orange oil.



4.6.2

Isocyano-isocyanates (Isocyanato-isocyanides)

A novel and unique class of orthogonal divalent compounds has recently been filed for European patent application, namely isocyano-isocyanates [1288].

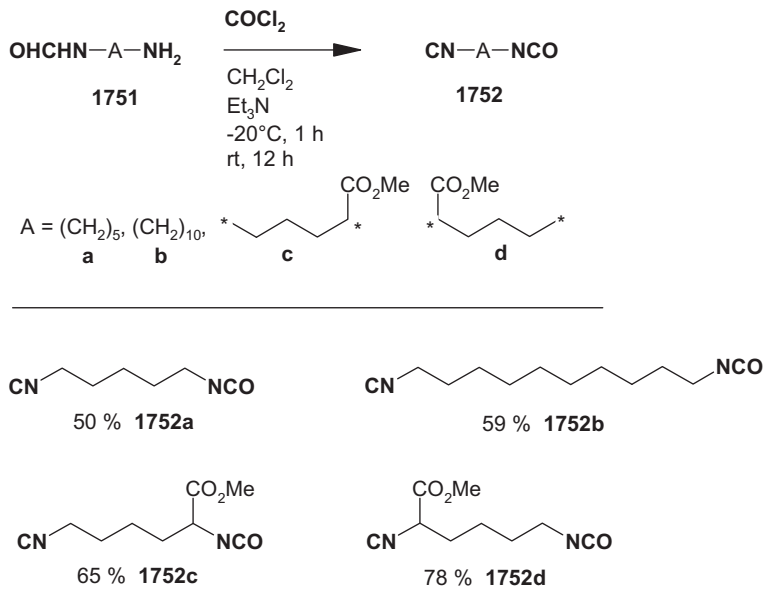
Besides presenting a concentration of functional groups, the isocyano-isocyanates provide an orthogonal selectivity, which permits the simultaneous formation of various functions at two different determined positions on reacting the two highly reactive functional groups with a pool of reactands and reagents. Last but not least, the functional groups isocyanide and isocyanate are precursors to various moieties such as carbamates, ureas, *N*-heterocycles (particularly via MCRs), Passerini- and Ugi-type products, which again are often important pharmacophores.

The installation of isocyanide and isocyanate functions in the same molecule can lead to a significant reduction in the number of reaction steps required to achieve a predetermined target molecule, thereby making the synthesis more economical. In an ideal case, *four* reaction steps can be reduced to *one*! (An example is a condensation reaction involving a sequence of protection of a functional group of one molecule, activation of another functional group, reaction with a second molecule, and removal of the protecting group. This reaction sequence can be substituted by *one* selective reaction; see below).

Phosgene

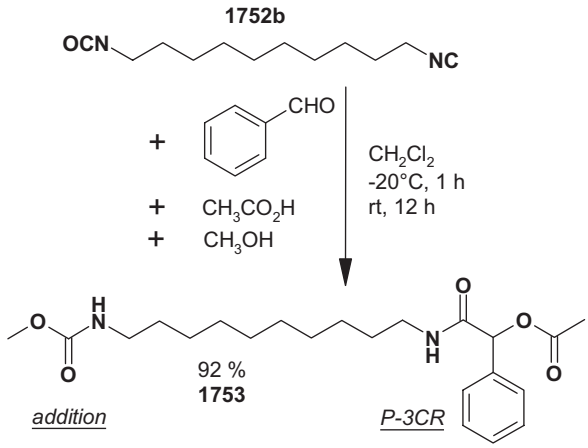
The isocyano-isocyanates **1752a–d** can easily be prepared in yields of 50–78% by parallel reaction steps in a one-pot synthesis from monoformyldiamines **1751a–d**

by dehydration with **phosgene** at −20 °C to room temperature in 12 h [1289]. Surprisingly, they can be stored neat in a freezer for several weeks. Above about 100 °C, they tend to undergo spontaneous decomposition through polyaddition.



Typical procedure. *Methyl 2-isocyanato-6-isocyanohexanoate* **1752c** [1289]: In a three-necked 1-L flask fitted with a gas-inlet tube, a reflux condenser (cooled to −20 °C, or a dry-ice reflux condenser), a thermometer, and a magnetic stirrer, ε-formyllysine-methyl ester **1751c** (21 g, 0.11 mol) and triethylamine (74.5 g, 0.74 mol) were dissolved in dichloromethane (300 mL) and the solution was cooled to −20 °C. **Phosgene** (for a *safe source*, see Chapter 7) (25.8 g, 0.26 mol) was passed into the mixture at the same temperature for 45 min and then stirring was continued at room temperature for 12 h. The excess **phosgene** was removed under reduced pressure by passage through a gas scrubber filled with ethanol. Dry diethyl ether (150 mL) was then added to the reaction mixture and the precipitate formed was filtered off by passage through Celite. The filtrate was concentrated in vacuum to afford 14 g (65%) of isocyano-isocyanate **1752c** as a colorless liquid. IR (neat): $\nu_{max} = 2260$ (NCO), 2140 (NC), 1730 cm^{-1} (CO).

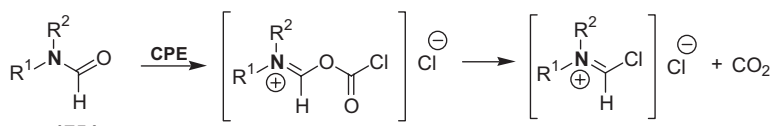
As an example supporting the above statements regarding parallel reaction steps, parallel reactions of isocyano-isocyanate **1752b** at both the isocyano and isocyanato groups can be accomplished in a one-pot procedure, whereby methanol is added to the isocyanato group and a Passerini three-component reaction (P-3CR) with benzaldehyde and acetic acid occurs at the isocyano group, simultaneously affording both the urethane and Passerini product moieties in 1-*N*-(*O*-methylcarbamato)-10-*N*′-[(2-acetoxy)-3-phenylacetamido]decane **1753** in 92% yield [1289].



Typical procedure. *1-N-(O-Methylcarbamato)-10-N′-[(2-acetoxy)-3-phenylacetamido]-decane* **1753** [1289]: To a mixture of dichloromethane (5 mL) and methanol (0.5 mL, 9.3 mmol), freshly distilled benzaldehyde (0.26 g, 2.5 mmol), acetic acid (0.15 g, 2.5 mmol), and 1-isocyanato-10-isocyanodecane **1752b** (0.52 g, 2.5 mmol) were added sequentially at room temperature. After 50 h (DC control), the solution was concentrated in vacuo to leave a residue, which solidified completely; 0.92 g (92%) of the carbamate/P-3CR product **1753** was obtained as crystals; ^{1}H NMR ($CDCl_3$): $\delta = 1.17$ (s, 16 H), 2.12 (s, 3 H), 3.16 (t, 4 H), 3.61 (s, 3 H), 4.85 (br, 1 H), 6.07 (s, 1 H), 6.34 (br, 1 H), 7.36 (s, 5 H).

4.7 Miscellaneous Reactions

Chlorocarbonyl addition followed by carbon dioxide and hydrogen chloride eliminations is also a typical reaction sequence in the case of carbonyl substrates, e.g., aldehydes, amides, ureas or oxygenated sulfur or phosphorus compounds.

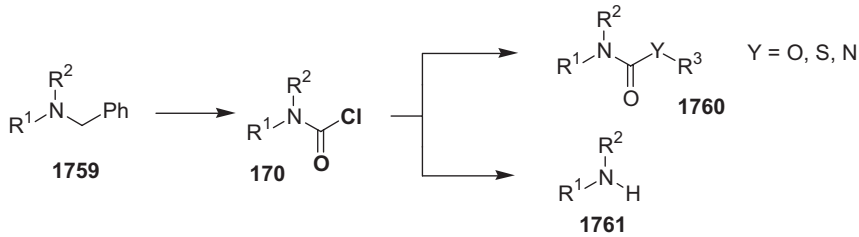


1754 1755 1756

1757 1758

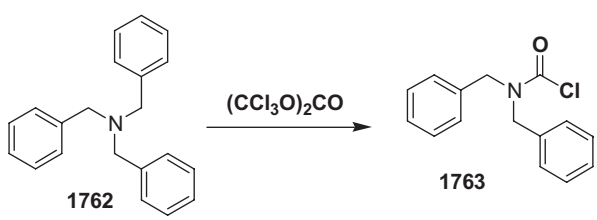
4.7.1 *N*-Dealkylation of Tertiary Amines

Direct transformation of *N*-benzyl-protected tertiary amines **1759** into **carbamoyl chlorides 170**, which are versatile intermediates for the direct preparation of amides, ureas, carbamates, and heterocyclic derivatives, is an attractive alternative to save deprotection and activation steps involving the free amine as an intermediate [135, 735].



In a well-established protocol, the above reaction is very useful for the preparation of the free secondary amines. Several available **chloroformates** are traditional reagents for the *N*-dealkylation of tertiary amines by cleavage of the intermediate carbamates [134].

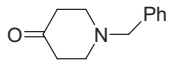
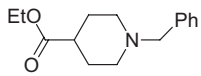
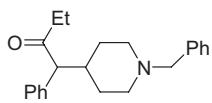
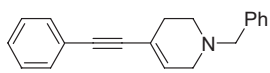
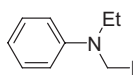
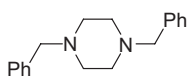
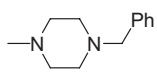
The reaction between **phosgene** itself and triethylamine has been reported to give diethylcarbamoyl chloride [133], but, surprisingly enough, when tribenzylamine was used, no C–N bond-breaking was observed, and no carbamoyl chloride was formed. Instead, tribenzylamine **1762** reacts smoothly with one-third of an equivalent of **triphosgene** in dichloromethane to give, very selectively, the expected carbamoyl chloride **1763** (71% conversion) [135].



The reaction most probably proceeds according to the mechanism described for chloroformates **1764**. Indeed, an equimolar amount of benzyl chloride along with the carbamoyl chloride **170** has been isolated in all reported reactions.

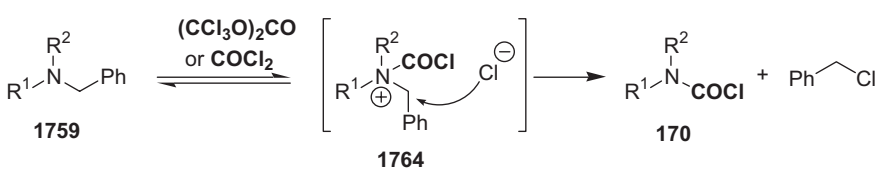
The results in Table 4.49 also show that the method is compatible with various functional groups (ketone, ester, amide, unsaturation). However, the presence of a phenyl group on the nitrogen atom seems to prevent the reaction from occurring since, in this particular case, the starting material is entirely recovered. Interest-

Tab. 4.49. **Triphosgene**-mediated transformation of tertiary benzylamines **1759** into carbamoyl chlorides **170** [135].

Entry	*Starting compound 1759*	*Reaction time (h)*	*Yield of 170 (%)*
1		7	90
2		7	70
3		6	86
4		23	36[a]
5		5	0
6		24	74
7		24	77

[a] low yield due to the product instability

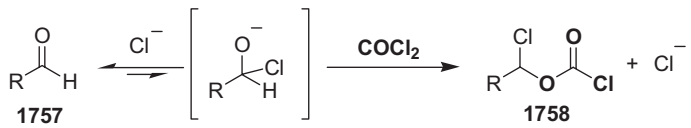
ingly, the same order of reactivity between benzyl and alkyl groups as with chloroformates is observed: benzyl reacts much more rapidly than an ethyl or methyl group, thus leading to regioselective *N*-debenzylation.



General procedure. *Carbamoyl chlorides* **170** *from tertiary benzylamines* **1759** [135]: A solution of the benzylamine **1759** (1 equiv.) in dichloromethane (0.3 M) is added to a solution of **triphosgene** (0.33 equiv.) in dichloromethane (0.1 M) at 0 °C under inert atmosphere. The mixture is then allowed to warm to room temperature and is stirred until no further change is seen by TLC. The reaction mixture is then concentrated under reduced pressure and purified by flash chromatography.

4.7.2
α-Chlorinated Chloroformates. Chlorination of Carbonyl Compounds

The addition of **phosgene** to aldehydes **1757**, as catalyzed by "naked" chloride anions, opened a synthetic route to α-chlorinated chloroformates **1758** and their derivatives, which are useful as pharmaceutical intermediates [49, 1290–1292].



1757 **1758**

R = H (42 %), Me (96 %), Et (89 %), Cl_3C (65 %), *i*-Pr (87 %), Cyclohexyl (87 %), Ph (68 %)

The large-scale synthesis of α-chloroethyl chloroformate (**ACE-Cl**) by the above method (stirring acetaldehyde with 1.1 equiv. of neat **phosgene** for 1 h in the presence of 3.0% benzyl tri-*n*-butylammonium chloride (BTBAC), giving an isolated yield of 96%) has a particular value since its ethanolysis product, α-chloroethyl ethyl carbonate, is a commercial alkylating agent used to mask carboxyls in *penicillins* and *cephalosporins*.

Several classes of catalyst have been reported, including alkyl-substituted guanidines, hexasubstituted guanidinium chlorides or bromides, substituted biguanidinium chlorides or bromides, phenyl dialkyliminium tetraalkylguanidinium chlorides or bromides, dialkylimidazolinium tetraalkylguanidinium chlorides or bromides, phenyltetraalkylamidinium chlorides or bromides, and *N*,*N*-dialkyl-*N*′-alkylpyrrolidinium chlorides or bromides [1293].

According to a recent reference [1293], acetaldehyde reacts with **phosgene** in the presence of pentabutylguanidine, producing 1-chloroethyl chloroformate in 88.9% yield.

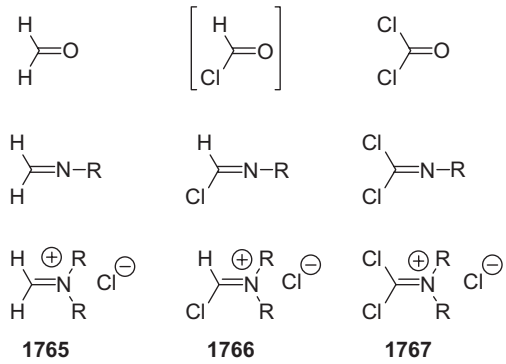
Phosgene can be replaced with either **diphosgene** or **triphosgene** under the same conditions to give the corresponding 1-alkyl chloroformates in very good yields [51, 1292, 1294], as discussed in Section 4.2 "Chloroformates".

4.7.3
Chlorination of Amides and Ureas. Vilsmeier-Type Salts

The Vilsmeier reaction, whereby amides are converted to highly electrophilic iminium ions, which may then react with carbonyl compounds or weakly nucleophilic groups such as aromatic rings, has long been known. Comprehensive reviews on carbonic acid derivatives obtained from formamides are available [1295–1297]. In a wider sense, these derivatives belong to the chemistry of formaldehyde.

Whereas the chemistry of formaldehyde, the unstable **formyl chloride**, **phosgene**, and their imines is well developed, the corresponding imonium salts, i.e. the dichloromethyleneammonium salts ("**phosgeneiminium salts**") **1767**, were almost

forgotten until 1969 [1298]. Mannich reagents **1765**, such as methyleneammonium salts, react with nucleophiles by aminomethylation.

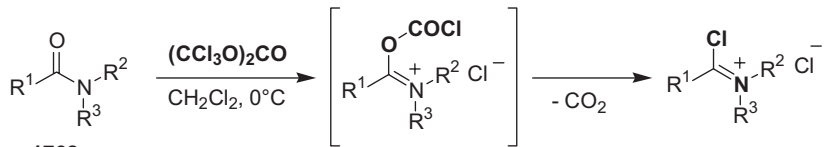


1765 **1766** **1767**

Dichloromethyleneammonium salts **1767** having a tertiary nitrogen (chlorinated Vilsmeier salts) are relatively easy to obtain, some even being commercially available, while those with secondary and primary nitrogen can be prepared at least in situ from dichloromethyleneamine and cyanogen chloride [1298]. These salts are generally strongly electrophilic reagents, and may be compared with methylammonium and chloromethyleneammonium salts (Mannich reagents and Vilsmeier–Haack or Arnold reagents). Recent applications of dimethylphosgeneiminium chloride (''Viehe's salt'') have been as a dehydrating agent for the preparation of carbodiimides from ureas (see Section 5.4.3.1) [1254], and its use in the direct conversion of tetrahydro-2-pyranyl (THP) protected alcohols into the corresponding halides in the presence of a tetraalkylammonium halide (see also Section 4.4.1 on the chlorination of alcohols) [997].

As chloromethyleneammonium salts, the *Vilsmeier–Haack* [$\mathbf{ClCH{=}NR_2^+}$ $\mathbf{PO_2Cl_2^-}$] and *Arnold* [**1766**] reagents give the corresponding imonium compounds and particularly, by their hydrolysis, aldehydes. They have found extensive use as formylating, halogenating, and dehydroxylating reagents [1299].

The following section highlights some selected recent applications of the use of phosgene equivalents in the preparation of Vilsmeier-type chlorinated derivatives of amides and ureas. **Thionyl chloride**, **carbonyl bromides**, **phosphorus oxychloride**, **phosgene**, **triphosgene**, **oxalyl chloride**, and ***p*-toluenesulfonyl chloride** are all efficient oxophilic promoters capable of generating Vilsmeier-type chloro iminium ion intermediate **1770** by reaction with formamides, particularly dimethylformamide, and ureas.

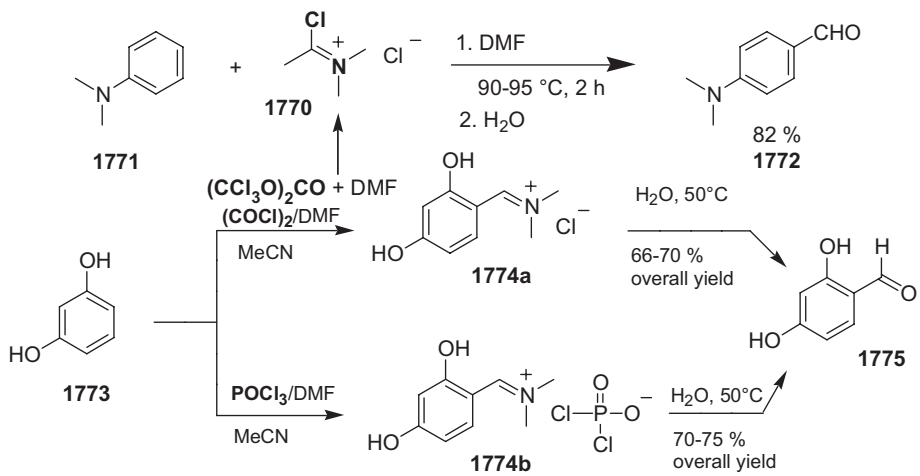


1768 **1769** **1770**

Aromatic compounds are formylated using **triphosgene**/**DMF** [1300], **phosphorus oxychloride**/**DMF**, or **oxalyl chloride**/**DMF** [1301].

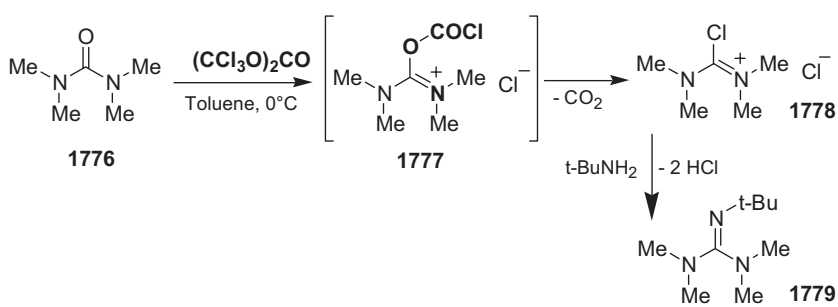
N,*N*-Dimethylaniline **1771** was treated with **Vilsmeier complex 1770** (prepared by reaction of DMF with **triphosgene** below 20 °C for 10–30 min) in DMF at 90–95 °C for 2 h to give *p*-$Me_2NC_6H_4CHO$ **1772** in 82% yield [1300].

An efficient synthesis of 2,4-dihydroxybenzaldehyde **1775** from resorcinol **1773** by a Vilsmeier–Haack reaction using either **phosphorus oxychloride**/**DMF** or **oxalyl chloride**/**DMF**, working below room temperature in acetonitrile, has been reported [1301].



A **triphosgene**-based procedure for the convenient preparation of large quantities of the strong, non-nucleophilic base 2-*tert*-butyl-1,1,3,3-tetramethylguanidine **1779** has been described [1302].

2-*tert*-Butyl-1,1,3,3-tetramethylguanidine **1779** provides an inexpensive alternative to the amidine bases, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which suffer from being easily alkylated. Additionally, the hazards of using **phosgene** in the previous preparations [1303–1307] are reduced by employing **triphosgene**.



Typical procedure. *2-tert-Butyl-1,1,3,3-tetramethylguanidine* **1779** [1302]: To an oven-dried, 500-mL, three-necked, round-bottomed flask, equipped with a nitrogen inlet with gas bubbler, magnetic stirring bar, thermometer, condenser, and a 250-mL dropping funnel, were added triphosgene (14.8 g, 0.05 mol) and anhydrous toluene (120 mL). The mixture was kept under argon and cooled to ca. 10 °C with the aid of an external ice bath. A solution of *N*,*N*,*N*′,*N*′-tetramethylurea (18.0 mL, 0.15 mol) in dry toluene (50 mL) was then slowly added over a period of 30 min. After completion of the addition, the mixture was allowed to warm to ambient temperature, and stirring was continued for a further 1 h. During this time, a white precipitate formed, consisting of the *Vilsmeier salt*. Then, *tert*-butylamine (47.3 mL, 0.45 mol) was slowly added to the mixture over a period of 30 min. After completion of the addition, the mixture was heated under reflux for 5 h and then cooled to room temperature. Anhydrous diethyl ether (200 mL) was added and the white precipitate was quickly removed by filtration. This precipitate had to be collected as quickly as possible to avoid hydrolysis to the starting urea. The precipitate turns pale-yellow if hydrolysis is occurring. In some instances, additional diethyl ether (300 mL) was needed to ensure complete transfer of the solids to the filtration apparatus. The precipitate was washed with a further quantity of anhydrous diethyl ether (300 mL) (the filtrate must be colorless, indicating that all impurities have been removed) and immediately dissolved in aqueous 25% sodium hydroxide solution (100 mL). The mixture was then extracted with diethyl ether (3 × 300 mL). The combined organic layers were dried (potassium carbonate), filtered, and the solvent was removed under reduced pressure. The resulting colorless liquid was purified by distillation (bp 88–89 °C/36 mmHg) to afford 18.7 g (73%) of 2-*tert*-butyl-1,1,3,3-tetramethylguanidine **1779**.

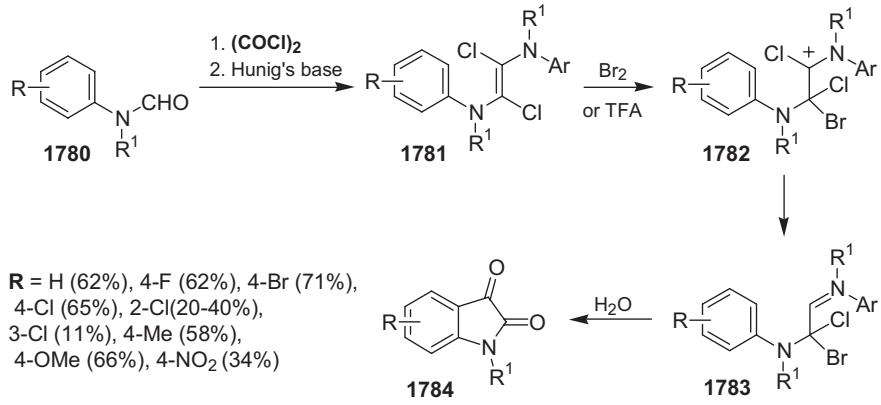
Versatile syntheses of 3-chloroisoxazolium chlorides by the reaction of 4-isoxazolin-3-ones with **phosgene** or **diphosgene** have been reported [1308]. 3-Chloroisoxazolium chlorides were obtained in good yields, and were converted to 4-isoxazoline-3-thiones on treatment with NaSH. Pyrolysis of 3-chloro-2-methylisoxazolium chlorides afforded 3-chloroisoxazoles. In the presence of Bu_3N, 3-chloro-2-methyl-5-phenylisoxazolium chloride condensed carboxylic acids with alcohols or amines to give the corresponding esters or amides in high yields, together with 2-methyl-5-phenyl-4-isoxazolin-3-one.

When *N*-substituted formanilides **1780** are treated briefly and sequentially with oxalyl chloride, Hunig's base, and bromine, isatins **1784** are rapidly formed, many in good yields. The reaction involves deprotonation of the Vilsmeier reagent, dimerization of the carbene thus formed, and electrophilic cyclization of the dimer by the action of bromonium ion followed by aqueous hydrolysis [1309, 1310]. The reaction sequence has been developed into a simple and efficient one-pot isatin synthesis from formanilides.

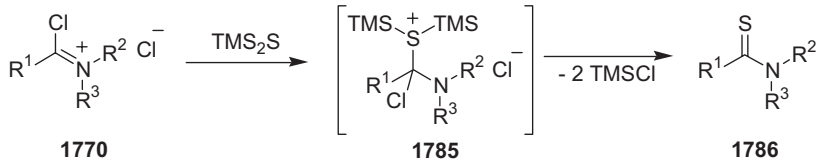
Alternatively, isatins **1784** can be synthesized from secondary aromatic amines with oxalyl chloride followed by a Friedel–Crafts cyclization [1311].

There are numerous procedures for the conversion of amides and lactams to thioamides and thiolactams, e.g. using Lawesson's reagent, P_2S_5, H_2S, R_3OBF_4/NaSH, R_2PSX, or $(Et_2Al)_2S$. Many of these methods require protracted reaction

times, high temperatures, or inconvenient reaction conditions for their execution, and are often accompanied by painstaking chromatographic separations to remove spent reagents from the desired products.

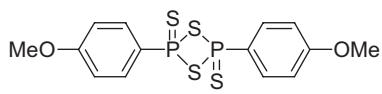


An interesting protocol for converting amides and lactams to their corresponding thio derivatives **1786**, through *in situ* thionation of intermediate chloro iminium ions **1770** with hexamethyldisilathiane TMS_2S, has been reported [1312].



The procedure seems to be sensitive to the degree of substitution at nitrogen and relatively insensitive to the size of the alkyl groups on the nitrogen or α to the carbonyl. **Oxalyl chloride** and **phosphorus oxychloride** were both found to be quite effective in mediating iminium ion **1770** formation (at −78 °C); however, it should be noted that oxalyl chloride was only effective in instances where no protons were α to the carbonyl. **Triphosgene** also provided a convenient method for monitoring the formation of these Vilsmeier intermediates as the evolution of CO_2 occurred with concomitant formation of the iminium ion **1770** (at 0 °C). The methodology was found to give results comparable to those obtained with **Lawesson's reagent**.

Lawesson's reagent



General procedure. *Thioamides* **1786** *or thiolactams with* **oxalyl chloride** [1312]: A solution of the amide or lactam (ca. 1 mmol) in dry dichloromethane (2 mL) was

cooled to −78 °C and **oxalyl chloride** (0.14 mL, 1.5 mmol, 1.5 equiv.) was added dropwise over a period of 10 min. The resulting solution was stirred for an additional 10 min, and the bath was removed to permit gradual warming to 0 °C. After 30 min, the solution turned a pale-amber color and gas evolution (CO and CO_2) was observed. Gas evolution ceased after approximately 30 min, and at this point TMS_2S (0.65 mL, 3.1 mmol, 3.1 equiv.) (Stench!) was added dropwise over 5 min. The reaction mixture was warmed to room temperature over a period of 1–3 h and the progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated in vacuo and filtered through a short plug of 60–200 mesh silica gel. Pure samples of the desired thioamides **1786** were obtained upon concentration of the eluent (yields of 92% and 100% were obtained for 1-(thiobenzoyl)pyrrolidine and *N*,*N*-dimethylthiobenzamide, respectively).

General procedure. *Thioamides* **1786** *or thiolactams with* **triphosgene** [1312]: To a solution of the amide or lactam (ca. 1 mmol) in dry dichloromethane (5 mL) at 0 °C, **triphosgene** (313 mg, 1.05 mmol, 1.05 equiv.) was added portionwise, and the resulting solution was allowed to warm to room temperature over a period of 1 h. During this time, the solution turned a pale-amber color and gas (CO_2) was evolved. When gas evolution had ceased, TMS_2S (0.64 mL, 3.05 mmol, 3.05 equiv.) (Stench!) was added dropwise over 5 min. The course of the reaction was monitored by TLC, and reactions were typically complete within 1–3 h. Upon completion, the reaction mixture was diluted with water (10 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL) and the combined organic phases were dried over Na_2SO_4, concentrated in vacuo, and filtered through a short plug of 60–200 mesh silica gel. Concentration of the eluent afforded pure thioamides **1786** or thiolactams (a yield of 86% was obtained for *N*-methyl thiocaprolactam).

General procedure. *Thioamides* **1786** *or thiolactams with* **phosphorus oxychloride** [1312]: A solution of the amide or lactam (ca. 1 mmol) in dry dichloromethane (2 mL) was cooled to −78 °C and **phosphorus oxychloride** (0.12 mL, 1.3 mmol, 1.3 equiv.) was added dropwise over 10 min. The solution turned a pale-amber color after approximately 10 min at −78 °C. The formation of chloro iminium ion intermediate **1770** was monitored by following the disappearance of the starting material by TLC. (Note: Warming to room temperature may be required to ensure complete formation of the Vilsmeier intermediate. In instances where complete iminium ion formation was not observed, TMS_2S (Stench!) was added after 30 min). After 30 min, the solution was treated with TMS_2S (0.65 mL, 3.1 mmol, 3.1 equiv.) and the resulting mixture was allowed to warm to room temperature over approximately 1–4 h. Upon completion of the reaction, water (10 mL) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to afford a pale-yellow oil, which was filtered through a short plug of 60–200 mesh silica gel. The eluent was concentrated in vacuo to af-

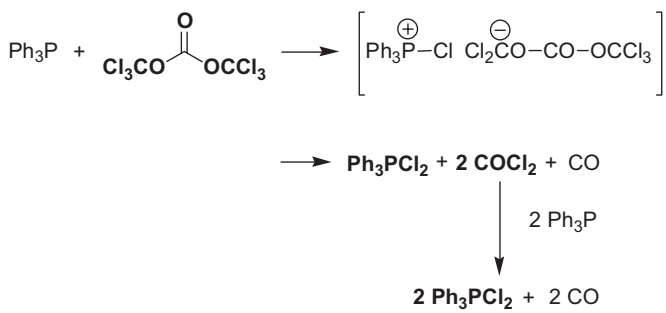
ford pure samples of the desired thioamides **1786** and thiolactams (yields of 77%, 91%, and 30% were obtained for *N*-methylthioacetamide, 1-(thioacetyl)pyrrolidine, and thiobenzamide, respectively).

4.7.4 Chlorination of Phosphorus Compounds

Triphenylphosphine dichloride, $\mathbf{Ph_3PCl_2}$ is a very effective chlorination (of acids, alcohols, epoxides, aldehydes), dehydration (of amides, ureas, aldoximes, formamides), and cyclization (heterocycles) agent. Whilst this reagent is commercially available, its preparation and use *in situ* usually gives cleaner reactions and higher yields due to the high sensitivity of $\mathbf{Ph_3PCl_2}$ to the atmosphere. $\mathbf{Ph_3PCl_2}$ is usually synthesized by oxidation of Ph_3P with reagents such as Cl_2, CCl_4, $COCl_2$, thionyl chloride, diphosgene, sulfuryl chloride, phosphorus trichloride, or C_2Cl_6. These methods involve the use of toxic gases or liquids, or generate undesirable phosphorus and chlorocarbon by-products.

High purity triphenylphosphine, as required in the Wittig ylide synthesis of alkenes such as vitamin A, is prepared by the reaction of triphenylphosphine dichloride $\mathbf{Ph_3PCl_2}$ with Mg, Al, and/or Fe in the presence of an inert solvent. The $\mathbf{Ph_3PCl_2}$ content of phosgene, chlorine, diphosgene, HCl, thionyl chloride, sulfuryl chloride, phosphorus trichloride and/or aliphatic halogen compounds (active chlorine compounds) must total less than 1000 ppm of free chlorine [1313].

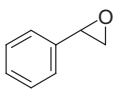
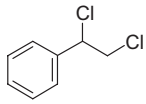
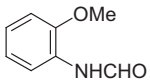
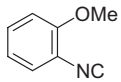
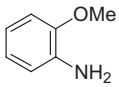
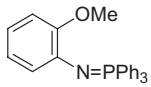
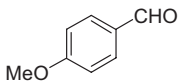
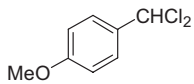
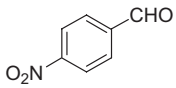
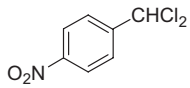
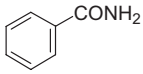
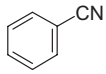
Triphosgene reacts with Ph_3P according to a simple mechanism to produce exclusively $\mathbf{Ph_3PCl_2}$ as the sole phosphorus product [988].



Ph_3P was dissolved in dichloromethane or 1,2-dichloroethane (1:5 v/v) and a solution of **triphosgene** (0.33 equiv.) in the same solvent was added dropwise whilst cooling to maintain the temperature at 20 °C. After completion of the addition, the reaction mixture was stirred until gas evolution ceased. A solution of the substrate (Table 4.50), containing triethylamine where necessary, was then added (or inverse addition by means of syringe or cannula, if required). After the reaction, the products were isolated by standard techniques.

Reaction of the chlorinated Lewis acids carbonic dichloride, phosphoryl chloride, chloroiminium chloride, and chlorine with hexamethylphosphoric triamide

Tab. 4.50. Reaction of various substrates with phosphines and one-third of an equivalent of **triphosgene** [988].

Substrate	*Product*	*Yield (isolated)%*
H_2O	Ph_3PO	100 (a)
		75 (a)
		75 (a, b)
(*o*-TolylNH)$_2$CO	*o*-Tolyl–N=C=N–*o*-Tolyl	73 (a, b)
		88 (a, b)
		80 (a) 95 (c)
		50 (a)
		78 (a, b) 72 (b, c)

(a) Phosphine = Ph_3P; (b) Et_3N also present; (c) Phosphine = Ph_2P attached to cross-linked polystyrene.

(HMPT) has been investigated [1314]. A structural study of the electrophilic intermediates obtained from carboxamides and chlorinated Lewis acids was extended to the phosphoric amides. The action of **phosgene** and **$POCl_3$** on hexamethylphosphoric triamide (HMPT) can lead to a chlorophosphonium salt $(Me_2N)_3PCl^+Cl^-$, the structure of which has been proved by NMR (^1H, ^{13}C, ^{31}P, ^{15}N). The mechanism of its formation is comparable to that for formation of the chloroiminium chloride (Vilsmeier reagent) from the corresponding amide. The action of chlorine on HMPT does not lead to a stable salt of the same kind, but essentially to the substitution product $Me_2NP(O)ClNMe_2$. A new biphosphorylated compound $(Me_2N)_2P(O)OPCl(NMe_2)_3$ was identified when an excess of chlorine was reacted with HMPT.

The **Vilsmeier reagent** prepared by treating DMF with **$COCl_2$** is a useful reagent in nucleic acid chemistry, e.g. for chlorination and formylation of nucleosides, and in the synthesis of oligonucleotides [1315].

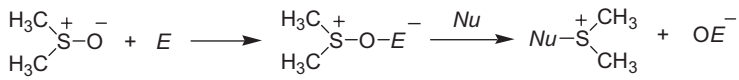
4.7.5

Oxidation of Alcohols to Carbonyl Compounds with Activated Dimethyl Sulfoxide via Alkoxysulfonium Ylides. The Swern, Moffatt, and Related Oxidations

Mild oxidation of alcohols to carbonyl compounds via alkoxysulfonium ylides is a very important transformation in organic synthesis and several reviews cover many of the practical and mechanistic aspects of the Moffatt, Swern, and related oxidations [1316–1320].

Swern oxidation has been the procedure of choice in several multistep syntheses of key intermediates en route to natural products [1321, 1322] or therapeutic agents [1323–1329].

Dimethyl sulfoxide **1787** undergoes reactions in which nucleophilic attack occurs on the sulfur atom. The lone pair of electrons on sulfur, however, cannot be expected to favor the approach of a nucleophile, in spite of the presence of a partial positive charge and vacant *d* orbitals on the sulfur. Therefore, it is not surprising that most reactions in which nucleophilic attack takes place readily on sulfur are aided by prior electrophilic attack on the oxygen atom to give dimethylsulfonium species **1788**. A nucleophile can now perform a facile displacement on sulfur with departure of a leaving group. The formation of the sulfonium species **1789** is usually followed by further reactions.



1787 **1788** **1789**

Electrophilic reagents *E* that activate dimethyl sulfoxide **1787** include **trifluoroacetic anhydride** (**TFAA**) [1330–1333], **TFFA**/$\mathbf{P_4O_{10}}$ [1334], **thionyl chloride** [1318, 1335], **oxalyl chloride** [1329, 1336–1350], ***t*-butyl hypochlorite** [1351], **chlorine or *N*-chlorosuccinimide** [1352–1355], **acetic anhydride** [1331, 1356, 1357], **acetyl chloride, benzoyl chloride, methanesulfonyl chloride, and toluenesulfonyl chloride** [1358], **phosgene** [1359], **chloroformates** [1359, 1360], **diphosgene** [1361], **triphosgene** [1362, 1363], **sulfur trioxide**/**pyridine** [1346], **trifluoromethanesulfonic anhydride** ($\mathbf{Tf_2O}$) [1364], **dicyclohexylcarbodiimide** (**DCC**), **DCC**/$\mathbf{SO_3}$ [1334], **1-ethyl-3-(3-dimethylaminopropyl)carbodiimide** (a water-soluble carbodiimide derivative) [1365], **phosphorus pentoxide** [1366], **polyphosphoric acid** [1367], **bromine** [1368], **ethoxyacetylene** [1356, 1357], and **diphenylketene-*N*-*p*-tolylimine** [1369, 1370].

Activation of dimethyl sulfoxide by **oxalyl chloride**, as developed by Swern and co-workers [1317–1319, 1335, 1371–1373], has become the most used of these oxidation procedures, but several of the other methods are also convenient and efficient. The usual nucleophiles have been alcohols, phenols, enols, amines, and oximes.

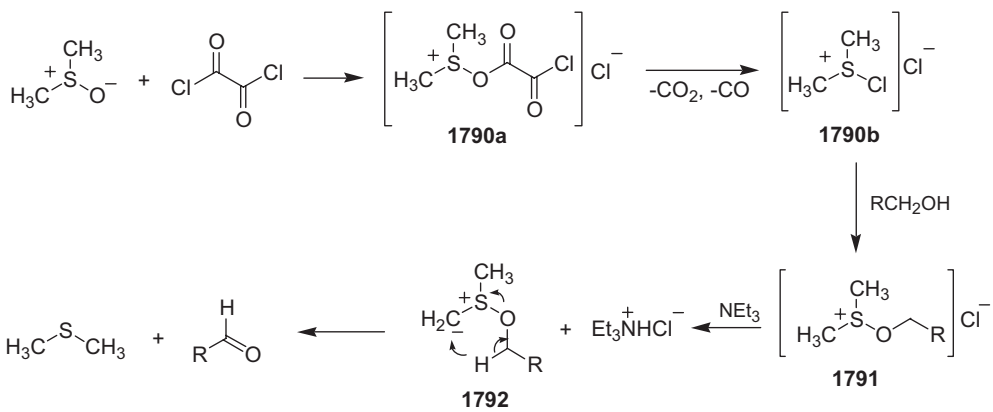
Despite the broad applicability and mild reaction conditions of the Swern oxidation, ''chemists abhor this reaction because of the stoichiometric amount of dimethyl sulfide that is released, causing problems of odor containment'' [1374].

The present section reviews the recent applications in the activation of dimethyl sulfoxide, with the aim of identifying alternative milder and more practical methods for the oxidation of hydroxylic compounds. Thereafter, we focus on **oxalyl dichloride**, the classical Swern reagent, on **diphosgene** and **triphosgene**, as well as on alternative non-chlorine activation methods.

4.7.5.1 Swern Oxidation

Oxalyl chloride reacts with dimethyl sulfoxide at low temperatures to initially form adduct **1790a**, which collapses to a dimethylchlorosulfonium species **1790b**. Reaction of **1790b** with an alcohol at −78 °C produces the alkoxysulfonium ion **1791**, which is converted into the product by reaction with an amine base to give ylide **1792**, which further reacts intramolecularly to give the carbonyl product.

A series of substituted *ortho*-phthalaldehydes has been prepared under mild conditions in respectable yields by oxidation of the corresponding dimethanols using **oxalyl chloride** activated **DMSO** [1343].

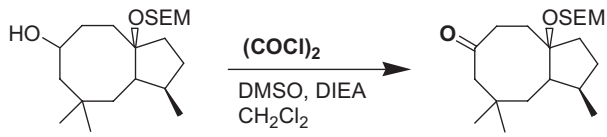


Primary and secondary alcohols have been oxidized under Swern conditions to furnish the ketones **1793** [1375] and **1794** [1376] as well as the aldehyde **1795** [1377].

Oxalyl chloride

Typical procedure. (1β,3$\alpha\alpha$,9$\alpha\beta$)-Decahydro-1,8,8-trimethyl-3a-[(2-trimethylsilyl)ethoxymethoxy]-6H-cyclopentacyclooctan-6-one **1793** [1375]: Dimethyl sulfoxide (0.536 mL, 0.397 g, 5.10 mmol) was added dropwise to a stirred solution of **oxalyl chloride** (0.213 mL, 0.311 g, 2.45 mmol) in dichloromethane (20 mL) at −78 °C. The mixture was stirred for 15 min at −78 °C, and then a solution of (1β,3$\alpha\alpha$,9$\alpha\beta$)-decahydro-1,8,8-trimethyl-3a-[(2-trimethylsilyl)ethoxymethoxy]-3aH-cyclopentacyclooctan-6-ol (0.74 g crude, ca. 2.04 mmol) dichloromethane (5 mL) was added dropwise by means of a syringe. After stirring for a further 15 min at −78 °C, N,N-diisopropylethylamine (2.83 mL, 2.10 g, 16.3 mmol) was added, and the reaction mixture was

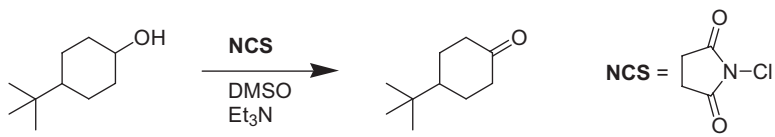
allowed to warm to room temperature. After 1 h, the mixture was poured into saturated aq. sodium hydrogen carbonate solution (10 mL). After shaking, the layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine (10 mL), dried, and concentrated. The residue was diluted with hexane (25 mL), washed with water (5 mL), dried, and concentrated. Purification by flash chromatography on 25 g of silica gel eluting with 10% ethyl acetate in hexane gave 0.546 g (79%) of **1793**.



1793

SEM = (trimethylsilyl) ethoxymethoxy

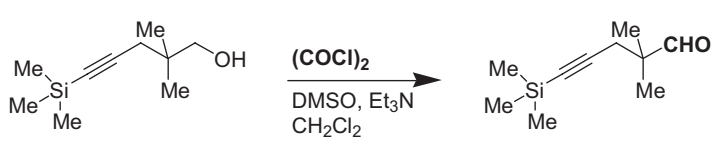
***N*-Chlorosuccinimide**



1794

Typical procedure. *4-tert-Butylcyclohexanone* **1794** [1376]: ***N*-Chlorosuccinimide** (**NCS**) (8.0 g, 0.060 mol) and toluene (200 mL) were cooled to 0 °C in a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a thermometer, a dropping funnel, and an argon inlet tube. Dimethyl sulfoxide (6.0 mL, 0.10 mol) was added and the mixture was cooled to −25 °C using a tetrachloromethane/dry-ice bath. A solution of 4-*tert*-butylcyclohexanol (6.24 g, 0.04 mol; mixture of *E* and *Z* isomers) in toluene (40 mL) was added dropwise over 5 min, stirring was continued for 2 h at −25 °C, and then a solution of triethylamine (6.0 g, 0.06 mol) in toluene (10 mL) was added dropwise over 3 min. The cooling bath was removed, and, after 5 min, diethyl ether (400 mL) was added. The organic phase was washed with 1% aq. hydrochloric acid (100 mL) and then with water (2 × 100 mL), and dried over anhydrous magnesium sulfate. The solvents were evaporated under reduced pressure, and the residue was transferred to a 50-mL, round-bottomed flask and bulb-to-bulb distilled at 120 °C (25 mmHg) to yield 5.72 g (93%) of *4-tert*-butylcyclohexanone **1794**; mp 41–45 °C. Recrystallization from petroleum ether at −20 °C gave an 88% recovery of **1794** with mp 45–46 °C.

Oxalyl chloride (on a 0.36 mol scale)



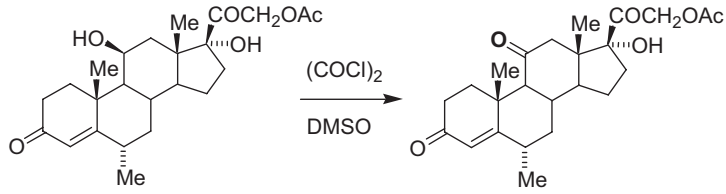
1795

Typical procedure. *2,2-Dimethyl-5-(trimethylsilyl)-4-pentynal* **1795** [1377]: A solution of dimethyl sulfoxide (62 mL, 68.3 g, 0.874 mol) in dichloromethane (200 mL) was added dropwise over a period of 2 h to a solution of **oxalyl chloride** (36.6 mL, 53.2 g, 0.420 mol) in dichloromethane (500 mL) cooled to −60 °C. The mixture was stirred for an additional 30 min, and then a solution of 2,2-dimethyl-5-(trimethylsilyl)-4-pentyn-1-ol (66.3 g, 0.360 mol) in dichloromethane (200 mL) was added dropwise over 2.5 h. The resulting solution was stirred for a further 40 min, and then triethylamine (251 mL, 182 g, 1.80 mol) was added dropwise over 1 h. The solution was stirred for an additional 45 min and then allowed to warm to room temperature, whereupon water (400 mL) was added. The aqueous layer was separated and extracted with dichloromethane (3 × 75 mL), and the combined organic layers were washed with 1 N hydrochloric acid (3 × 200 mL) and then with water. The individual washes were successively extracted with dichloromethane (3 × 50 mL) and all the organic layers were combined, washed with saturated sodium chloride solution, and dried over magnesium sulfate. The dried solution was concentrated and passed through a *florosil* column eluting with 10% diethyl ether in hexane and the solvent was removed from the eluate. The crude product was transferred in a vacuum train at room temperature, and small scale (2–4 g) medium-pressure liquid chromatography on silica gel using 3% diethyl ether in hexane afforded pure product **1795** in 80% yield.

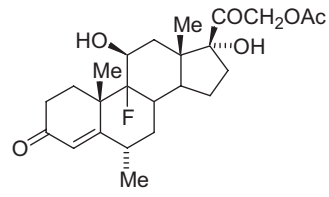
Reactivity–selectivity relationships in the Swern oxidation of alcohols using **dimethyl sulfoxide**/**oxalyl chloride** have been investigated [1378]. The competititive oxidation of a mixture of two alcohols by a sub-stoichiometric amount of oxidant under the conditions developed by Swern (reaction of the alcohols at −60 °C with Me_2SCl^+ Cl^- generated from **$(COCl)_2$** and Me_2SO in CH_2Cl_2 followed by reaction with Et_3N) showed significant selectivity, with sterically crowded alcohols and those bearing electron-withdrawing substituents being less reactive. Experiments in which the order of mixing of the alcohols and the oxidant was reversed and the time of reaction varied established that the process involves initial fast formation of a mixture of alkoxydimethylsulfonium ions, which equilibrate at a slower rate with the residual alcohols. Addition of Et_3N rapidly converts the existing mixture of alkoxydimethylsulfonium ions to carbonyl products. Intramolecular and intermolecular H/D isotope effects are consistent with this mechanistic scheme. In a practical application of these reactivity principles, pregnenol **1796**, with a crowded 11β-OH group, was smoothly oxidized in 58% yield to ketone **1797**, whereas the 9α-fluoro substituent in fluoropregnenol **1798** inhibited the reaction and the corresponding ketone was formed in only 5% yield.

A synthetic approach to 2-piperidylglycine using Swern oxidation as a synthetic step has been reported [1379]. Protection and Swern oxidation of 2-piperidinemethanol **1799** gave the corresponding *N*-protected aldehydes **1800**, which formed diastereomeric cyanohydrins **1801** on reaction with KCN. Treatment of these cyanohydrins with ammonia in methanol gave α-amino-2-piperidineace-tonitriles **1802**.

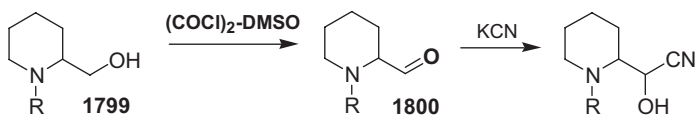
An improved preparation of (*S*)-*N*-(Boc)-cyclohexylalaninal by application of the Moffatt–Swern oxidation of α-amino alcohols has been described [1346]. Moffatt–Swern oxidation of protected (*S*)-alcohol **1803** with DMSO/**$(COCl)_2$**/Et_3N/



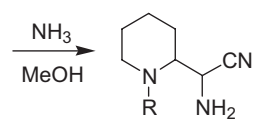
1796 **1797**



1798



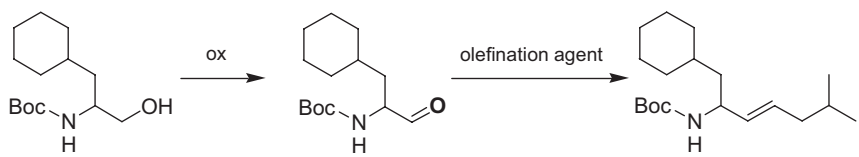
1799 **1800** **1801**



1802

R = $PhCH_2$, $PhCH_2OCO$ (Z), Me_3COCO (Boc)

$(CHMe_2)_2$ or DMSO/**pyridine-SO_3**/Et_3N gave the aldehyde **1804** with >95% enantiomeric excess. The chemical efficiency of this oxidation was demonstrated in the two-step conversion of **1803** to (*S*,*Z*)-**1805** in 60% yield by subsequent olefination of intermediate **1804** with $Ph_2P^+CH_2CH_2CHMe_2\ Br^-$.



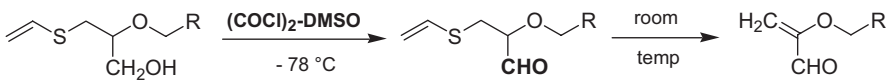
1803 ee > 95 % **1804** 60 % **1805**

Boc = Me_3COCO

ox = DMSO/$(COCl)_2$/Et_3N/$(CHMe_2)_2$ or DMSO/pyridine-SO_3/Et_3N

olef. agent = $Ph_2P^+(CH_2)_2CH(CH_3)_2\ Br^-$

A general method for the preparation of α-alkoxyacroleins, which includes a Swern oxidation step, has been reported [1348]. Swern oxidation of **1806** with oxalyl chloride/Me_2SO at −78 °C, followed by treatment with triethylamine, gave the corresponding aldehydes **1807**. As the crude reaction mixtures were allowed to warm to ambient temperature (0.5–3 h), β-elimination gave alkoxy aldehydes **1808** in 70–93% yield.



1806 **1807** **1808**

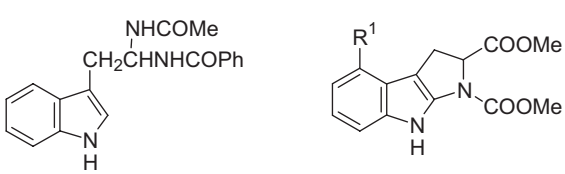
R = OCH_2CH_2OMe, $CH{=}CH_2$, oxiranyl, $(CH_2)_3Br$, $(CH_2)_3N_3$

Swern oxidation of various indolic substrates has been described, and a range of products resulting from overall oxidation at the 2-position have been observed. For example, indolylpropanol **1809** [R = $(CH_2)_3OH$] is oxidized with DMSO and either **trifluoroacetic anhydride** or **oxalyl chloride** to give the unsaturated aldehyde **1810** [R = $(CH_2)_2CHO$] [1333].

1809 **1810**

Depending on the substrate and the reaction conditions, indolealkyl alcohols may be oxidized to α,β-unsaturated systems, and indoles can either be oxidized to introduce a nucleophile regioselectively at the 2-position or to introduce both a nucleophile at the indole 2-position and a $MeSCH_2$ group at the indole 4-position through an unprecedented rearrangement of a Swern intermediate [1333].

For example, after oxidation of *N*-acetyltryptophan methyl ester **1811** with DMSO and **trifluoroacetic anhydride** at −78 °C, subsequent addition of triethylamine at this temperature gives the dihydropyrroloindole **1812** (R^1 = H) in 35% yield, while warming to room temperature and then adding triethylamine gives **1812** (R^1 = $MeSCH_2$) in 35% yield [1333].



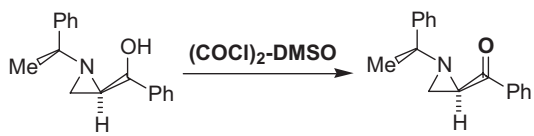
1811 **1812**

Swern oxidation has been used as a key synthetic step in the construction of 3-aryloxy-4-arylfuran-2-ones, which are useful as inhibitors of COX-2 [1323], and in the synthesis of spirocyclic ketones as intermediates in the preparation of a *tachykinin antagonist* [1324, 1325].

N-(*tert*-Butoxycarbonyl)-*N*,*O*-isopropylideneserinal can be prepared in 94% yield and 96–98% enantiomeric purity from the corresponding serine-derived methyl ester by reduction to the alcohol and subsequent Swern oxidation. This method avoids some of the problems encountered in the synthesis of the same aldehyde by direct controlled DIBAL reduction [1341].

The effect of different amine bases on the Swern oxidation of β-amino alcohols has been studied. Swern oxidation of β-amino alcohols containing tertiary amino groups afforded the corresponding α-amino carbonyl compounds in fair to excellent yields. Yields were dependent on the steric requirement of the amine base used for the reaction and were optimized by the use of *N*-methylpyrrolidine, *N*-ethylpiperidine, or triethylamine, depending on the β-amino alcohol substrate [1380].

Various enantiomerically pure aziridino ketones, e.g. **1814**, have been prepared from the corresponding secondary alcohols **1813** by Swern oxidation. The configurationally stable α-amino ketones were stereoselectively reduced by L-*Selectride*® to provide the corresponding alcohols with high diastereoselectivities and in high chemical yields [1381].

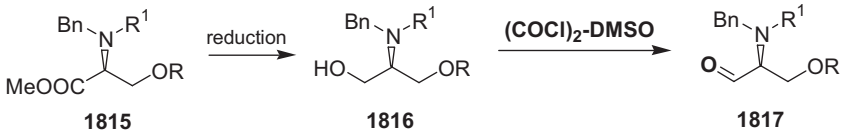


1813 **1814**

Swern oxidation is a key step in the preparation of *N*-protected amino aldehydes. The *N*-protected amino aldehyde function is a key feature of intermediates en route to reduced-form peptides containing a CH_2NH bond, e.g. (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (statine), and derivatives thereof, e.g. (3*S*,4*S*)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid (cyclostatine), which, in turn, is an important intermediate for inhibitors of acidic protease such as renin. This process is accompanied by little racemization and gives products with excellent optical activities in excellent yields [1365].

A synthesis of *N*,*N*-diprotected L-serinals **1817** [1382] and a straightforward synthesis of *N*-Boc-L-serinal and *N*-Boc-L-threoninal acetonides [1383], with a Swern oxidation as the final step, have been reported. Protected L-serinals were synthesized from L-serine by reduction of the methyl esters **1815** followed by Swern oxidation of the corresponding alcohols **1816**.

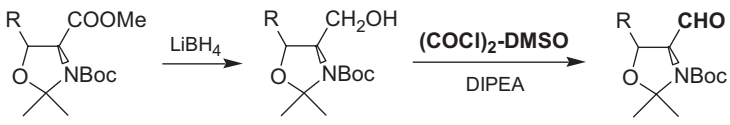
An improved procedure for the synthesis of optically active acetonides **1820** from the ester precursors **1818** has been described. Thus, acetonides **1818** were reduced with $LiBH_4$ to give alcohols **1819** in 88–93% yield, which were then oxidized with



1815 **1816** **1817**

R = benzyloxymethyl, *tert*-butyldiphenylsilyl
R^1 = Boc, $COOCH_2Ph$
Bn = benzyl

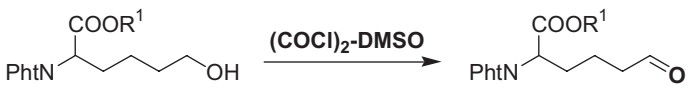
oxalyl chloride/**DMSO** in the presence of DIPEA to give aldehydes **1820** in 77–96% yield [1383].



1818 **1819** 77-96 % **1820**

R = H, Me
Boc = Me_3COCO

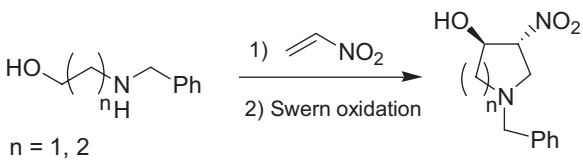
Oxidation of protected hydroxynorleucine derivatives **1821** gives the corresponding aldehyde **1822**, which is amenable to further transformations, opening a versatile synthetic route for the generation of C-7 substituted azepinones [1326].



1821 **1822**

Pht = phthalimido
R^1 = Me, Bn

Nitrohydroxylated pyrrolidine and piperidine ring systems **1824** have been conveniently obtained by a one-pot procedure involving sequential Michael–Henry reaction between nitroethene and a nitrogen nucleophile **1823** suitably predisposed for the oxidative generation (Swern reaction) of an aldehyde group, which is directly trapped in the subsequent nitroaldolization step [1384].



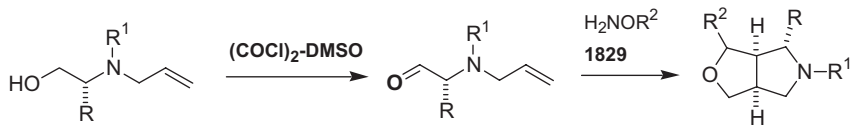
n = 1, 2

1823 **1824**

Tetrahydroisoquinoline **1826**, a useful intermediate for the preparation of 8,11-iminoazepino[1,2-*b*]isoquinoline derivatives as antitumor agents, has been synthesized by a reaction sequence including a Swern oxidation [1327].

1825 **1826**

Swern oxidation has been used in the synthesis of homochiral 3-oxa-2,7-diazabicyclo[3.3.0]octanes from amino acids by intramolecular 1,3-dipolar cycloaddition of nitrones [1347].

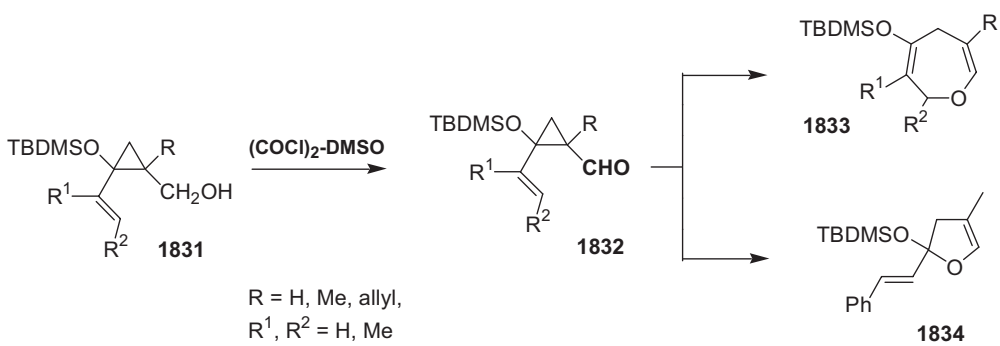


1827 **1828** **1830**

R = Me, *i*-Pr
R^1 = allyl, CH_2Ph
R^2 = CMe_3, CH_2Ph, H

(*S*)-Amino alcohols **1827** have been prepared from amino acids by various methods. Swern oxidation of **1827** afforded aldehydes **1828**. Reaction of **1828** with *O*-alkylhydroxylamines **1829** gave nitrones, which spontaneously underwent a diastereoselective intramolecular 1,3-dipolar cycloaddition to yield the bicyclic compounds **1830**.

The synthesis of functionalized 2,5-dihydrooxepines by [3,3]sigmatropic rearrangement of cyclopropane derivatives [1338] includes a Swern oxidation of 2-alkenyl substituted 2-siloxycyclopropyl alcohols **1831**, which provides 2,5-dihydrooxepine derivatives **1833** in 74–98% yield, while alcohols **1831** (R = H, Me; $R^1 = R^2 = H$) bearing a 2-styryl substituent give dihydrofurans **1834**. The forma-

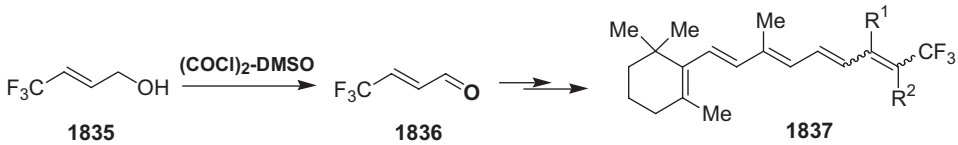


1831 **1832** **1833** **1834**

R = H, Me, allyl,
R^1, R^2 = H, Me

tion of these heterocycles can be rationalized in terms of ring-enlargement of intermediate cyclopropyl aldehydes giving 2,5-dihydrooxepines by [3,3]sigmatropic rearrangement, or dihydrofurans through a stabilized 1,3-zwitterion.

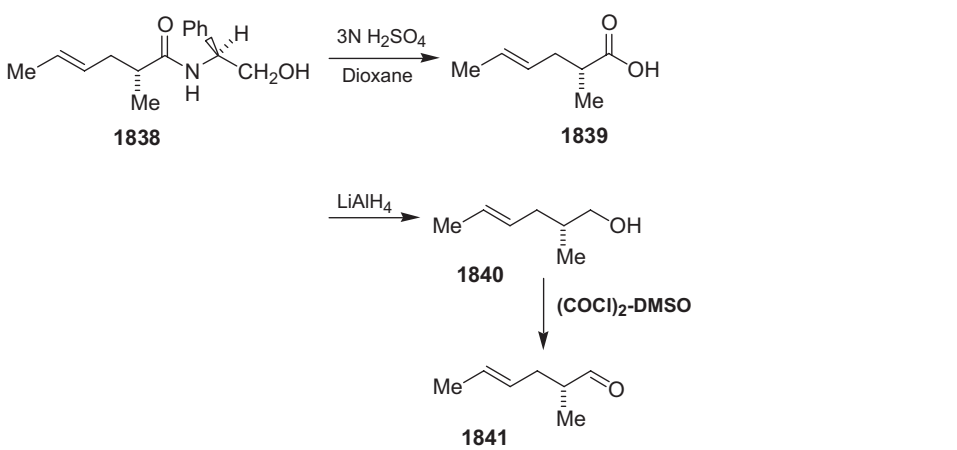
In the preparation of trifluoromethyl retinoid analogues **1837** as anticancer agents [1328], a key intermediate, 3-trifluoromethylpropenal **1836** was synthesized by Swern oxidation of the corresponding alcohol **1835**.



1835 **1836** **1837**

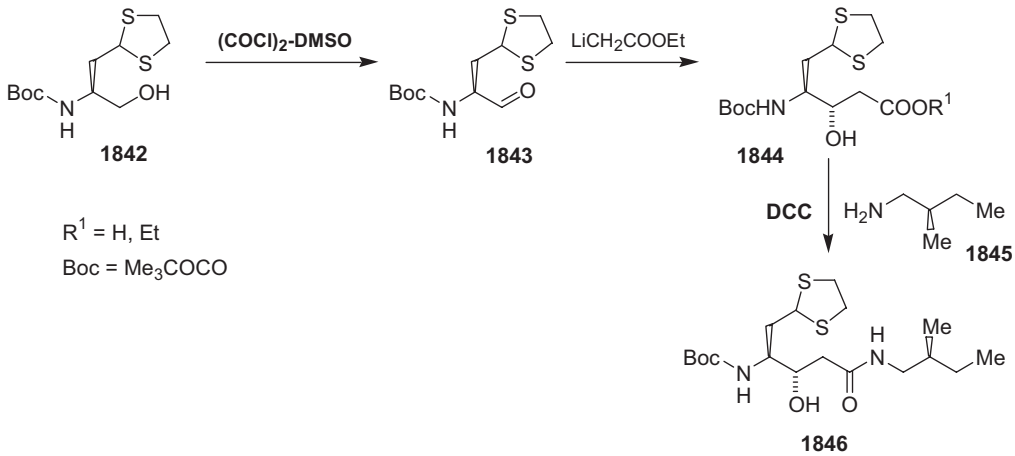
R1 = H, lower alkyl; R2 = H, CO2H, CH2OH, CHO, fluoroalkyl, lower alkyl or alkoxycarbonyl

A facile, preparative-scale synthesis of (2*R*,4*E*)-2-methyl-4-hexenal **1841**, a key intermediate in the synthesis of (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-methylamino-6-octenoic acid (MeBmt), has been reported [1337]. The hexenal **1841** was prepared by hydrolyzing the starting amide **1838** with sulfuric acid, reducing the resulting acid **1839** with $LiAlH_4$, and oxidizing the resulting alcohol **1840** under the Swern conditions.

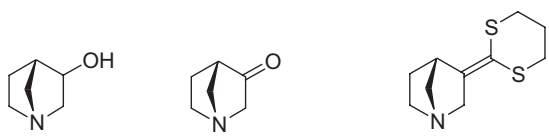


1838 **1839** **1840** **1841**

The novel statine analogue **1844** has been synthesized from $PhCH_2O_2C$-L-Asp-OH in several steps. Key steps were the Swern oxidation of amino alcohol **1842** to the aldehyde **1843** followed by an aldol condensation with $LiCH_2CO_2Et$ to give a mixture of **1844** and its (3*R*,4*S*)-diastereomer. The latter were hydrolyzed and then condensed with (*S*)-$H_2NCH_2CHMeEt$ **1845** in the presence of **DCC** to give amide **1846** and its (3*R*,4*S*)-diastereomer, which were separated by column chromatography on silica gel [1329].



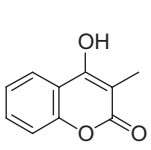
Racemic *exo*-1-azabicyclo[2.2.1]heptan-3-ol **1847** has been resolved by fractional crystallization of its hydrogen tartrate salts. The (+)- and (−)-enantiomers of **1847** were oxidized to the respective (−)- and (+)-enantiomers of the corresponding ketones **1848** with **DMSO/oxalyl chloride**. CD spectroscopy suggested that the (−)-ketone, (−)-**1848**, possesses the (1*R*,4*S*)-configuration. This absolute configuration was confirmed by single-crystal X-ray diffraction analysis of the derivative (+)-(1*R*,4*R*)-3-(1,3-dithian-2-ylidene)-1-azabicyclo[2.2.1]heptane, (+)-**1849** [1386].



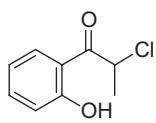
1847 **1848** **1849**

The reaction of 4-hydroxycoumarin derivatives with activated dimethyl sulfoxide has been investigated experimentally. The Swern reaction of 3-alkyl-4-hydroxycoumarins **1850** affords in high yield α-chloro-α-alkyl-*o*-hydroxyacetophenone derivatives **1851**, as a result of halogenodecarbonylation of the pyranone ring. Using a model compound, other activators of DMSO (**TFAA/P_4O_{10}**, **DCC/SO_3/pyridine**) gave mixtures of methylthiomethyl derivatives **1852**, accompanied by dimeric product **1853** in the case of P_4O_{10}. The formation of the halogenated acetophenones and of the dimeric product can be rationalized by assuming the initial formation of a chromanedionyl sulfonium salt, followed by nucleophilic displacement by the chloride counterion or by the unchanged 4-hydroxycoumarin. The resulting 3,3-disubstituted chromanediones are then hydrolytically decarboxylated during the aqueous work-up [1334].

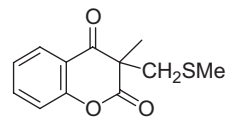
Oxidation of aryloxy amino alcohols **1854** with activated DMSO provided a convenient one-pot method for synthesizing hydroxyimines **1856** without isolation of the unstable intermediate ketones **1855** [1387]. Assignment of the (*Z*)- and (*E*)-



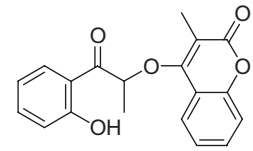
1850



1851

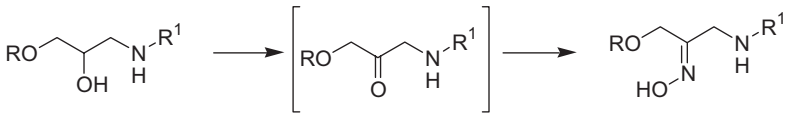


1852

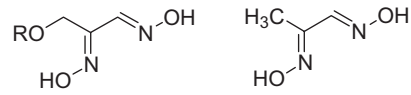


1853

stereoisomers of **1856** was based on ^{1}H and ^{13}C NMR studies. Spontaneous isomerization of **1856** was also observed. Compounds **1857** and **1858** were first isolated as by-products from the oxidation of **1854**, and subsequently an improved synthetic method for **1857** was developed. The novel C–N oxidation step involved in the formation of **1857** from **1854** was rationalized in terms of a neighboring-group effect.



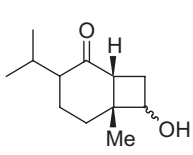
1854 **1855** **1856**



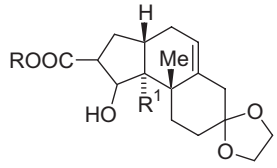
1857 **1858**

R = 1-naphthyl, *o*-CH_2=$CHCH_2C_6H_4$, *m*-tolyl, etc.;
R^1 = $CHMe_2$, CMe_3, $CH_2CH_2C_6H_3(OMe)_2$-3,4

The Swern oxidation of structurally diverse alcohols, such as **1859** and **1860**, employing the **oxalyl chloride**/**DMSO** protocol, unexpectedly gave rise to products resulting from concomitant electrophilic chlorination. This potential problem can be avoided either by using the reagents in stoichiometric quantities or by employing **$(CF_3CO)_2O$/DMSO** or **Ac_2O/DMSO** [1331].



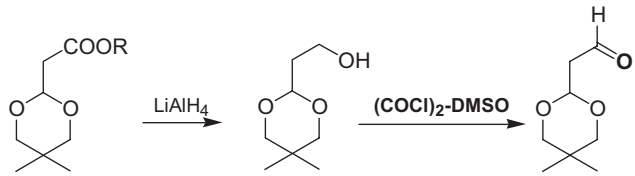
1859



1860

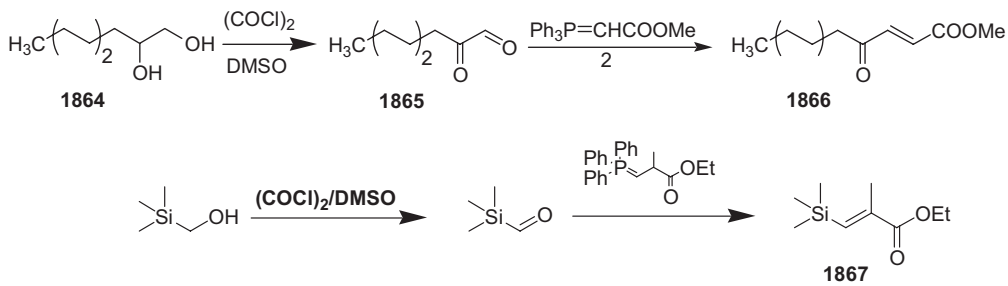
R = CH2CH2SiMe2, R1 = CN
R = H, R1 = Me

Highly efficient syntheses of alkyl 3,3-dialkoxypropanoates, alkyl 4-ethoxy-2-oxo-3-butenoates, and monoprotected malonaldehydes have been reported [1340]. Reduction of acetals **1861** with $LiAlH_4$ and oxidation of **1862** with **oxalyl chloride**/**DMSO** gave monoprotected malonaldehyde **1863**.



1861 **1862** **1863**

Application of the Swern oxidation to the manipulation of highly reactive carbonyl compounds has been reported [1388]. The transient existence of monomeric Me_3SiCHO, generated at −78 °C by Swern oxidation of Me_3SiCH_2OH, has been established by isolation of the Wittig condensation product. Direct addition of nucleophilic reagents to crude Swern oxidation product mixtures circumvents the deleterious side reactions characteristic of highly reactive carbonyl compounds. Hexylglyoxal **1865**, produced by Swern oxidation of 1,2-octanediol **1864**, condenses with $Ph_3P{=}CHCO_2Me$ to give the corresponding olefination product **1866**.



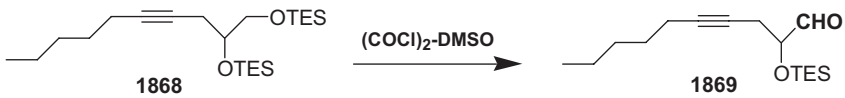
1864 **1865** **1866**

1867

Typical procedure. *Ethyl (E)-3-(trimethylsilyl)methacrylate* **1867** [1388]: To a stirred solution of **oxalyl chloride** (131 μL, 0.190 mg, 1.50 mmol) in dichloromethane (8.0 mL) at −78 °C was added dimethyl sulfoxide (121 μL, 0.133 mg, 1.70 mmol). After 10 min, a solution of (trimethylsilyl)methanol (104 mg, 1.00 mmol) in dichloromethane (2 mL) was added over 4 min, and, after 15 min, triethylamine (0.52 mL, 377 mg, 3.7 mmol) was added over 1 min. After 5 min at −78 °C, a solution of ethyl 2-(triphenylphosphoranylidene)propionate (690 mg, 1.9 mmol) in dichloromethane was added over 3 min. The reaction mixture was then allowed to warm to room temperature, diluted with diethyl ether (70 mL), and then washed with water (40 mL) and brine (40 mL). The organic phase was dried over magnesium sulfate and then concentrated under reduced pressure. Chromatography of the residue eluting with diethyl ether/petroleum ether, 3:97, afforded 101 mg (54%) of product **1867** as a colorless oil.

The synthesis of enantiomerically pure α-*N*,*N*-dibenzylamino aldehydes, e.g. (*S*)-2-(*N*,*N*-dibenzylamino)-3-phenylpropanal prepared from L-Phe-OH by *N*- and *O*-benzylation, reduction of the ester to the alcohol, and Swern oxidation, has been described [1389].

Swern conditions have been applied in the selective oxidation of primary silyl ethers, intermediates in the synthesis of natural products [1322]. Thus, primary trimethylsilyl or triethylsilyl ethers **1868**, in the presence of secondary trimethylsilyl or triethylsilyl ethers, are selectively oxidized to the corresponding aldehydes **1869** under Swern conditions. A short synthesis of key intermediates towards various natural products, e.g. leukotrienes, has been achieved.



The reactivity of trimethylsilyl ethers of primary and secondary alcohols towards the Swern reagent (**oxalyl chloride**/**DMSO**) has been investigated [1336]. Useful selectivity is possible when the competing ether groups have widely differing degrees of steric hindrance. Dimethyl-*tert*-butylsilyl ethers are unaffected by this reagent. Thus, oxidation of octanyl trimethylsilyl ether with the Swern reagent gave octanal, which was isolated as the 2,4-dinitrophenylhydrazone in 92% yield.

Selective Swern oxidation of the primary alcohol groups of allylamino alcohols, as a key step in the formation of enantiopure β-amino alcohols with a 3-oxa-2,7-diazabicyclo[3.3.0]octane framework, has also been reported [1339].

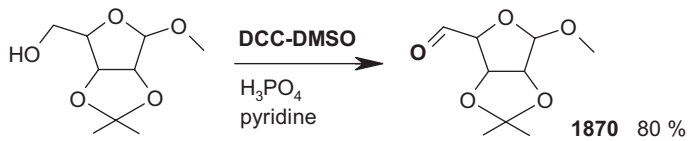
4.7.5.2 Miscellaneous Methods for the Oxidation of Alcohols

Dicyclohexylcarbodiimide/DMSO

The original discovery of Pfitzner and Moffatt [1390] that alcohols are oxidized to carbonyl compounds by dimethyl sulfoxide, **dicyclohexylcarbodiimide** (**DCC**), and phosphoric acid at room temperature was immediately recognized as an effective and mild procedure for sensitive substrates.

Typical procedure. *Methyl 2,3-O-isopropylidene-β-D-ribo-pentodialdo-1,4-furanoside* **1870** [1391]: A solution of anhydrous crystalline orthophosphoric acid (0.98 g, 10 mmol) in dimethyl sulfoxide (2.0 mL) was added to a solution of methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (4.08 g, 20 mmol), pyridine (0.8 mL, 10 mmol), and **DCC** (12.4 g, 60 mmol) in dimethyl sulfoxide (50 mL). The mixture was kept at around 25 °C for 3 h by occasional ice-cooling, then diluted with ethyl acetate (100 mL), and a solution of oxalic acid dihydrate (5.04 g, 40 mmol) in methanol (10 mL) was added. The mixture was subsequently poured into saturated sodium chloride solution (200 mL), filtered, and the aqueous phase was extracted with ethyl acetate (100 mL). The combined organic phases were washed successively with dilute sodium hydrogen carbonate solution (100 mL), saturated sodium chloride solution (2×100 mL), and iced water (100 mL). The organic phase was dried with magnesium sulfate, concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (25 mL) and filtered to remove residual *N*,*N*′-dicyclohexylurea. The solution was concentrated to a syrup (4.7 g), which was purified by sublimation at 60–70 °C (0.1 Torr) to give the product **1870** as a white crystalline solid, 3.23 g

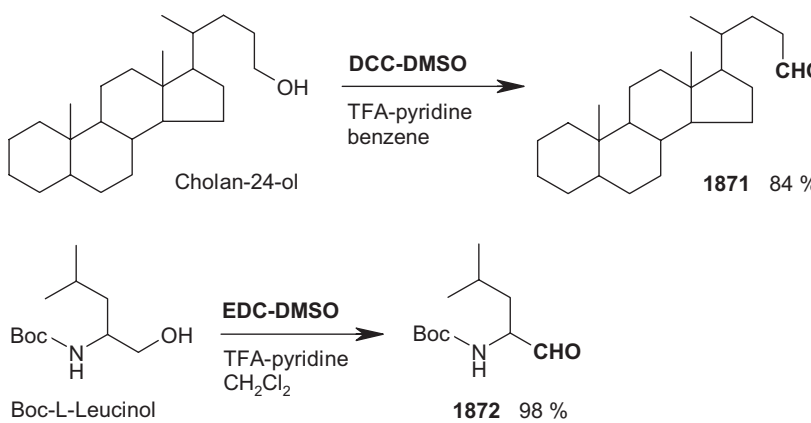
(16 mmol, 80%), mp 50–56 °C. The product contained about 3% of the 5-thiomethylmethyl ether, as estimated by ^{1}H NMR. Recrystallization from hexane at ca. 18 °C gave material with mp 60–61 °C, $[\alpha_D] = -214°$ ($c = 0.1$, $CHCl_3$).



Typical procedure. *Cholan-24-al* **1871** [1392]: Cholan-24-ol (1.033 g, 3 mmol) was dissolved in dry benzene (10 mL) by gentle warming and dry dimethyl sulfoxide (10 mL) was added, followed successively by dry pyridine (0.24 mL, 3.0 mmol), distilled trifluoroacetic acid (0.12 mL, 1.5 mmol), and **dicyclohexylcarbodiimide** (1.85 g, 9 mmol). The flask was tightly stoppered and left at room temperature for 18 h. Benzene (30 mL) was then added, and the crystalline dicyclohexylurea formed was removed by filtration and washed with benzene. The combined filtrate and washings were washed with water (3 × 50 mL), dried over sodium sulfate, and concentrated under reduced pressure to give 2.12 g of a syrup, which partially crystallized. The crude product was dissolved in benzene/hexane, 1:1, and chromatographed on 125 g of silica gel with this solvent mixture to give cholan-24-al **1871** (0.87 g, 84%); mp 102–104 °C.

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC)

An *N*-protected amino aldehyde can be prepared by Swern oxidation of an *N*-protected amino alcohol in the presence of an oxidizing agent comprising DMSO and a water-soluble carbodiimide derivative as **1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride** (**EDC**) in an organic solvent. The *N*-protected amino alcohol can be derived from an L-, D-, or L-/D-amino acid, but usually is the *N*-protected-(*S*)-α-amino alcohol derived from an *N*-protected L-amino acid.



Typical procedure. *N-tert-Butyloxycarbonyl-L-leucinal* **1872** [1365]: *N-tert*-Butyloxycarbonyl-L-leucinol (217 g), prepared by the reduction of Boc-Leu-OMe with sodium borohydride/sodium chloride, was dissolved in dichloromethane (1.5 L) and then DMSO (250 mL) was added. To the homogeneous solution, anhydrous pyridine (900 mL), trifluoroacetic acid (40 mL), and **EDC** (576 g) were added, and the mixture was stirred at room temperature for 24 h. Work-up gave a 98% yield of crude *N-tert*-butyloxycarbonyl-L-leucinal **1872** as a syrup, which could be used directly for aldol condensation in the preparation of statine.

N-tert-Butyloxycarbonyl-L-phenylalaninal was similarly prepared from *N-tert*-butyloxycarbonyl-L-phenylalaninol.

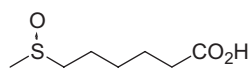
Aliphatic polysulfoxides and polymer-bound sulfoxides

Attempts to replace **dimethyl sulfoxide** by stoichiometric amounts of an easily separable, recyclable, and odorless sulfoxide that can be polymer-bound have also been reported [1393, 1394]. Aliphatic polysulfoxides having sulfoxide groups on the main chain were prepared by the selective oxidation of aliphatic polysulfides using aqueous H_2O_2 in chloroform. The degree of oxidation to sulfoxides was calculated from the integral ratios of methylene H adjacent to S atoms in the ^1H NMR spectra. Use of the aliphatic polysulfoxides as polymeric oxidizing reagents was studied. Poly(hexamethylene sulfoxide) was applied in the Swern oxidation of primary or secondary alcohols, whereby 1-octanol and 6-undecanol were oxidized to give quantitative yields of octanal and 6-undecanone, respectively [1395].

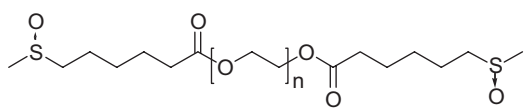
The readily available 6-(methylsulfinyl)hexanoic acid **1873** is employed as a substitute for DMSO in Swern oxidation reactions using **oxalyl chloride**, whereby primary or secondary alcohols are smoothly converted to the corresponding aldehydes or ketones in high yield.

The resulting 6-(methylthio)hexanoic acid is easily separable by aqueous extraction or by filtration through silica gel and can be reoxidized to **1873** with sodium metaperiodate in 97% yield. Low temperature (−60 °C) ^{13}C NMR spectrometry has been used to examine the intermediates of this Swern process. The results indicate that any residual unoxidized alcohol is generated during Pummerer elimination of the alkoxysulfonium intermediate and can be minimized by prolonged exposure to triethylamine at −40 °C. Reaction of the potassium salt of **1873** with cross-linked chloromethyl polystyrene affords a polymer-bound reagent that quantitatively oxidizes borneol to camphor when used in two-fold excess [1394].

1873

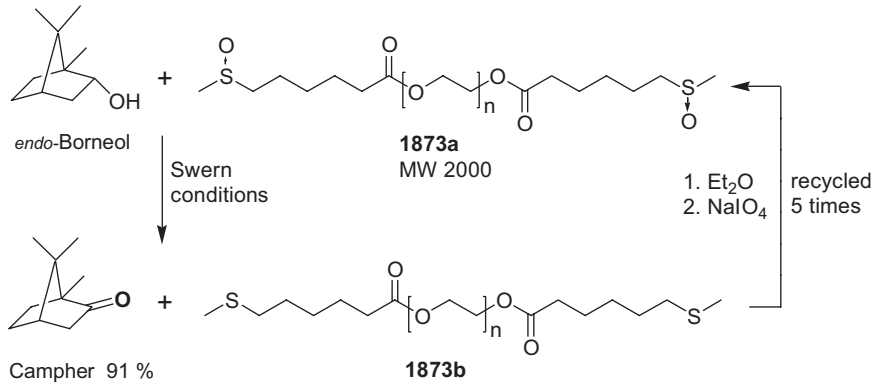


1873a



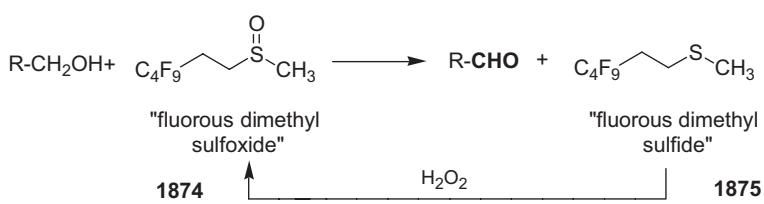
Modification of the Swern oxidation has also been achieved by the use of a soluble, polymer-bound, recyclable, and odorless sulfoxide **1873a** [1394]. Sulfoxides bound

to poly(ethylene glycol) chains meet these criteria and have been used in the Swern oxidation of alcohols. The reaction gives ketones and aldehydes in yields comparable to those achieved by usual Swern oxidation with DMSO.



For example, Swern oxidation of *endo*-borneol with the sulfoxide **1873a** (MW 2000) yields camphor in 91% yield. The resulting sulfide by-product **1873b** can be recovered by precipitation from the solution with diethyl ether, and then reoxidized with $NaIO_4$ to give **1873a** in 99% yield. It can be recycled five times with no observable loss in oxidation capacity. **1873a** gives yields comparable to, or better than, those achieved with 6-(methylsulfinyl)hexanoic acid **1873** in the Swern oxidation, and offers improved recoverability with no odor.

Progress in making the Swern oxidation more 'nose-friendly' has recently been reported [1396]. Dimethyl sulfoxide was replaced with ''fluorous dimethyl sulfoxide'' **1874**, the by-product being the corresponding ''fluorous dimethyl sulfide'' **1875**, which is odorless and easily recovered. Adding hydrogen peroxide regenerates the starting sulfoxide.



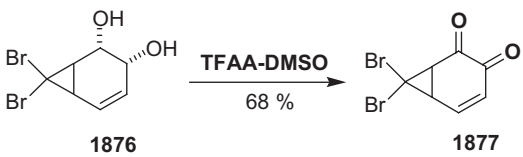
cis-Dioxomolybdenum(VI) complexes/DMSO

Catalytic oxidation of alcohols by ***cis*-dioxomolybdenum(VI)** complexes, involving oxygen atom transfer from sulfoxides has been reported [1397]. Catalytic amounts of ***cis*-dioxomolybdenum(VI)** complexes in association with sulfoxides can be used to oxidize alcohols to carbonyl compounds. For primary alcohols, the oxidation to the aldehyde is selective, and no further oxidation to the carboxylic acid is observed. The oxidation is most effective for benzylic and allylic alcohols. The mechanism

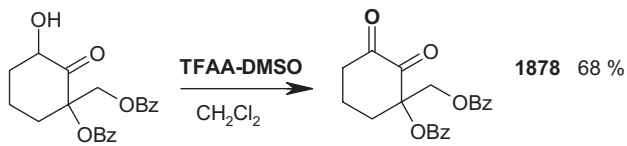
has been shown not to be of a Swern-type Me_2SO oxidation, but probably involves a hydride transfer from a coordinated alkoxide to an oxo ligand on the Mo(VI), thereby forming the aldehyde and an Mo(IV) species, the latter being reoxidized to Mo(VI) by the sulfoxide in an oxygen atom transfer step.

Trifluoroacetic anhydride-activated DMSO

Trifluoroacetic anhydride-activated DMSO is an effective oxidant for the conversion of vicinal diols into the corresponding α-dicarbonyl compounds or products derived therefrom [1330]. Unlike the Swern oxidant, the title reagent system gives good yields of products derived from halogenated substrates. The method has permitted syntheses of previously inaccessible compounds, including tropolones, a σ-homo-*o*-benzoquinone, and a hyper-reactive α-keto aldehyde (isolated as its monoenolic tautomer 2-hydroxy-2-dodecenal). Thus, oxidation of dibromobicycloheptenediol **1876** gave dibromobicycloheptenedione **1877** in 68% yield.



1876 **1877**



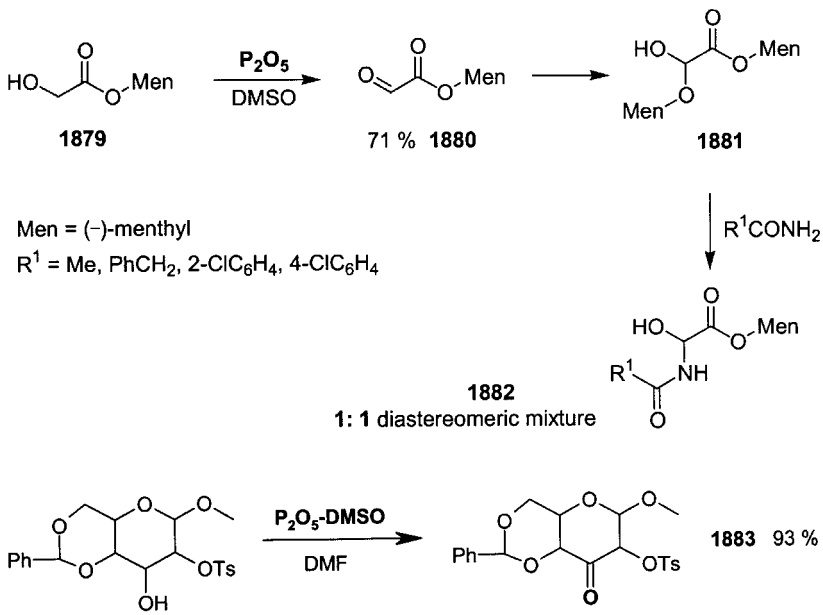
1878 68 %

Typical procedure. *3-(Benzoyloxy)-3-[(benzoyloxy)methyl]cyclohexane-1,2-dione* **1878** [1398]: **Trifluoroacetic anhydride** (104 μL, 155 mg, 0.74 mmol) was added over 5 min to a solution of dimethyl sulfoxide (70 μL, 77 mg, 0.99 mmol) in dry dichloromethane (1.1 mL) at −70 °C under argon. After stirring for 20 min at −70 °C, 2-(benzoyloxy)-2-[(benzoyloxy)methyl]-6-hydroxycyclohexane (192 mg, 0.5 mmol) was added over 5–10 min, and stirring was continued for a further 30 min. Triethylamine (20 μL, 15 mg, 0.1 mmol) was then added over 10–15 min, the solution was allowed to warm to room temperature, and water was added. The mixture was extracted with diethyl ether, and the combined extracts were washed with 5% aq. hydrochloric acid and water, dried over sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel (100–200 mesh, 15 g) eluting with 10% ethyl acetate/hexane to give the product, which was crystallized from methanol; yield 125 mg (0.34 mmol, 68%) of **1878**.

Phosphorus pentoxide/DMSO

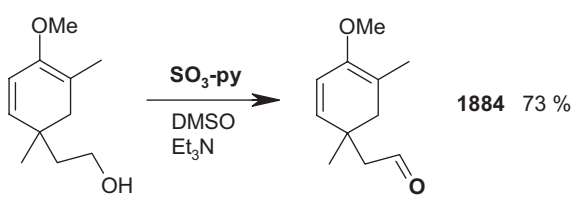
The (−)-menthyl ester group has been employed as a chiral auxiliary in electrophilic glycine derivatives. Modified Swern oxidation of (−)-menthyl glycolate **1879** using **phosphorus pentoxide** for activation of DMSO instead of oxalyl chloride gave

the glyoxalate $OHCCO_2Men$ **1880** in 71% yield. Conversion of **1880** to its (−)-menthyl hemiacetal **1881**, followed by condensation with amides R^1CONH_2 gave 1:1 diastereomeric mixtures of adducts **1882**. One isomer of **1882** (R = 4-ClC_6H_4) could be isolated by fractional crystallization [1366].



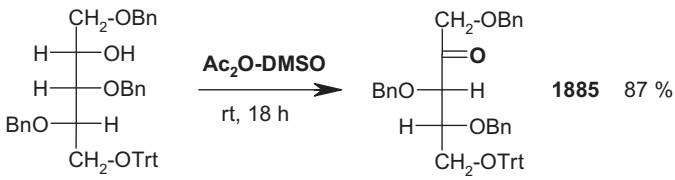
Typical procedure. *Methyl 4,6-O-benzylidene-2-O-p-toluenesulfonyl-α-D-ribo-hexopyranosid-3-ulose* **1883** [1400]: A mixture of methyl 4,6-*O-benzylidene-2-O-p*-toluenesulfonyl-α-D-glucopyranoside (7.2 g, 16.5 mmol), dimethyl sulfoxide (5.0 g, 65 mmol), **phosphorus pentoxide** (8.0 g, 56 mmol), and dimethylformamide (200 mL) was heated for 2 h at 65–70 °C with stirring. The reaction mixture was then poured into iced water and the solution was kept in a refrigerator overnight. The crystals deposited were collected by filtration and washed with water; yield 6.7 g (15.4 mmol, 93%). The product **1883** contained no impurities detectable by TLC on silica gel eluting with benzene/methanol (98:2, *v*/*v*). Crystallization from ethanol gave white crystals; mp 162–164 °C, $[\alpha]_D^{28} = +45°$ ($c = 1.0$, $CHCl_3$).

Sulfur trioxide–pyridine complex/DMSO



Typical procedure. *1,5-Dimethyl-4-methoxycyclohexa-2,4-dienylacetaldehyde* **1884** [1399, 1401]: To a solution of 2-(1,5-dimethyl-4-methoxycyclohexa-2,4-dienyl)ethanol (450 mg, 2.47 mmol) in anhydrous triethylamine (5 mL) and anhydrous dimethyl sulfoxide (5 mL) was added a solution of **sulfur trioxide–pyridine complex** (1.90 g, 11.9 mmol) in anhydrous dimethyl sulfoxide (7 mL). The reaction mixture was stirred at room temperature for 2.25 h and then partitioned between water and diethyl ether. The aqueous phase was further extracted with diethyl ether and the combined ethereal extracts were washed with water and brine and dried over magnesium sulfate. The solvent was removed to give 3.23 mg (1.79 mmol, 73%) of virtually pure product **1884**. Column chromatography on alumina eluting with benzene gave pure material.

Acetic anhydride/DMSO



1885 87 %

Typical procedure. *1,3,4-Tri-O-benzyl-5-O-triphenylmethyl-keto-D-threo-pentulose* **1885** [1402, 1403]: 2,3,5-Tri-*O*-benzyl-l-*O*-triphenylmethyl-D-arabinitol (5.0 g, 7.5 mmol) was dissolved in DMSO/**acetic anhydride** (3:2, *v*/*v*; 30 mL) and the solution was kept at room temperature for 18 h. Cold water (120 mL) was then added, the mixture was stirred for 30 min, and the aqueous phase was decanted off. The remaining yellowish syrup was washed twice with water and dissolved in hexane, and this solution was washed repeatedly with water, once with 10% aqueous silver nitrate solution, and concentrated under reduced pressure to yield 4.9 g of a syrup. Chromatography on 250 g of silica gel (0.05–0.20 mm, Merck no. 7734) eluting with benzene/diethyl ether (9:1, *v*/*v*) gave the product **1885**, pure by TLC, as a syrup (4.3 g, 6.5 mmol, 87%); $[\alpha]_D^{21} = -26.2^\circ$ ($c = 2.1$, $CHCl_3$).

Triphosgene/DMSO

Triphosgene is an excellent activator of DMSO for carrying out mild oxidations of alcohols to carbonyl compounds [1362, 1363]. Oxidations proceed in good to excellent yield at −78 °C to room temperature in the presence of triethylamine, and the system is adaptable for large-scale operations. Diisopropylethylamine (DIPEA) may also be employed as a base in such oxidation processes. This hindered base is known to prevent racemization in other sensitive substrates [1404].

The **triphosgene**/**DMSO** reagent may be a good substitute for **trifluoroacetic anhydride**/**DMSO** as well as **acetic anhydride**/**DMSO**, which are often employed in such oxidation reactions. The former usually gives the corresponding oxidized products along with variable amounts of trifluoroacetate esters [1373] and although

the latter may be used for large-scale oxidations, it suffers from a need for long reaction times and also the formation of acetate esters as well as (methylthio)-methyl ethers [1316, 1317, 1319, 1320]. The formation of methylthiomethyl ethers is proposed to involve the generation of $MeSCH_2^+$, which alkylates the alcohol [1318, 1405, 1406].

The use of **triphosgene** as a DMSO activator has several advantages over oxalyl chloride. It is a solid that can be weighed accurately and is less susceptible to hydrolysis. Furthermore, the oxidation of β-phenylethanols with **triphosgene**/**DMSO** gave better yields compared to oxidation with **oxalyl chloride**/**DMSO** or **TFAA**/**DMSO** [1363].

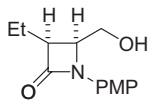
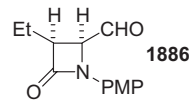
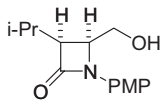
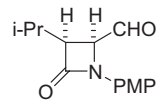
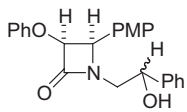
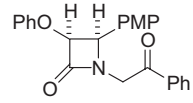
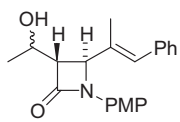
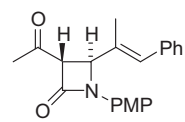
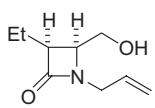
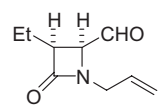
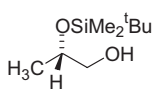
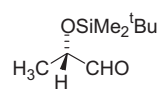
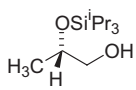
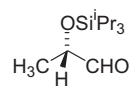
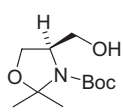
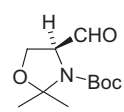
Although for 3 equivalents of substrate, 1 equivalent of the reagent is sufficient to achieve a high yield oxidation process, in practice a 2.5:1 reagent/substrate ratio was used [1362]. Extension of the above procedure to a variety of structurally different hydroxy compounds is shown in Table 4.51.

As can be seen from the data listed in Table 4.51, the oxidation reaction works well with hydroxy compounds having a variety of functional groups, such as α-silyloxy, α-amino, and α-amido alcohols, to provide the corresponding α-silyloxy aldehydes and α-amino and α-amido carbonyl compounds in good yields. Furthermore, the optical purities of these compounds, as indicated by their specific optical rotations, show that no epimerization occurred at the α-position to the nascent carbonyl carbon under the described reaction conditions. Oxidation of a 3-(1′-hydroxyethyl) β-lactam (entry d) and 1-allyl-3-ethyl-4-(hydroxymethyl)azetidin-2-one (entry e) without any detectable amounts of chlorinated products also shows the potential advantage of the **triphosgene**/**DMSO** system for other substrates sensitive to oxidizing reagents.

Typical procedure. *cis-3-Ethyl-4-formyl-1-(4-methoxyphenyl)azetidin-2-one* **1886** (entry a, Table 4.51) [1362]: To a stirred solution of **triphosgene** (11.9 g, 40 mmol) in dichloromethane (120 mL) at −78 °C was added DMSO (17 mL, 0.24 mol). The reaction mixture was stirred for 15 min and then a solution of *cis*-3-ethyl-4-hydroxymethyl-1-(4-methoxyphenyl)azetidin-2-one (23.5 g, 0.1 mol) in dichloromethane (160 mL) was added dropwise, maintaining the temperature below −70 °C. After the addition, the resulting suspension was stirred at −78 °C for 5 min and then the acetone/dry-ice bath was removed. The reaction mixture was stirred at room temperature for 2 h and then washed with 1 N HCl (150 mL) and brine (3 × 400 mL). Evaporation of the solvent under reduced pressure gave a residue, which was purified by crystallization from hexane; yield 19.1 g (82%) of solid **1886**; mp 86–89 °C.

A slightly different procedure for oxidizing alcohols to carbonyl compounds has been applied by Rivero and co-workers [1363]. When **triphosgene** was added to DMSO at −78 °C, no evolution of carbon dioxide was observed prior to addition of the alcohol, possibly suggesting the formation of a mixture of reactive intermediates **1887** and **1888**. At room temperature, DMSO reacts exothermically with **triphosgene** with the evolution of carbon dioxide [1363].

Tab. 4.51. Oxidation of alcohols using the **triphosgene/DMSO** system[a] [1362].

Entry	*Substrate*	*Product*[b]	*Yield (%)*[c]
a		 **1886**	82
b			80
c			95
d			79
e			83
f			83
g			84
h			81

[a] Reactions conducted on a 10-mmol scale, except for entry a and b;
[b] All compounds are racemic except entries f, g, and h;
[c] Yield of pure isolated product checked by GLC/EIMS.

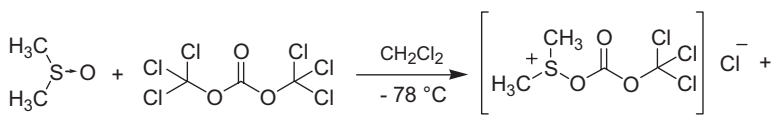
Table 4.52 compares the results obtained for the oxidation of alcohols with the **triphosgene/DMSO** reagent with those obtained using the traditional Swern method (**oxalyl chloride/DMSO**) [1363].

Typical procedure. *2-(p-Anisyl)ethanal* **1889** *(Table 4.52) with triphosgene* [1363]: To a solution of **triphosgene** (0.29 g, 0.97 mmol) in dry dichloromethane (40 mL) at

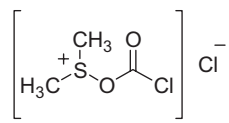
Tab. 4.52. Oxidation of alcohols using **triphosgene**.

Alcohol	*Product*	*Yield (%)[a] Method A*	*Yield (%)[b] Method B*
n-Heptanol	Heptanal	82	–
n-Octanol	Octanal	91	95
Geraniol	Geranial	95	95
Citronellol	Citronellal	95	85
n-Dodecanol	Dodecanal	90	100
2-Phenyl-1-propanol	2-Phenylpropanal	75	38
2-(*p*-Anisyl)ethanol	2-(*p*-Anisyl)ethanal **1889**	79	27
2-Phenylethanol	2-Phenylethanal	51	23
4-Methoxybenzyl alcohol	4-Anisaldehyde	95	–
Cinnamyl alcohol	Cinnamaldehyde	95	97
3-Pentanol	3-Pentanone	90	–
2-Hexanol	2-Hexanone	92	–
3-Methylcyclohexanol	3-Methylcyclohexanone	92	100
2-Octanol	2-Octanone	95	98
3-Methyl-2-heptanol	3-Methyl-2-heptanone	78	–
5-Nonanol	5-Nonanone	68	–
Benzoin	Benzil	95	95

[a] Method A: **triphosgene**/**DMSO**; [b] Method B: **oxalyl chloride**/**DMSO** [1319].



triphosgene **1887**



1888

−78 °C, anhydrous DMSO (0.5 mL, 7.06 mmol) was added dropwise with stirring. After 5 min, 2-(*p*-anisyl)ethanol (0.403 g, 2.63 mmol) in dry dichloromethane (10 mL) was added dropwise. The mixture was stirred at −78 °C for an additional 15 min, then triethylamine (2.0 mL, 14.28 mmol) was added, and the reaction mixture was allowed to warm to room temperature (∼ 10 min). It was quenched with water (50 mL) and the organic phase was washed sequentially with 5% aq. HCl (50 mL), 5% aq. $NaHCO_3$ (50 mL), saturated NaCl solution, and water. The final organic layer was dried over Na_2SO_4, subjected to flash chromatography (15 g of silica gel), and the solvent was removed under reduced pressure to give the aldehyde **1889** in 79% yield.

Cyanuric chloride/DMSO, Ph_3PCl_2/DMSO, SiO_2–Cl/DMSO

As *activating agents* for DMSO in *Swern*-type oxidation reactions have been also employed **cyanuric chloride** (**CyCl**) [1386] and **triphenylphosphane dihalide** (**Ph_3PX_2**, X = Cl, Br) [1407]. An heterogeneous *Swern oxidation* has been described using a **SiO_2–Cl**/DMSO system [1408].

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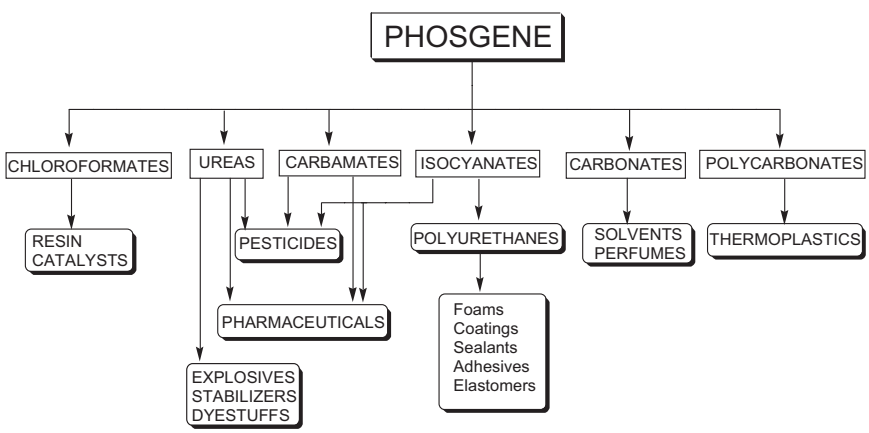
5
Topics on Specific Synthetic Applications of Phosgenation Reactions

Phosgene is an important *building block* in organic synthesis. Many patents describe the potential uses of phosgene for a wide variety of applications, but the single most important use of **phosgene** is in the preparation of polymeric materials. Its versatility is unanimously accepted and demonstrated in the large-scale synthesis of polymer intermediates (e.g. isocyanate manufacture). The principal commercial applications of **phosgene** are illustrated in the figure below.



Phosgene is high ranking among industrially produced chemicals. Although its production output is almost exclusively captive and therefore only approximate production statistics are available, a yearly worldwide production of about 5–6 MT can be roughly estimated [1].

The aim of this chapter is to present the state of the art concerning the use of **phosgene** and phosgene equivalents in organic synthesis, with particular emphasis on applications in the manufacture of *pharmaceuticals* and *agrochemicals*, as well as in one rather astonishing application (Section 5.5).

Phosgenations – A Handbook. L. Cotarca, H. Eckert

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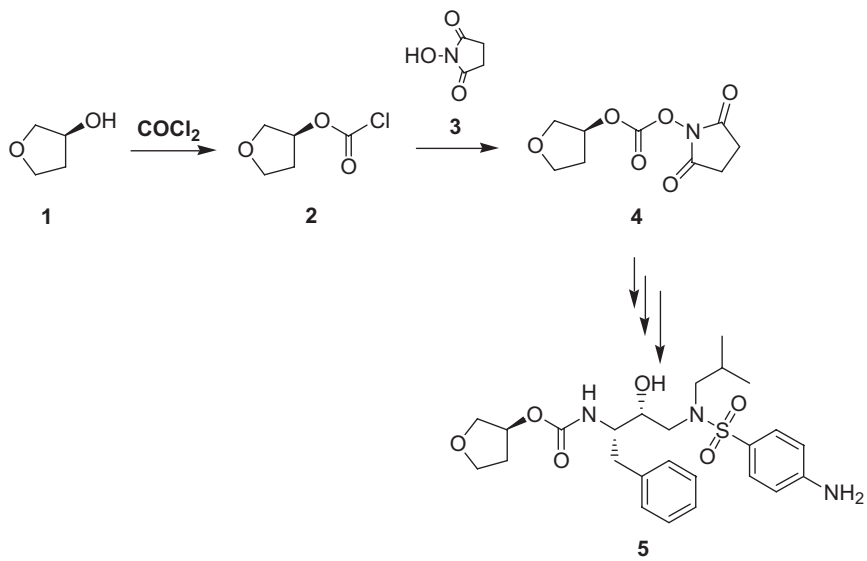
5.1
Active Pharmaceutical Ingredients (APIs) Synthesized with Phosgene

Many compounds useful as *active pharmaceutical ingredients* (APIs) are synthesized with **phosgene** or **phosgene equivalents**. The following section presents the *phosgenation steps* disclosed in the originator's patents, and identifies various improved and alternative reaction routes that can be found in the open literature. The compounds and the synthetic routes thereto are selected on the basis of the well-known monograph of Kleemann [2].

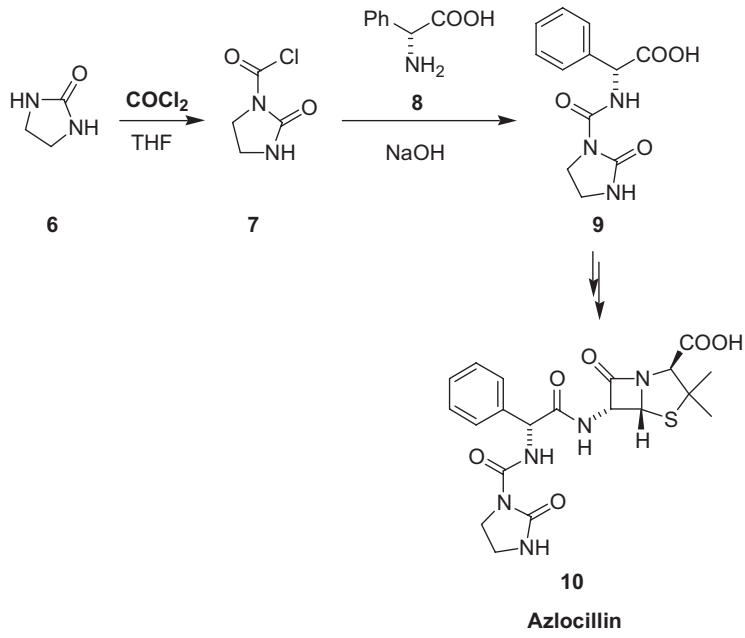
Amprenavir *[161814-49-9], antiviral, HIV protease inhibitor,* **5**. The key intermediate succinimido (*S*)-3-tetrahydrofuryl carbonate **4** [3–6] is synthesized with **phosgene** through (*S*)-3-tetrahydrofuryl chloroformate **2.**



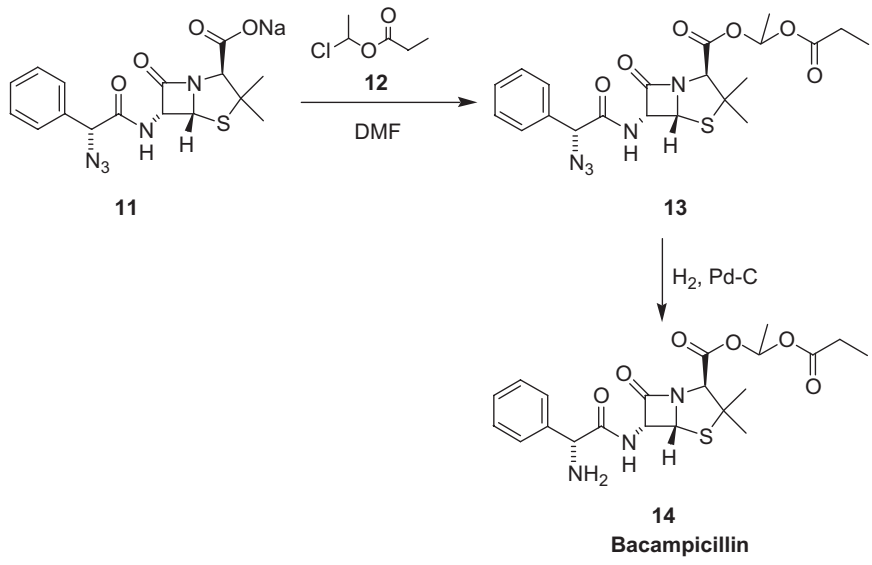
Azlocillin *[37091-66-0], antibiotic,* **10**. Phosgenation of 2-imidazolidinone **6** with **phosgene** in THF gives 1-chloroformyl-imidazolidinone **7**, a key intermediate that forms the corresponding urea **9** upon reaction with D-(−)-α-phenylglycine **8** [7–9].

An improved **phosgenation** of *N*,*N*′-disubstituted cyclic urea **6** to form 1-chloroformyl-imidazolidinone **7**, using **phosgene** in DCE at 80 °C (1 h, 86% yield) has been reported [8, 9].

Bacampicillin *[50972-17-3], antibiotic (broad spectrum penicillin),* **14**. **1-Haloalkyl chloroformates** and **1-haloalkyl carbonates**, important derivatives of **phosgene** and phosgene equivalents (see Chapter 4), were originally employed to mask the acid function of an API. *Bacampicillin* is a prodrug of *Ampicillin*, improving drug delivery by enabling transport through biological barriers. The prodrug is produced



from azidocillin **11** and **1-chloroethyl ethyl chloroformate 12**, with subsequent hydrogenation of intermediate **13** [10–12].

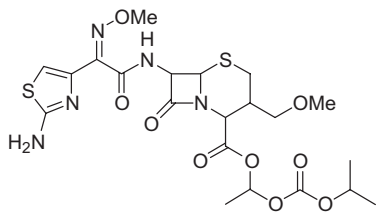


Besides *Ampicillin*, **1-chloroalkyl alkyl carbonates**, in particular **1-chloroethyl ethyl carbonate** (**CEEC**), **1-chloroethyl isopropyl carbonate** (**CEIC**), **1-chloroethyl cyclohexyl carbonate** (**CECC**), and **chloromethyl ethyl carbonate** (**CEMC**), have been

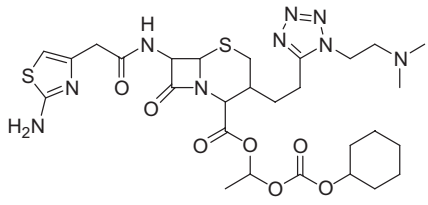
proposed for the modification of numerous compounds [13]. Among the many types of patented prodrugs which require this method, there are examples of:

- antibiotics such as *Cefpodoxime Proxetil* (Sankyo) [14] and *Cefotiam Hexetil* (Takeda Chem. Ind.) [15, 16]
- anti-inflammatories and analgesics such as *Ampiroxicam* (Pfizer and Toyama Chem. Co.) [17, 18] or a derivative of *Diflunisal* [19]
- anti-hypertensives, for example *TCV 116* (Takeda Chem. Ind. Ltd.) [20].

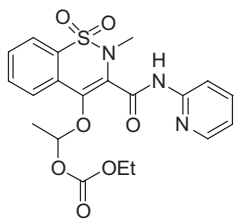
The structures of some of these pro-active ingredients are given below [13]:



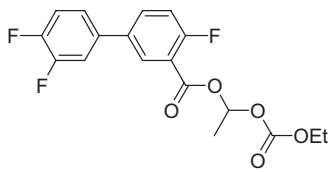
Cefpodoxime Proxetil (CS-807)



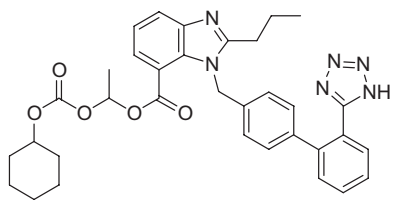
Cefotiam Hexetil (SCE-2174)



Ampiroxicam

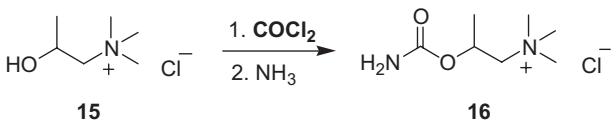


Diflunisal Derivative



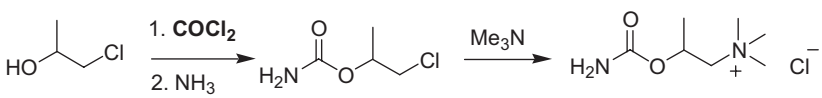
TCV-116

Bethanecol chloride *[590-63-6], parasympathomimetic,* **16**. Compound **16** is prepared by the **phosgenation** of *β*-methylcholine chloride **15** [21, 22] or 1-chloroisopropanol **17** by the following two routes:



15 **16**

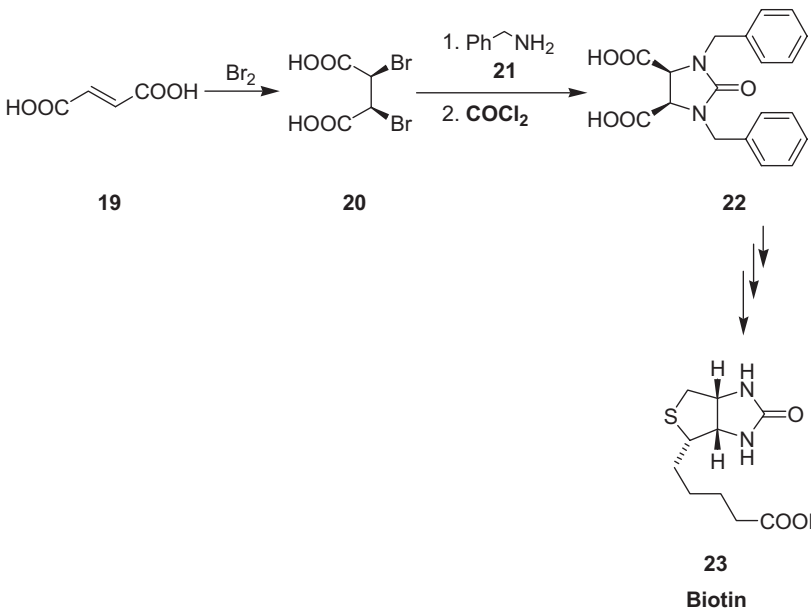
Bethanecol chloride



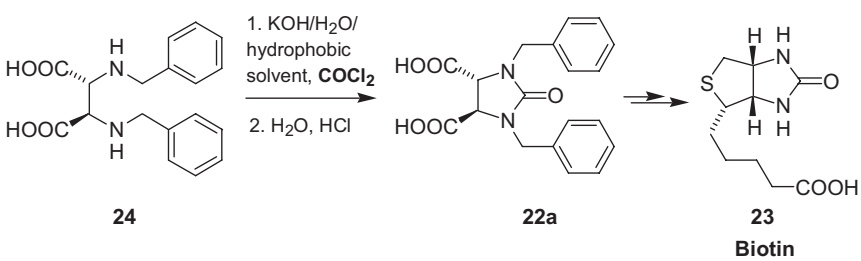
17 **18** **16**

Bethanecol chloride

***Biotin** [58-85-5], **Vitamina B_7, Vitamin H**, grow factor, vitamin,* **23**. The key step of the preparation is the synthesis of cyclic urea **22** by **phosgenation** of 2,3-*N*,*N*′-dibenzylamino-succinic acid **24** [23–27].

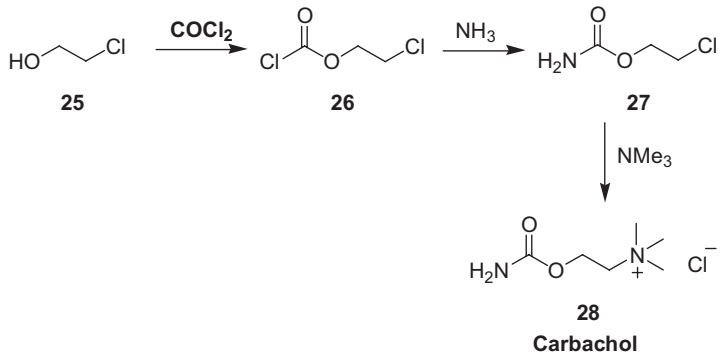


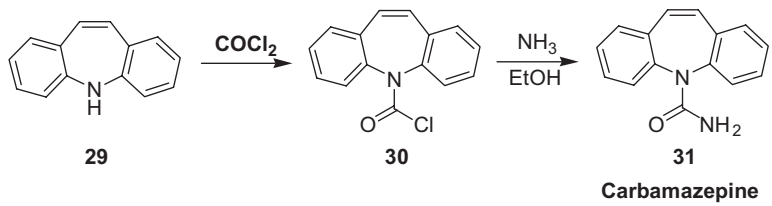
An improved interfacial process leading to the cyclic five-membered urea **22a** has been developed by SNPE [28].



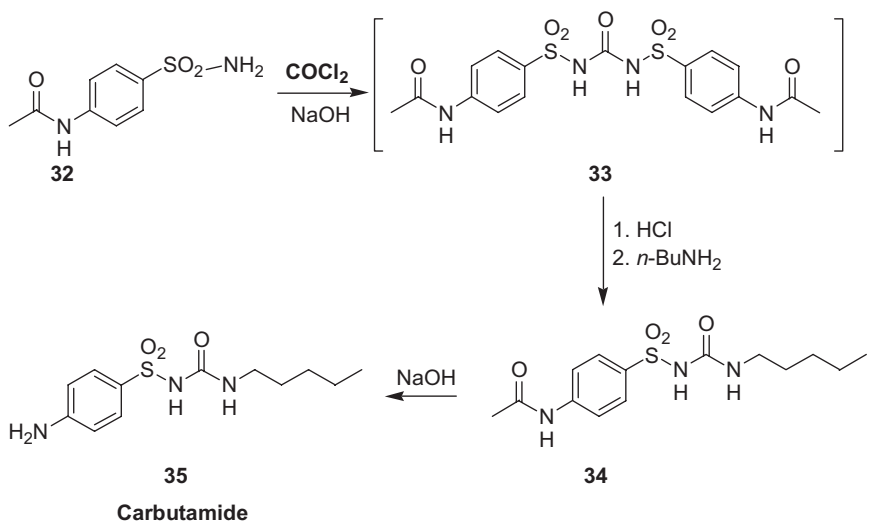
***Carbachol**, **Carbacholine** [51-83-2], parasympathomimetic,* **28**. **Phosgene** is used to prepare the 2-chloroethyl chloroformate **26**, the starting material in the synthesis of Carbachol **28**, a carbamate-trimethylethanaminium chloride [29, 30].

***Carbamazepine** [298-46-4], antiepileptic, anticonvulsant,* **31**. **Phosgene** is used to convert 5*H*-dibenz[*b*,*f*]azepine **29** to the corresponding 5-carboxamide **31** [31].

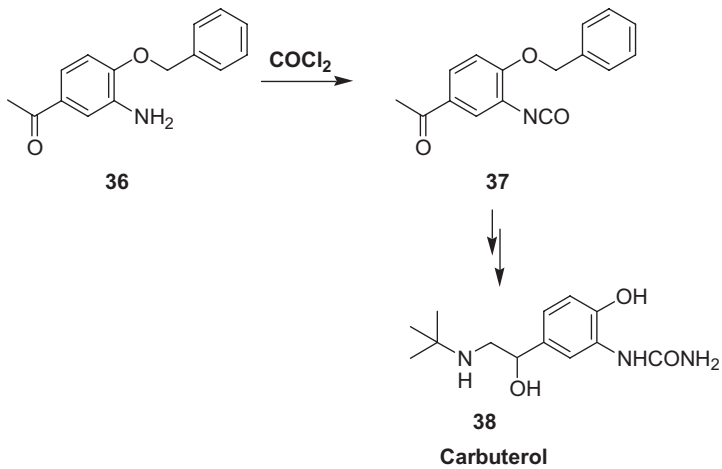




Carbutamide, *Butyl carbamide, Glybutamide [339-43-5], antidiabetic,* **35**. **Phosgene** is used to prepare the symmetrical *N*,*N*′-benzenesulfonyl urea **33** [32–34].



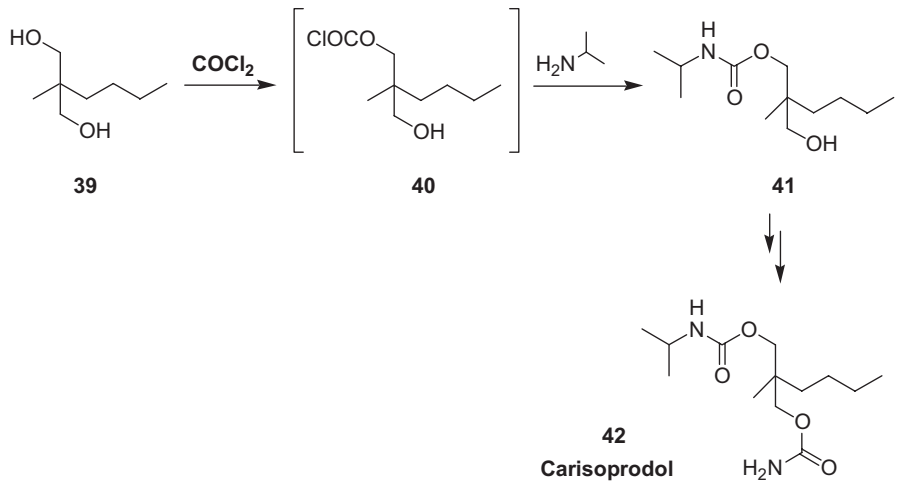
Carbuterol *[34866-47-2], selective β-adrenoceptor agonist, bronchodilator,* **38**. **Phosgene** is used to generate an isocyanate-bearing key intermediate **37** [35–37].



36 **37** **38**

Carbuterol

Carisoprodol *[78-44-4], muscle relaxant,* **42**. Carbamate **41**, the key intermediate, is synthesized via the corresponding chloroformate **40** [38].

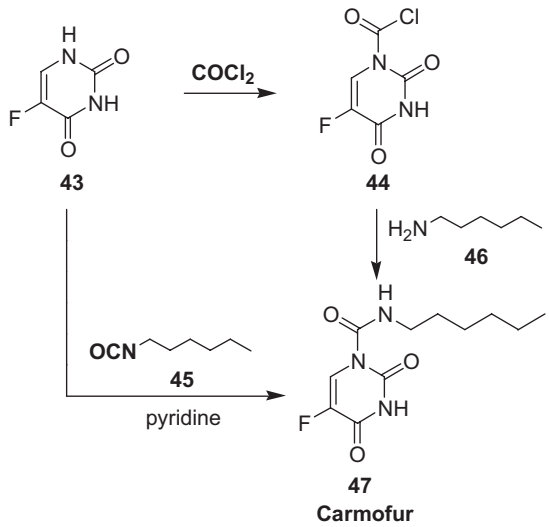


39 **40** **41**

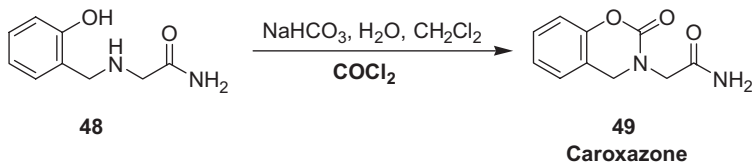
42

Carisoprodol

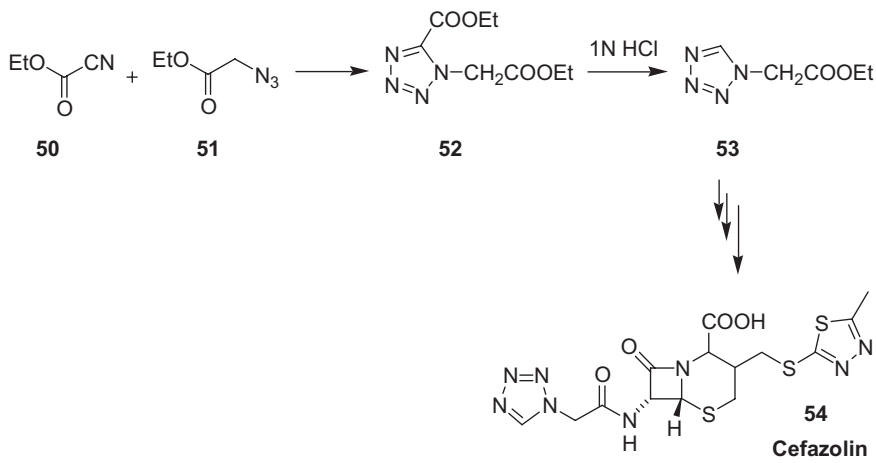
Carmofur *[61422-45-5], antineoplastic, orally active fluorouracil derivative,* **47**. **Phosgene** is employed to prepare the carbamoyl chloride intermediate **44**. A different route, using ***n*-hexyl isocyanate 45**, has also been applied [39, 40].



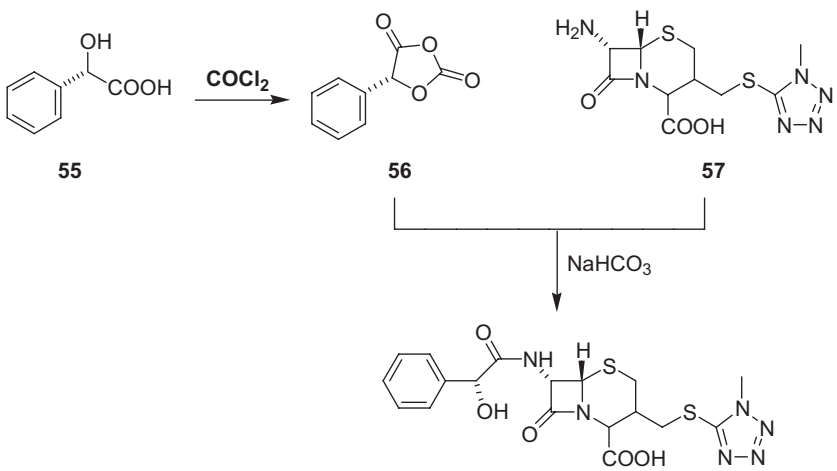
***Caroxazone** [18464-39-6], antidepressant,* **49**. **Phosgene** is used in the final cyclization step to synthesize the 2-oxo-2*H*-1,3-benzoxazine **49** from the amine precursor **48** containing a γ-hydroxyl group [41–43].



***Cefazolin** [25953-19-9], antibiotic,* **54**. The key intermediate, tetrazole-1-acetic acid ethyl ester **53** is prepared with **pivaloyl chloride** [44] or **ethyl cyanoformate 50** (an effective dipolarophile undergoing 1,3-dipolar addition to azide **51**) [45].



Cefamandole *[42540-40-9], antibiotic,* **58**. A key intermediate, the cyclic mixed carboxylic-carbonic anhydride **56**, prepared by phosgenation of mandelic acid **55**, is used as an activated form of acid function in reaction with an amine to afford the active antibiotic [46].

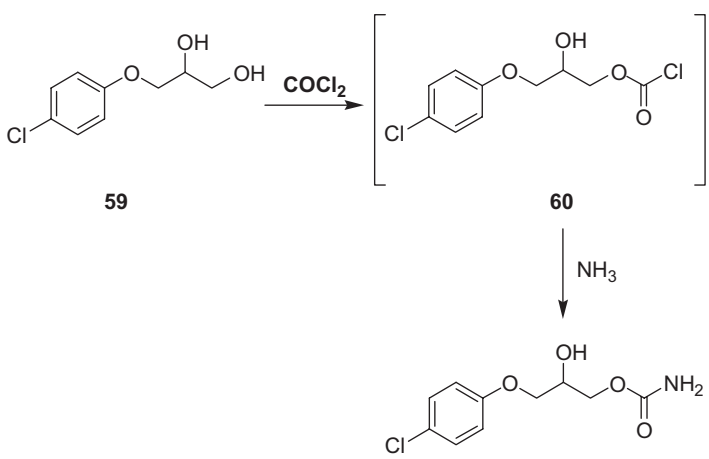


55 **56** **57**

58

Cefamandole

Chlorphenesin carbamate *[886-74-8], analgesic, muscle relaxant, tranquilizer,* **61**. **Phosgene** is used to prepare the intermediate chloroformate **60** [47, 48].

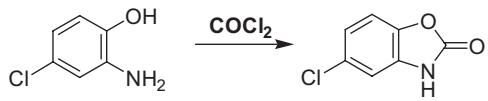


59 **60**

61

Chlorphenesin carbamate

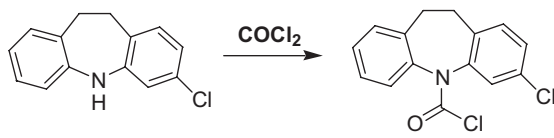
Chlorzoxazone *[95-25-0], muscle relaxant,* **63**. The 5-chloro-2(3*H*)-benzoxazolone **63** is prepared with **phosgene** [49].



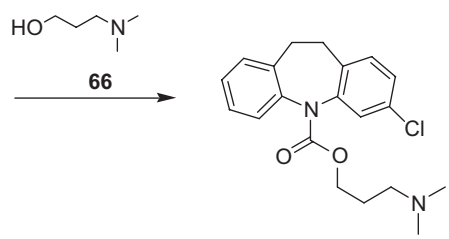
62 **63**

Chlorzoxazone

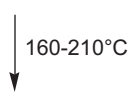
Clomipramine *[303-49-1], antidepressant,* **68**. **Phosgene** is used to prepare carbamoyl chloride **65**, an activated intermediate useful for the coupling of the side chain [50, 51].

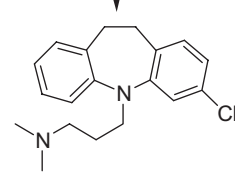


64 **65**



67



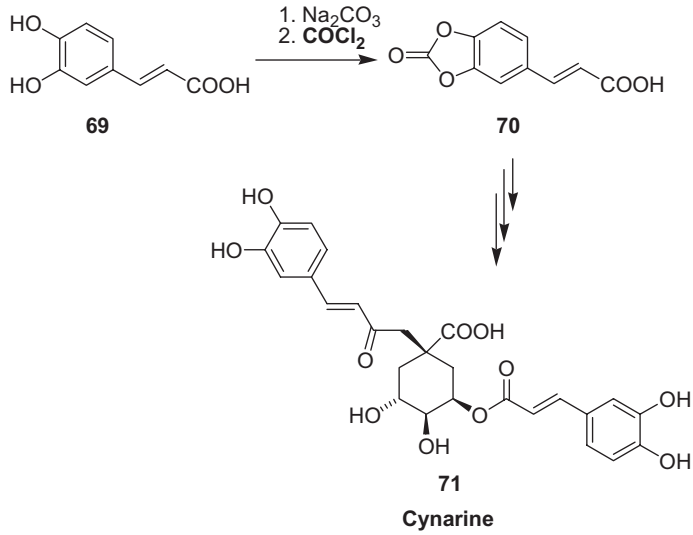


68

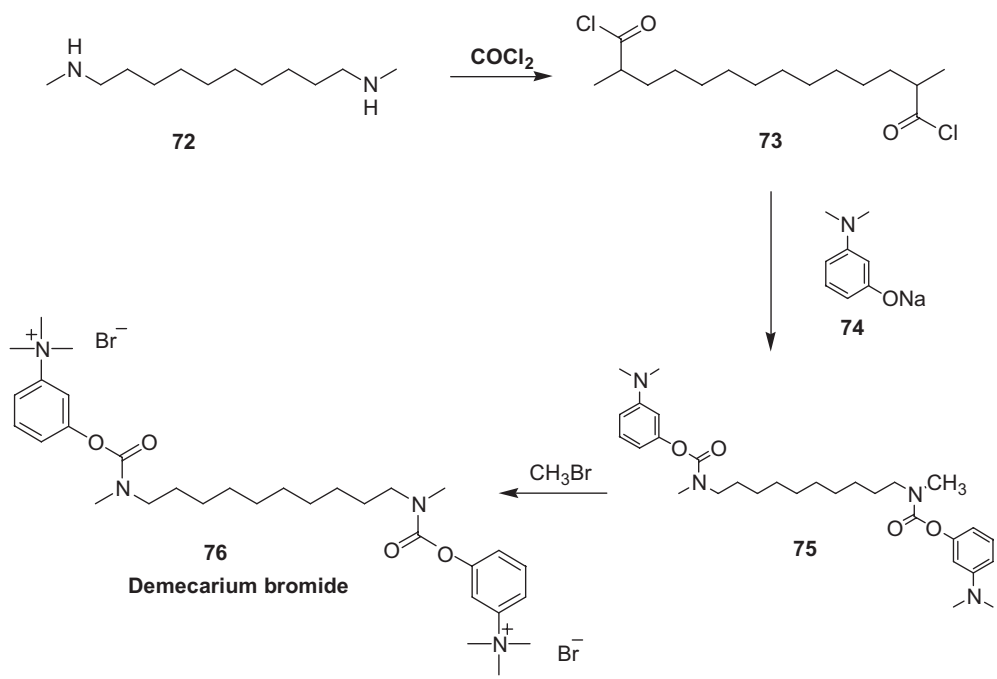
Clomipramine

Cynarine *[1182-34-9], choleretic,* **71**. Formation of 3,4-carbonyldioxy-cinnamic acid **70**, a cyclic carbonate and key intermediate, is achieved by **phosgene** cyclocarbonylation of caffeic acid **69** [52, 53].

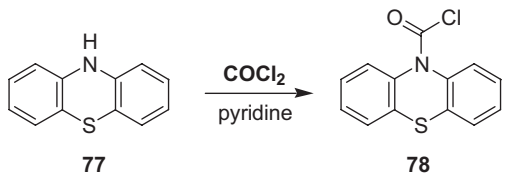
Demecarium bromide *[56-94-0], cholineesterase inhibitor,* **76**. **Phosgene** is use to activate the secondary bis(amine) [1,10-bis(methylamino)decane] **72** as a secondary

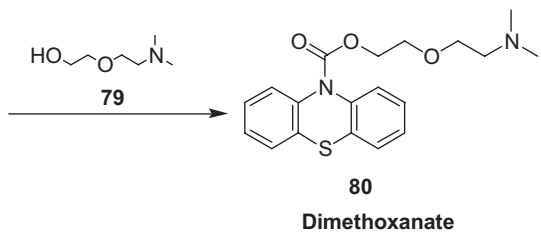


bis(carbamoyl chloride) **73**, the key intermediate for the preparation of the bis-(carbamate bromide) **76** [54].

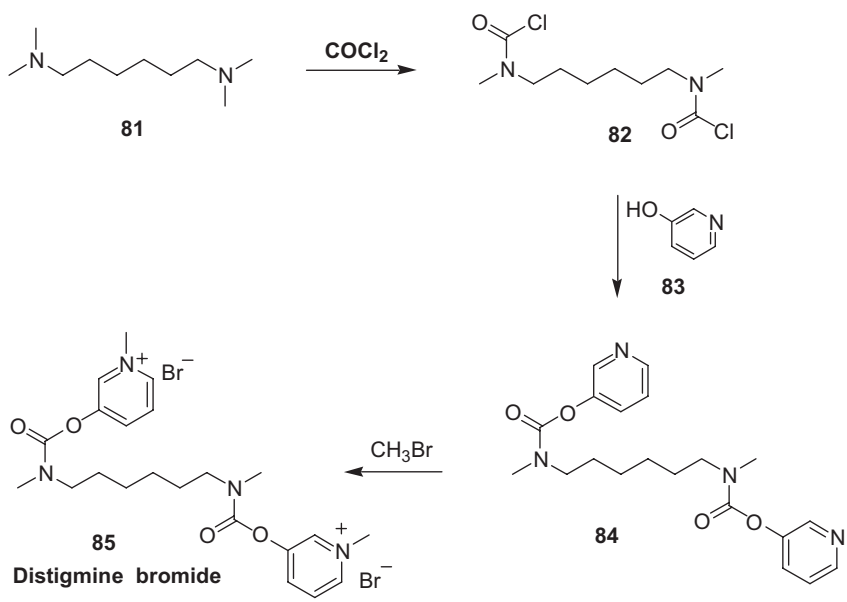


Dimethoxanate *[477-93-0], antitussive,* **80**. The synthesis includes as a key step the phosgenation of phenothiazine **77** to form the corresponding carbamoyl chloride **78** [55].

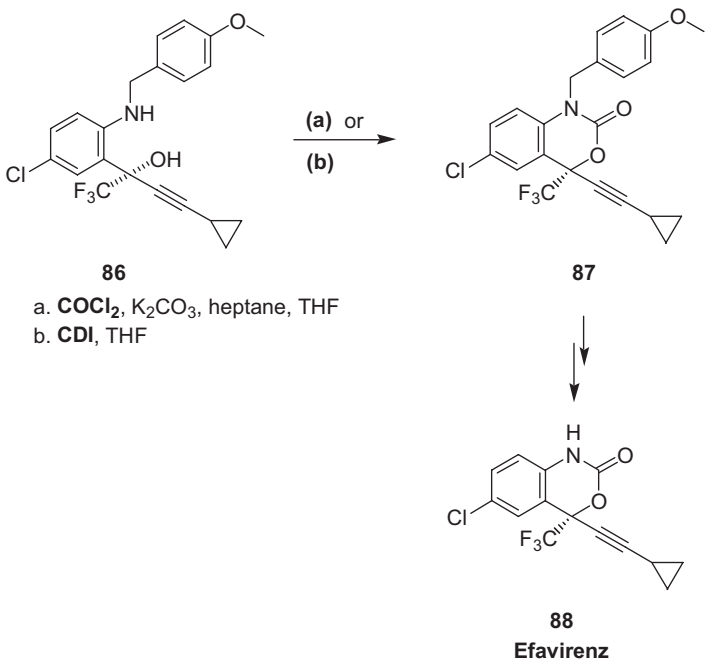




Distigmine bromide *[15876-67-2], parasympathomimetic,* **85**. *N*,*N*,*N*′,*N*′-Tetramethylhexamethylenediamine **81** is demethylated and chlorocarbonylated with **phosgene** to form the corresponding bis(carbamoyl chloride) **82**, the key intermediate in the synthesis of Distigmine bromide **85** [54].



Efavirenz *[154598-52-4], antiviral for AIDS, reverse transcriptase inhibitor,* **88**. Either **phosgene** or **CDI** can be employed to form the key intermediate, (4*S*)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-1-[(4-methoxyphenyl)methyl]-4-trifluoromethyl-2*H*-3,1-benzoxazin-2-one [56–67].



86

87

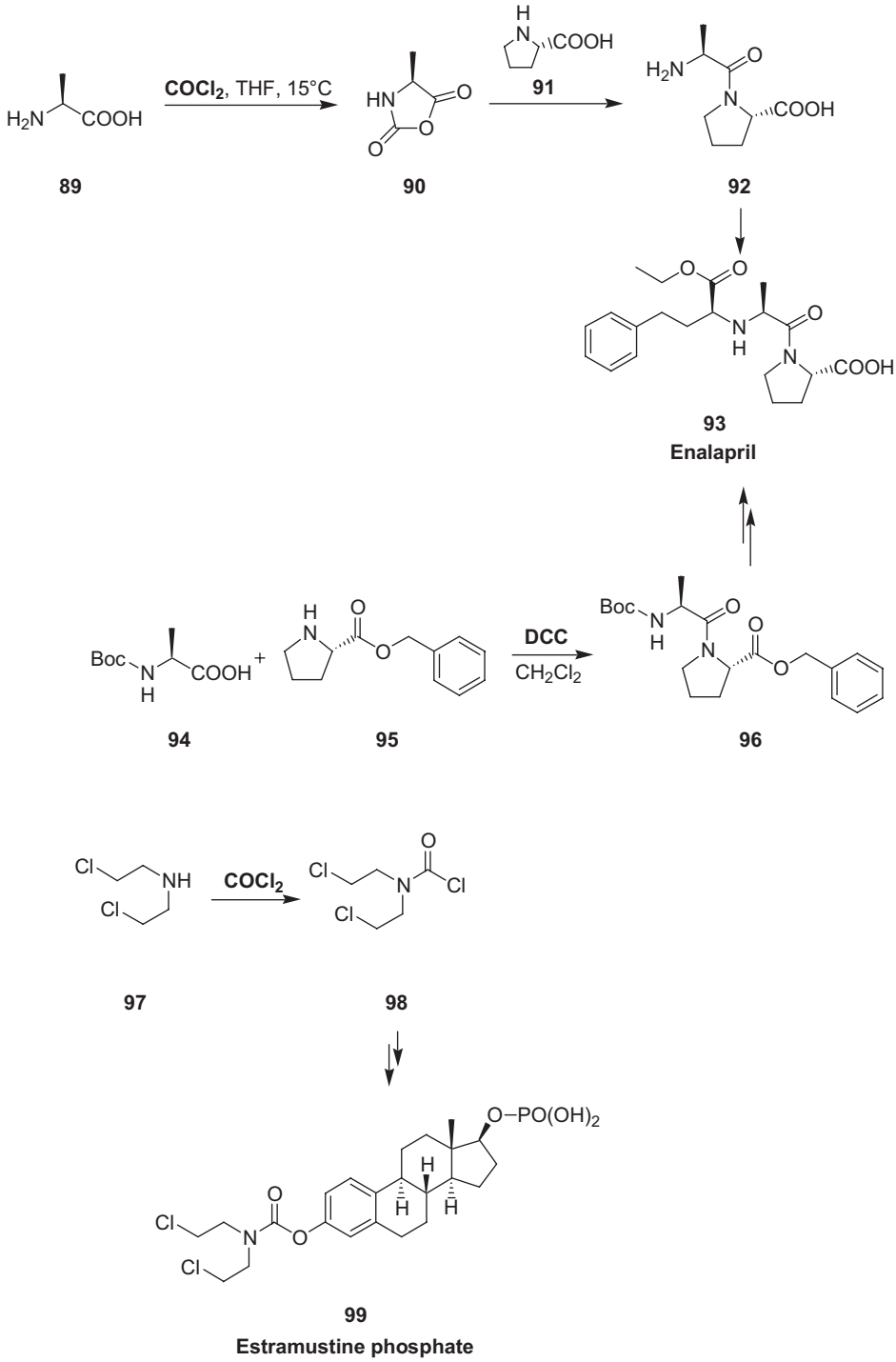
a. **$COCl_2$**, K_2CO_3, heptane, THF
b. **CDI**, THF

88
Efavirenz

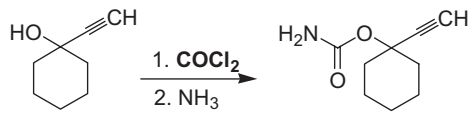
Enalapril *[75847-73-3], antihypertensive (ACE inhibitor),* **93**. In one method, **phosgene** is used to activate L-alanine **89** as its *N*-carboxy anhydride (NCA) **90**, which is then used to acylate the L-proline **91** affording the semisynthetic dipeptide Ala-Pro **92** [68]. Processes based on the reaction of activated derivatives of *N*-[1(*S*)-ethoxycarbonyl-3-phenylpropyl]-L-alanine with L-proline have also been reported [69–71].

DCC has also been reported to serve as an activating reagent in the acylation of L-proline benzyl ester **95** with *N-tert*-butoxycarbonyl-L-alanine **94** to form Enalapril [72–76].

Estramustine phosphate *[4891-15-0], antineoplastic,* **99**. *N*-Chloroformyl-bis(2-chloroethyl)amine **98**, prepared with **phosgene** from the corresponding amine **97**, is used to form the carbamate of estradiol **99** [77–79].


COCl2, THF, 15°C
91
89
90
92
93
Enalapril
DCC
CH2Cl2
94
95
96
COCl2
97
98
O–PO(OH)2
99
Estramustine phosphate

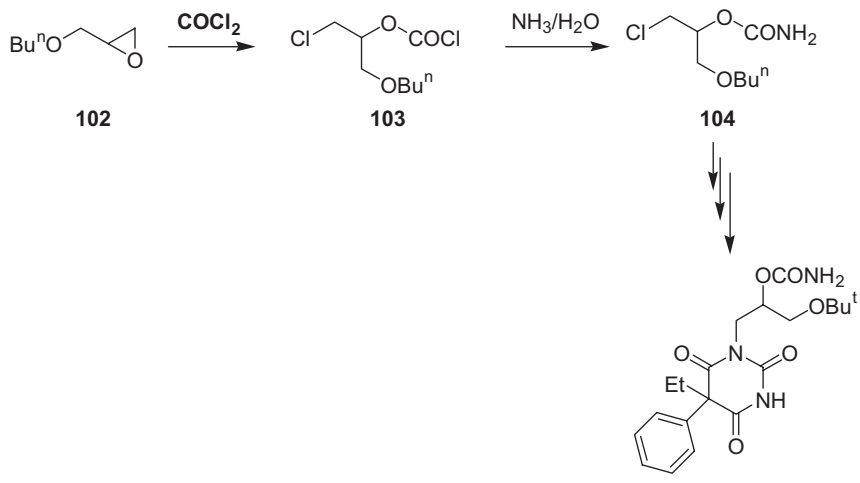
Ethinamate *[126-52-3], hypnotic, sedative,* **101**. The target molecule, 1-ethynylcyclohexanol carbamate **101**, is prepared by phosgenation of the corresponding cyclohexanol **100** followed by treatment with ammonia [80, 81].



100 **101**

Ethinamate

Febarbamate *[13246-02-1], tranquilizer,* **105**. Phosgenation of *n*-butylglycidyl ether **102** in toluene in the presence of 0.5 mol% hexabutylguanidinium chloride (HBGCl) at 30 °C for 2 h gave the corresponding 1-chloromethyl-2-*n*-butoxyethyl chloroformate **103** in 96% yield [82].

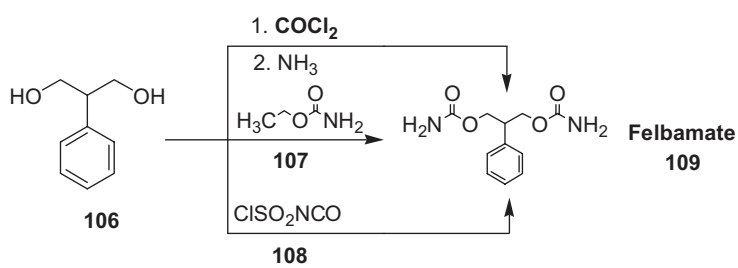


102 **103** **104**

105

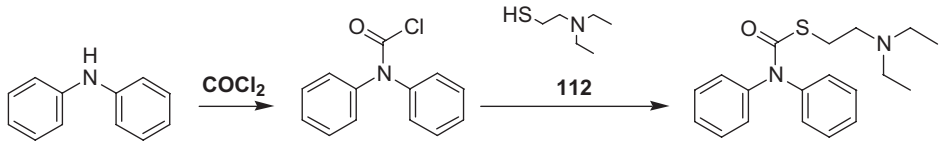
Febarbamate

Felbamate *[25451-15-4], anticonvulsant,* **109**. 2-Phenyl-1,3-propanediol dicarbamate **109** (Felbamate) is prepared from 2-phenyl-1,3-propanediol **106** with **phosgene** [83], ethyl carbamate **107** [84, 85], or chlorosulfonyl isocyanate **108** [84, 85].



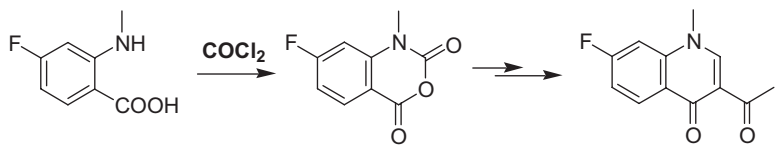
106 **107** **108** **Felbamate** **109**

Fencarbamide *[3735-90-8], antispasmotic,* **113**. The key step is the phosgenation of diphenylamine **110** [86].



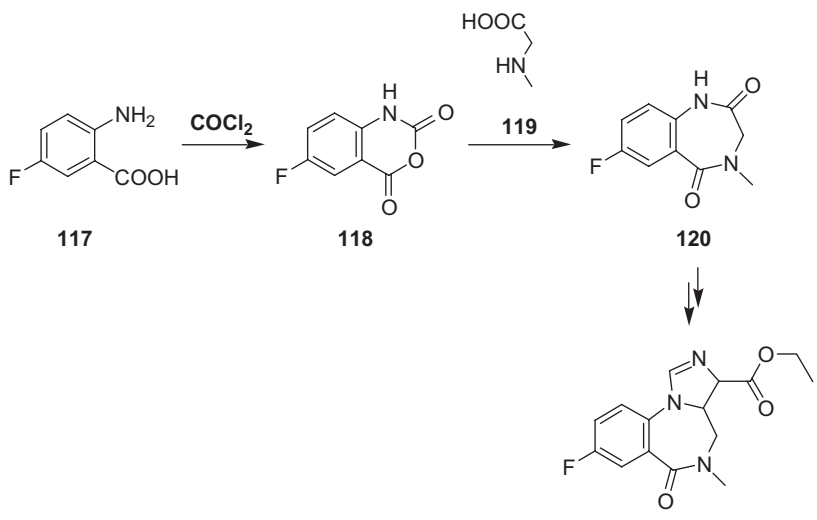
110 **111** **113**
Fencarbamide

Flosequinan *[76568-02-0], vasodilator, antihypertensive,* **116**. In one method, phosgenation is used to synthesize the benzoxazine-2,4-dione (isatoic anhydride), a key intermediate en route to **116** [87]. Other methods avoiding **phosgene** have also been reported [88, 89].



114 **115** **116**
Flosequinan

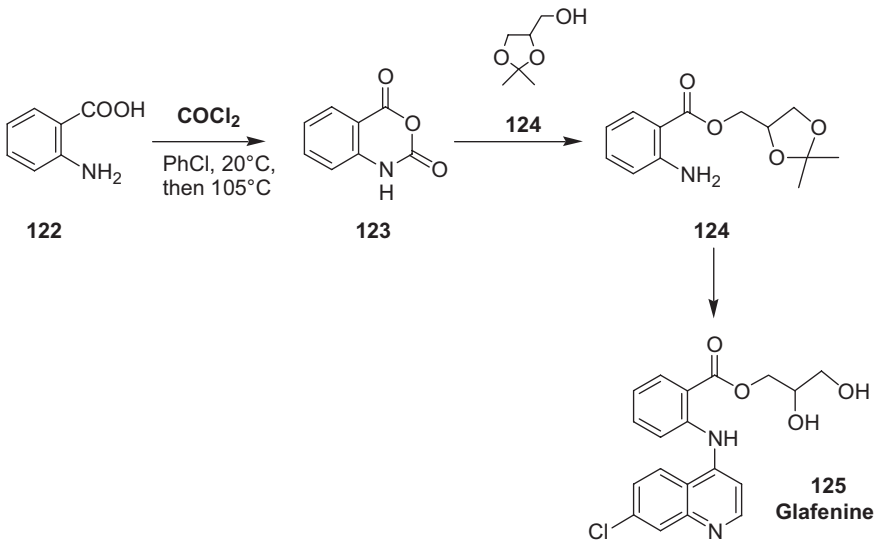
Flumazenil *[78755-81-4], benzodiazepine antagonist, treatment of benzodiazepine intoxication,* **121**. **Phosgene** is used to prepare the key intermediate 6-fluoroisatoic anhydride **118** [90–93].



117 **118** **120**

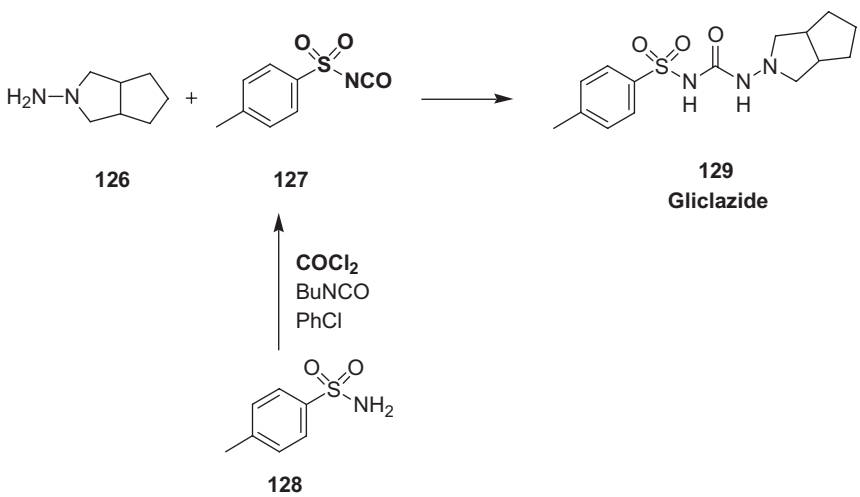
121
Flumazenil

Glafenine *[3820-67-5], analgesic, anti-inflammatory,* **125**. Isatoic anhydride, prepared from *o*-aminobenzoic acid **122** and **phosgene**, has been used as a starting material in the synthesis of *Glafenine* [94, 95].



122 **123** **124** **125 Glafenine**

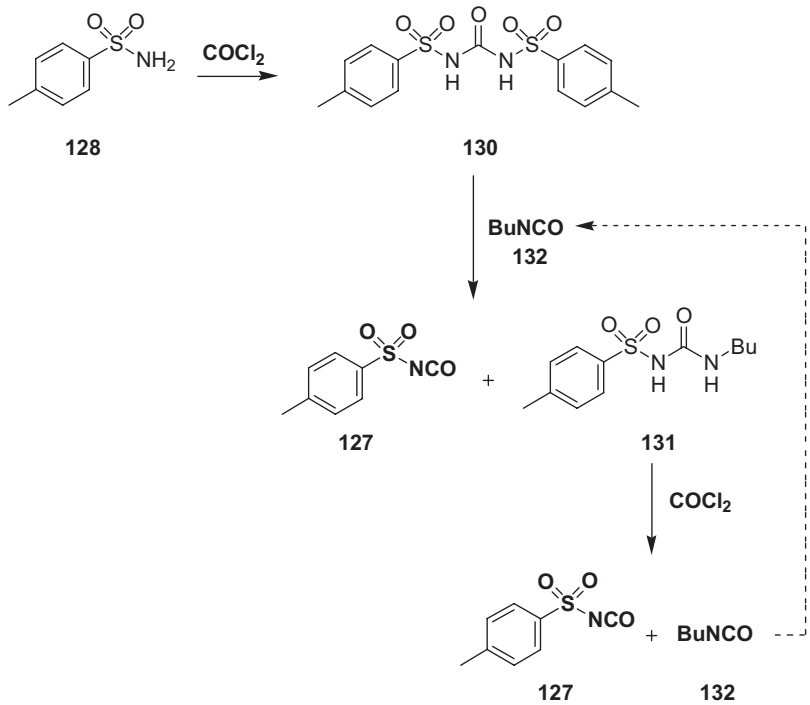
Gliclazide *[21187-98], antidiabetic,* **129**. 4-Toluenesulfonyl isocyanate (PTSI) **127** is an interesting, highly reactive isocyanate, which has found several valuable applications [96]. One of these applications is in the synthesis of the hypoglicemic API *Gliclazide*.



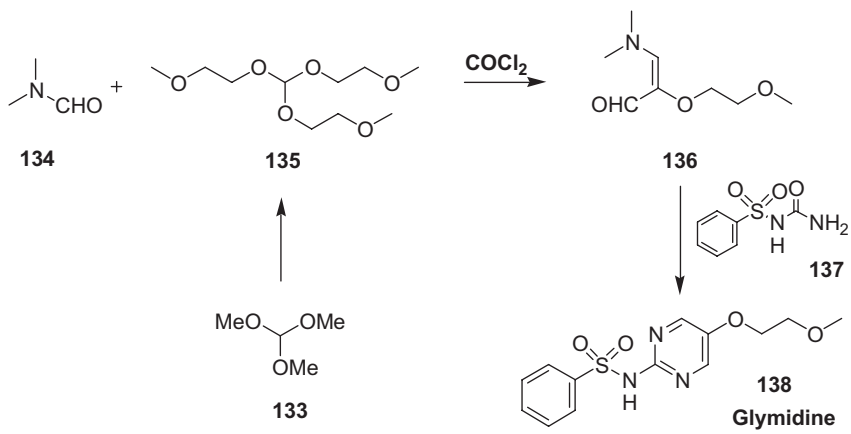
126 **127** **129 Gliclazide** **128**

The mechanism of the catalyzed synthesis of 4-toluenesulfonyl isocyanate (PTSI)

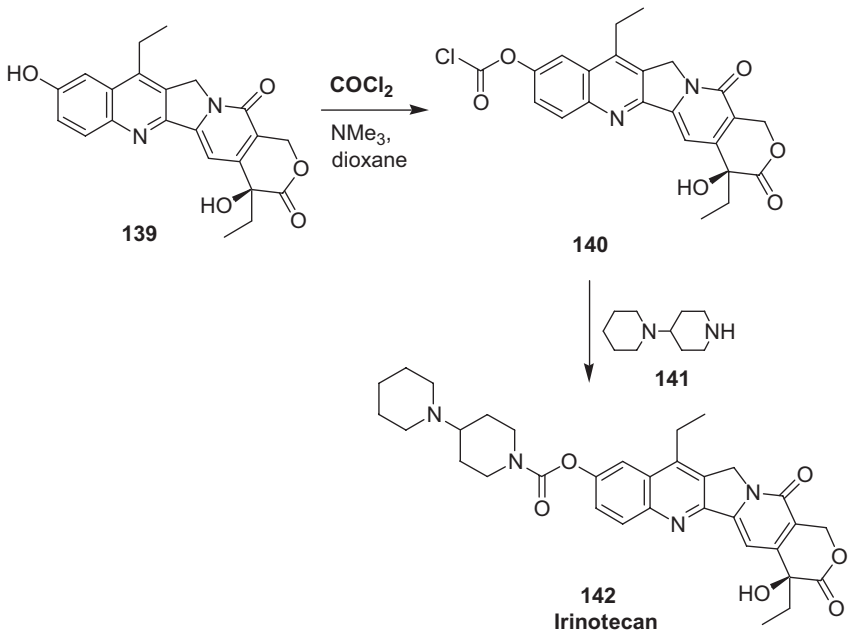
127 has been studied [96] and there is evidence that **butyl isocyanate 132** is regenerated, as shown in the scheme below.



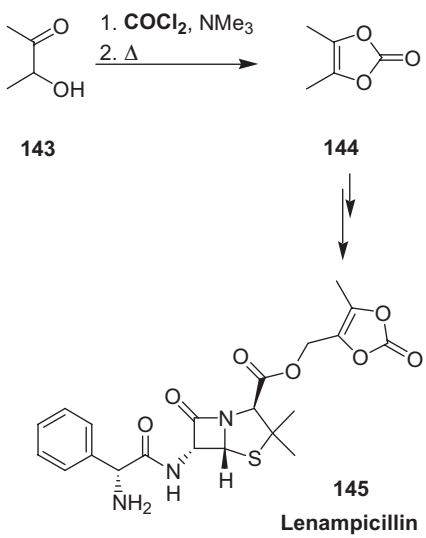
Glymidine *[339-44-6], antidiabetic,* **138**. **Phosgene** is employed to activate dimethylformamide **134** for the aminoformylation of 1,1,2-tris(2-methoxyethoxy)ethane **135** [97–100].



Irinotecan *[97682-44-55], antineoplastic, topoisomerase inhibitor,* **142**. The key intermediate **140** is prepared by **phosgenation** of 7-ethyl-10-hydroxy-camptothecin **139** [101, 102].

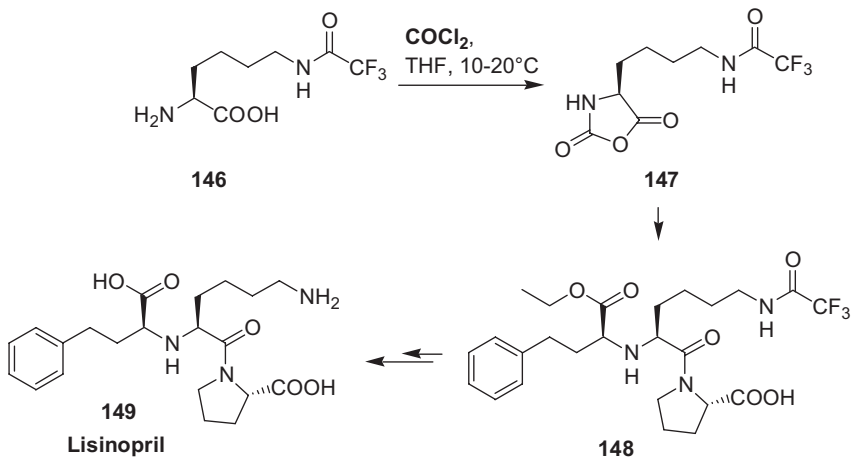


Lenampicillin *[86273-18-9], antibacterial, semisynthetic β-lactam antibiotic, derivative of ampicillin (prodrug for oral application),* **145**. The key reagent, the substituted vinylene carbonate **144**, is prepared by the **phosgenation** of acetoin **143** [103–111].

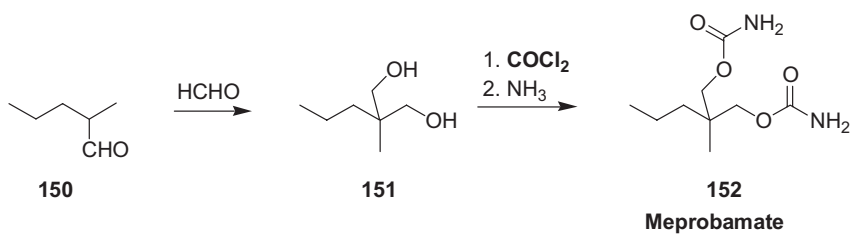


The monochlorinated vinylene carbonate is also used in the synthesis of *Cefcanel*, a new cephalosporin from Kyoto and Astra [112, 113].

Lisinopril *[76547-98-3], angiotensin-converting enzyme inhibitor (for use as antihypertensive and in congestive heart failure),* **149**. **Phosgenation** is employed to activate N^6-(trifluoroacetyl)-L-lysine **146** as N^2-carboxy anhydride **147**, a key intermediate in the acylation of L-proline [114, 115]. Alternative processes have also been described [116–119].

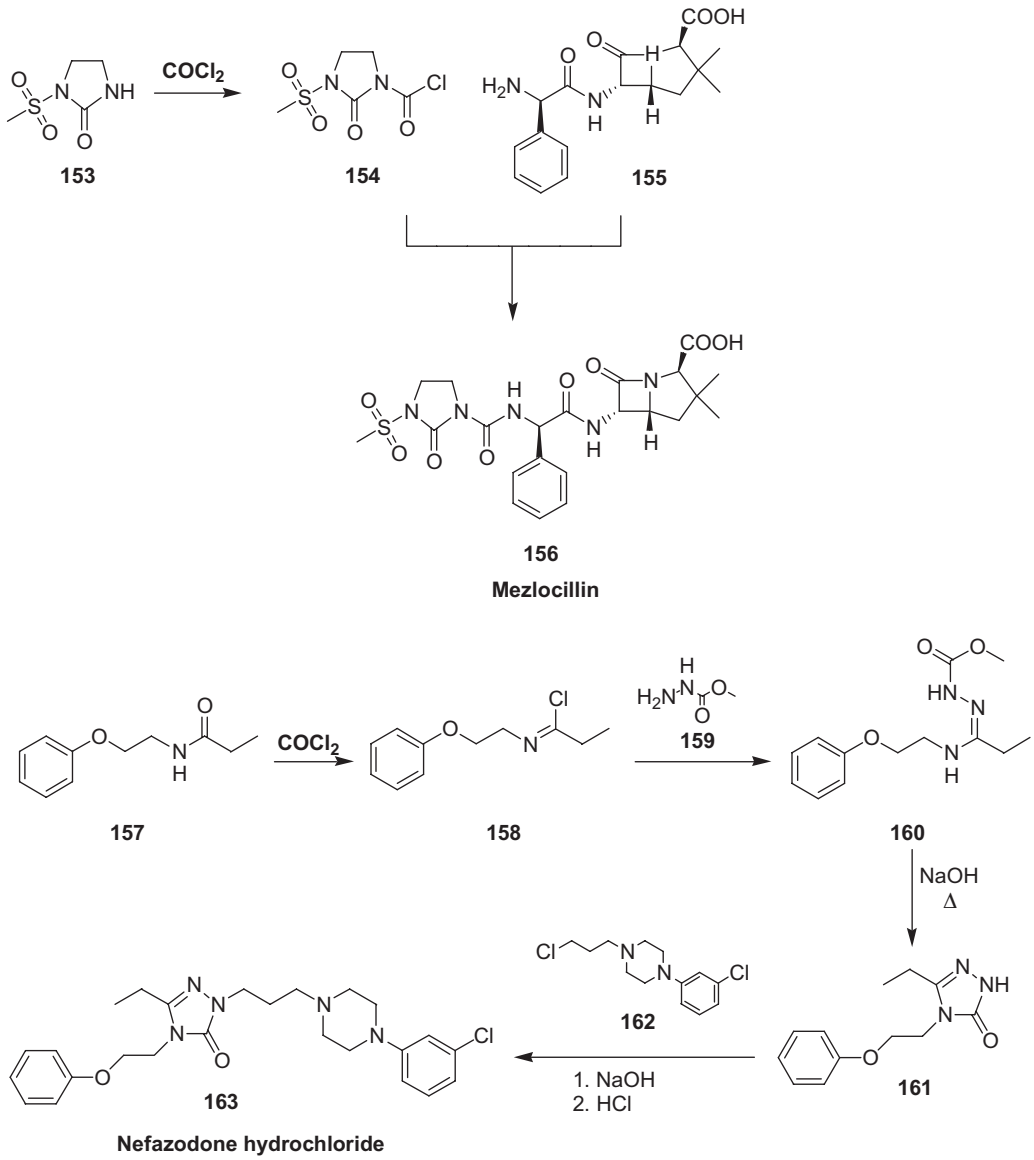


Meprobamate *[57-53-4], tranquilizer,* **152**. 2-Methyl-2-propyl-1,3-propanediol dicarbamate (Meprobamate) **152** is prepared by phosgenation of the corresponding diol **151** [120].



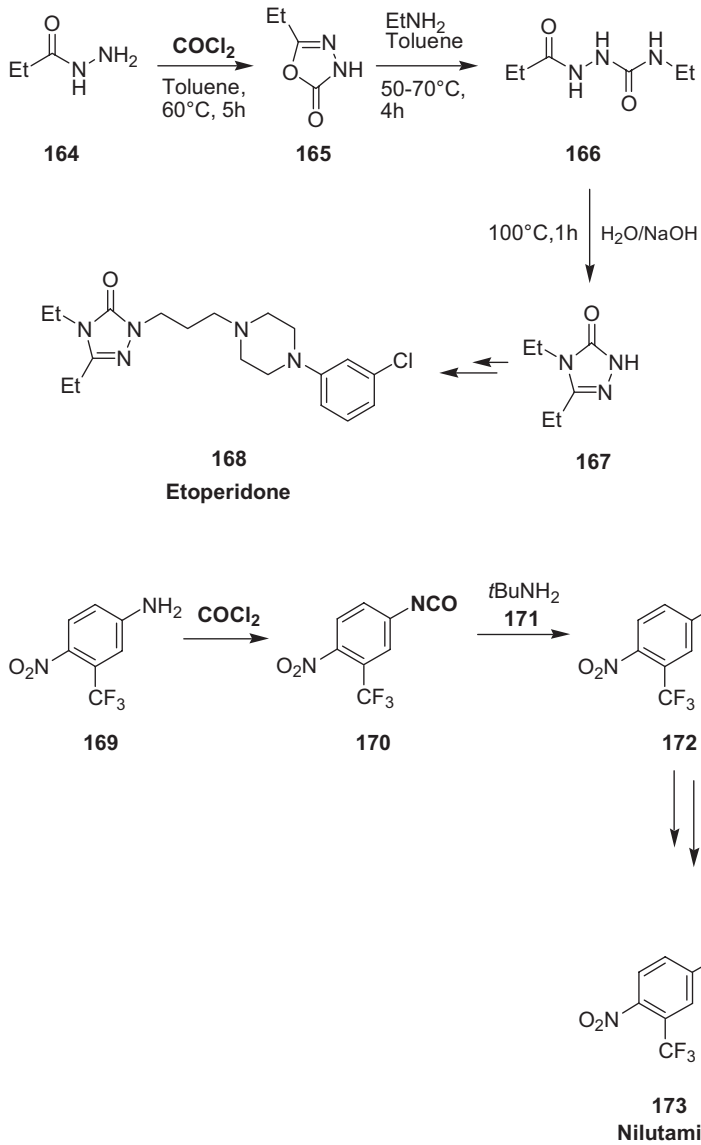
Mezlocillin *[51481-65-3], antibiotic,* **156**. Chloroformylation of 1-methanesulfonyl-2-imidazolidinone **153** with **phosgene** results in the key intermediate, 3-chloroformyl-1-methanesulfonyl-2-imidazolidinone **154** [121–125].

Nefazodone hydrochloride *[82752-99-6], antidepressant, 5-HT$_2$A-antagonist,* **163**. In one method, **phosgenation** is applied to prepare the key intermediate 2,4-dihydro-3*H*-1,2,4-triazol-3-one **161** [126].



Triazolone **167**, a useful building block for APIs such as *Nefazodone* or *Etoperidone* [52942-31-1] **168**, an antidepressant, can be obtained from 5-ethyl-1,3,4-oxadiazolinone **165**, which, in turn, is prepared by **phosgenation** of propionyl hydrazide **164** without the need for the highly toxic **ethyl isocyanate** [127].

Nilutamide *[63612-50-0], non-steroidal antiandrogen (for treatment of prostatic carcinoma),* **173**. 3-Fluoromethyl-4-nitrophenyl isocyanate **170** is synthesized with **phosgene** [128–130].



164 **165** **166**

167

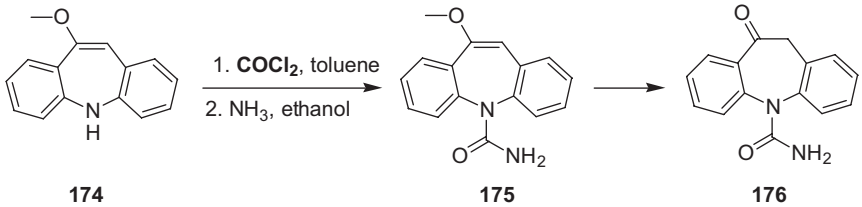
168
Etoperidone

169 **170** **172**

173
Nilutamide

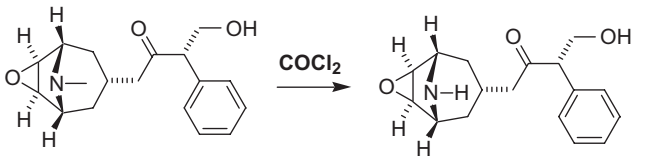
Oxcarbazepine *[28721-07-5], anticonvulsant,* **176**. The penultimate urea derivative **175** is prepared by **phosgenation** of 10-methoxy-5*H*-dibenzo[*b*,*f*]azepine **174** and subsequent treatment with ammonia [131–133].

Oxitropium bromide *[30286-75-0], anticholinergic, antiasthmatic,* **180**. **Phosgene** is employed to demethylate the tertiary amine group in (−)-scopolamine **177** [134–136].

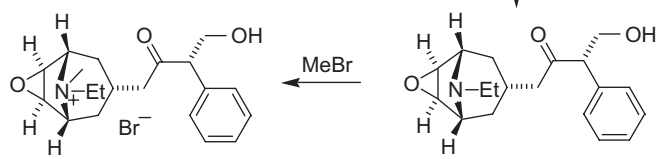


174 **175** **176**

Oxcarbazepine



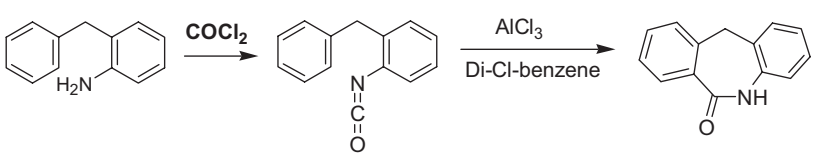
177 **178**



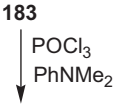
180 **179**

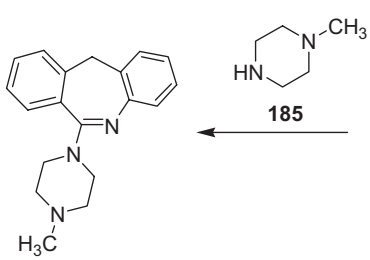
Oxitropium bromide

Perlapine *[1977-11-3], hypnotic,* **186**. **Phosgene** is used to generate 2-isocyanato diphenylmethane **182**, the precursor of the key lactam intermediate **183** [137].



181 **182** **183**



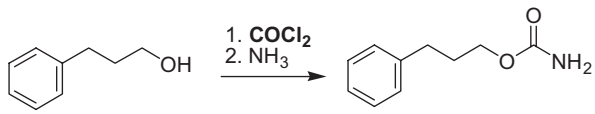


185 **184**

186

Perlapine

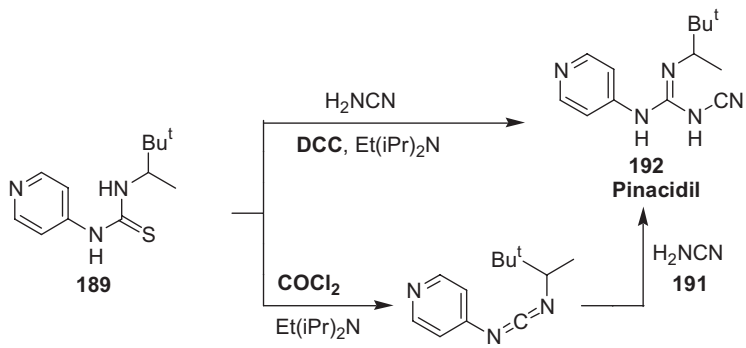
Phenprobamate *[673-31-4], muscle relaxant, tranquilizer,* **188**. Phosgenation is the key step in generating the final carbamate structure **188** [138].



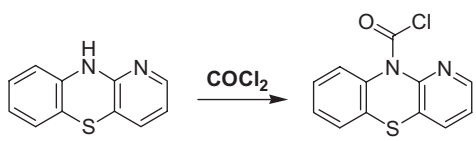
187 **188**

Phenprobamate

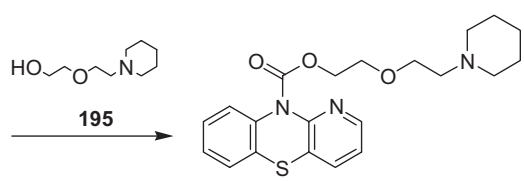
Pinacidil *[60560-33-0], antihypertensive, vasodilator, potassium channel activator,* **192**. Either **DCC** or **phosgene** in the presence of ethyldiisopropylamine can be used to generate the substituted guanidine structure from the substituted thiourea [139–143].



Pipazetate *[2167-85-3], antitussive,* **196**. **Phosgene** is employed to prepare 1-azaphenothiazine-10-carbonyl chloride **194**, the precursor of the final carbamate drug **196** [144, 145].



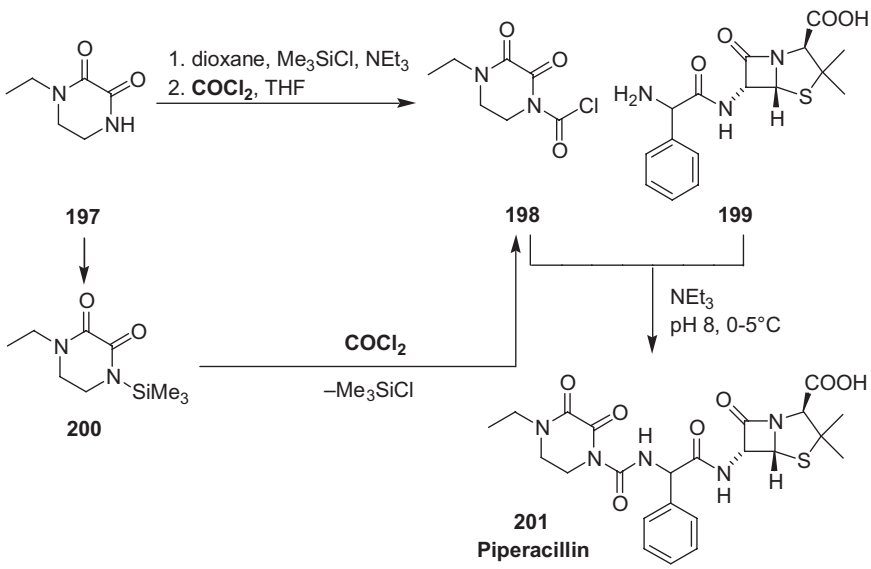
193 **194**



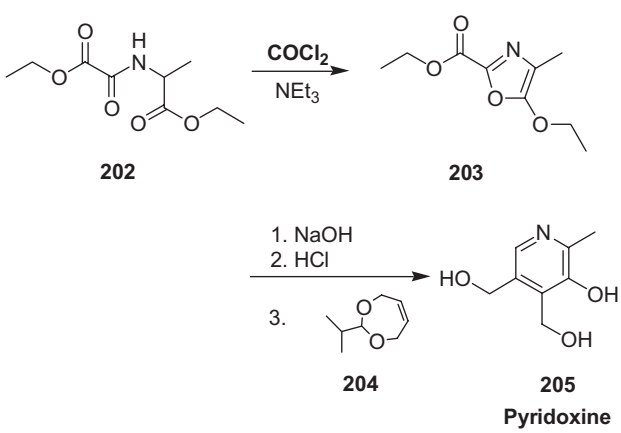
196

Pipazetate

Piperacillin *[61477-96-1], antibiotic,* **201**. **Phosgenation** of 2,3-dioxo-1-ethyl-piperazine **197** gives the corresponding carbamoyl chloride **198** through the intermediate trimethylsilyl derivative **200** [146]. 4-Ethyl-2,3-dioxo-1-piperazinecarbonyl chloride **198** condenses with *Ampicillin* **199** to form *Piperacillin* [147–151]. The same carbamoyl chloride is used for the preparation of *Cefoperazone* [62893-19-0], another antibiotic.

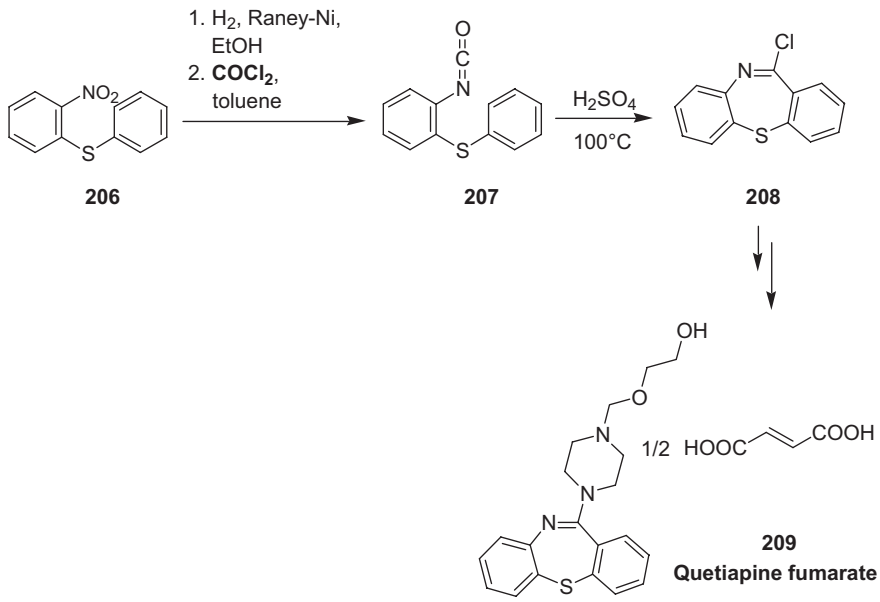


Pyridoxine *[65-23-6], vitamin (enzyme co-factor),* **205**. In one method, **phosgene** is employed to cyclize the oxalic amide **202** [152].

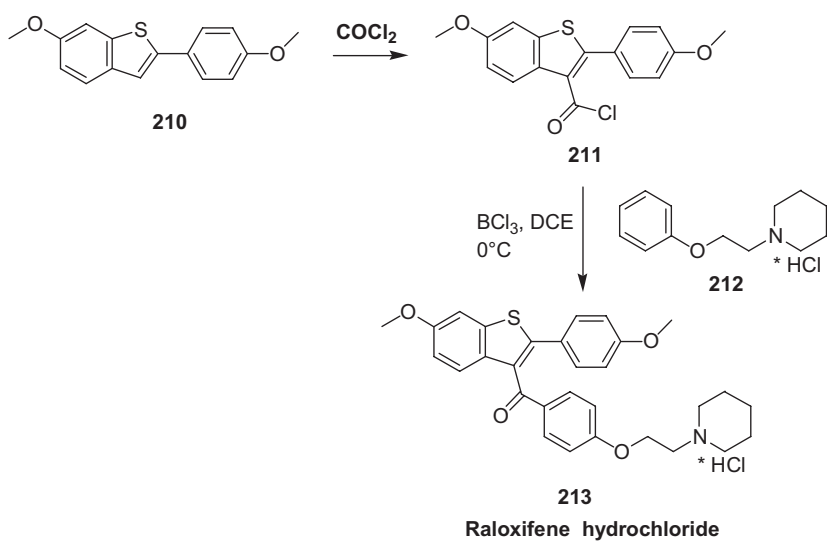


Quetiapine fumarate *[111974-72-2], antipsychotic,* **209**. In one method, **phosgene** is employed to generate *o*-isocyanato diphenyl sulfide **207**, which is converted into 11-

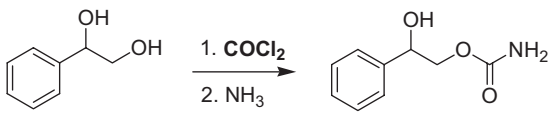
chlorodibenzo[*b*,*f*][1,4]thiazepine **208**, the penultimate intermediate in the synthesis of the drug **209** [153, 154].



Raloxifene hydrochloride *[82640-04-8], antiestrogen, prevention of osteoporosis,* **213**. In one reported method, **phosgene** is employed to chlorocarbonylate 6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene **210** [155].

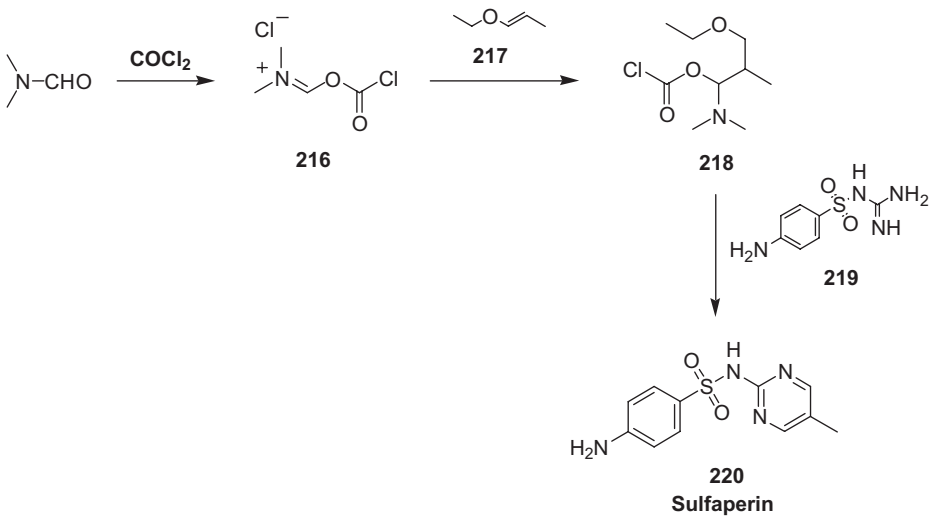


Styramate *[94-35-9], muscle relaxant, antispasmodic,* **215**. 1-Phenyl-1,2-ethanediol-2-carbamate **215** is obtained by phosgenation of the corresponding diol **214** [156].



214 **215**
Styramate

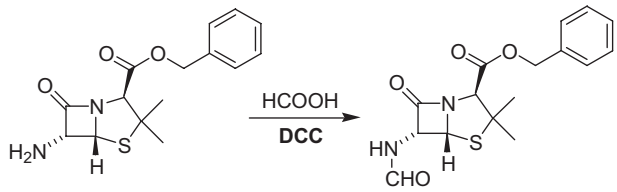
Sulfaperin *[599-88-2], chemotherapeutic,* **220**. **Phosgene** is reacted with *N*,*N*-dimethylformamide to give intermediate **216**, which is then treated with 1-ethoxy-1-propene to form a C-4 synthon. Reaction of the latter with the sulfaguanidine **219** forms the 1,3-diazine *Sulfaperin* **220** [157].



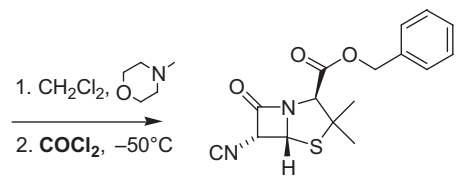
216 **218** **219** **220**
Sulfaperin

A similar method has been applied in the synthesis of *Trimethoprim* [738-70-5], a chemotherapeutic, antibacterial API (reaction of 3,4,5-trimethoxybenzylcyanoacetic acid with DMF and **phosgene**, followed by reaction with guanidine, leads directly to trimethoprim) [158, 159].

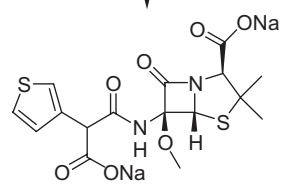
Temocillin *[66148-78-5], β-lactam antibiotic (penicillin derivative),* **224**. In one method, **phosgene** is employed to generate the isonitrile function of the penicillanic acid ester **223** [160–162].



221 **222**

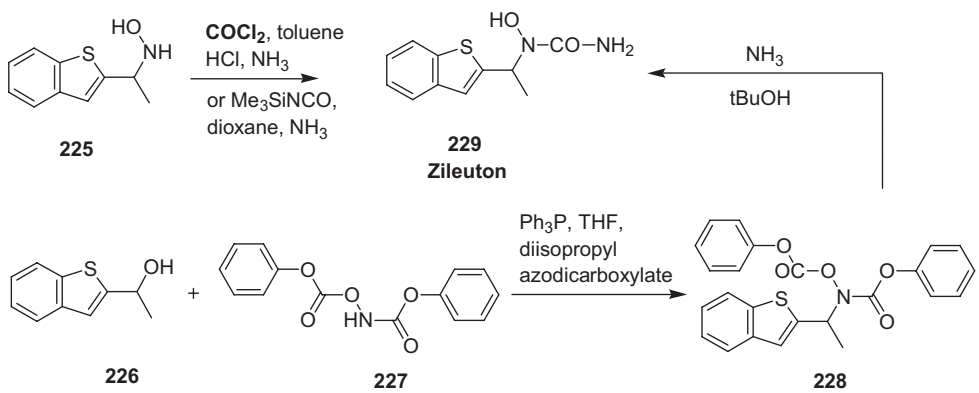


223



224
Temocillin disodium

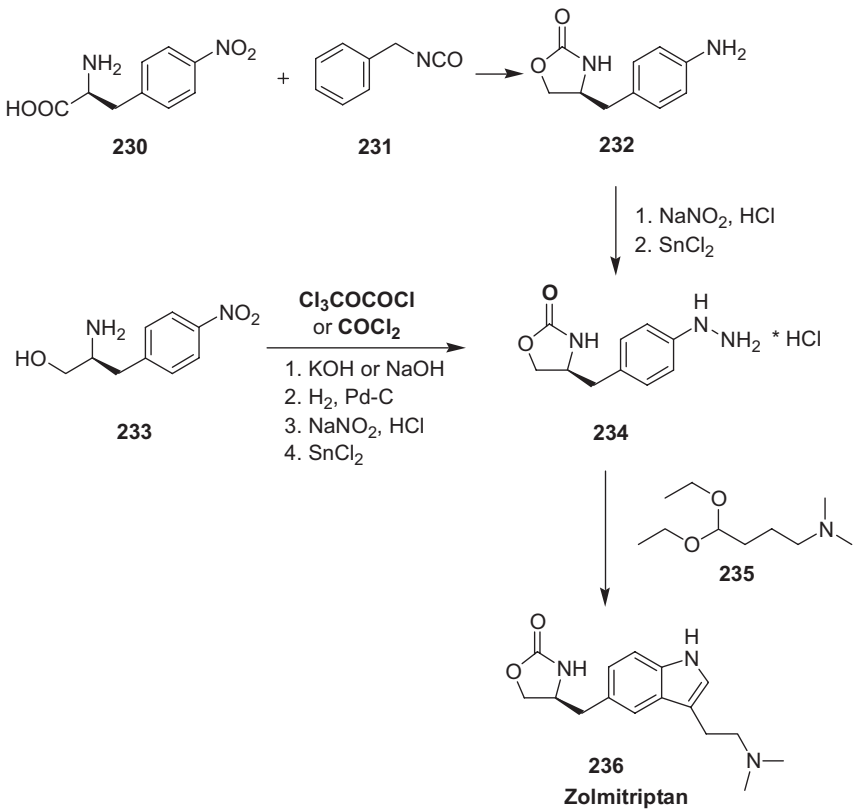
Zileuton *[111406-87-2], anti-inflammatory, antiasthmatic, 5-lipoxygenase inhibitor,* **229**. **Phosgene** or phosgene equivalents (**trimethylsilyl isocyanate**, **diisopropyl azodicarboxylate**) have been employed to prepare the hydroxy-urea compound *Zileuton* [163–169].



225 **229** **Zileuton**

226 **227** **228**

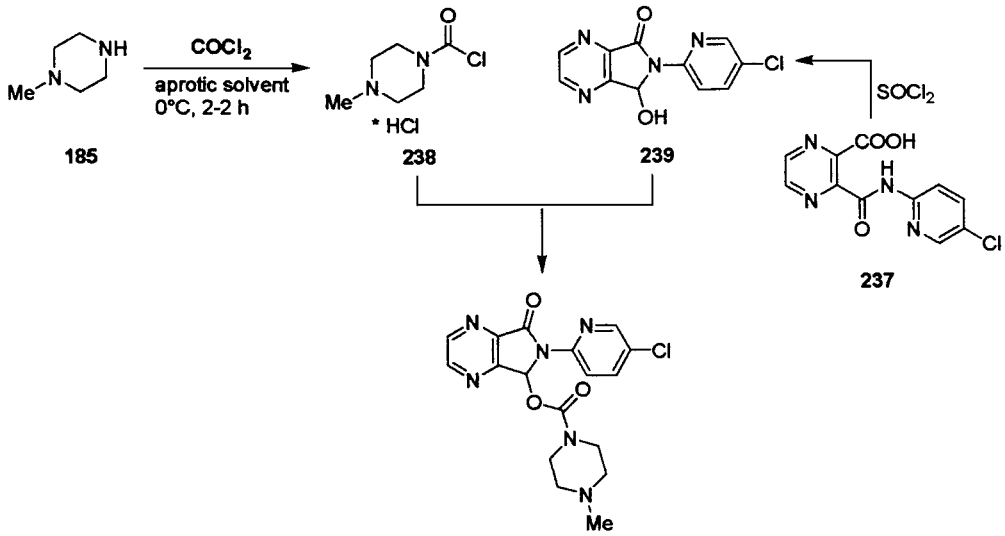
Zolmitriptan *[139264-17-8], antimigraine agent, 5-HT$_1$D-agonist,* **236**. Intermediates in various synthetic routes to *Zolmitriptan* are prepared with **phosgene**, phosgene equivalents, or phosgene derivatives [170, 171].



Zopiclone *[43200-80-2], anxiolytic, hypnotic,* **240**. 1-Chlorocarbonyl-4-methylpiperazine, **238**, a key intermediate en route to **Zopiclone**, an API having a carbamate structure, is prepared with **phosgene** [172, 173]. An improved synthesis of this intermediate has been reported by SNPE [174].

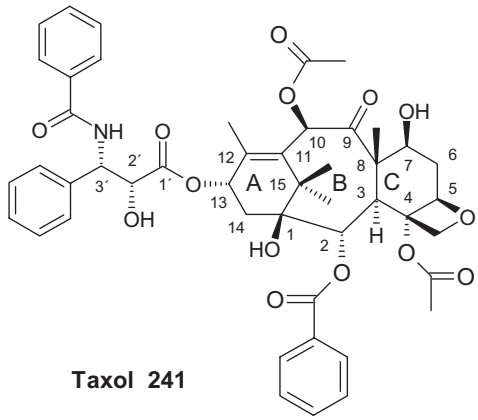
5.2
Phosgenation in Taxol Chemistry

In the early 1960s, the NCI (National Cancer Institute) began an ongoing program to discover new drugs. Following this initiative, botanist A. Barclay collected samples of the bark of the Pacific yew, *Taxus brevifolia* Nutt. Initial screening of a crude extract showed cytotoxic activity and inhibitory action against a variety of tumors.



The active component of the extract, *taxol* **241**, proved to be the most interesting of more than 110,000 compounds from 35,000 plant species tested [175]. Since that time, much effort has been directed towards the investigation of total and semi-synthetic approaches to, and medicinal applications of, this powerful anti-cancer drug. Some reviews on the chemistry and biology of *taxol* have been published [176–178]. Total syntheses were presented, particularly by Holton [179–181] and by Nicolaou [182] as well as by a report on the latter [183]. Modern, step-saving syntheses start from natural products such as *pinene*, as proposed by Wender [184], or (*S*)-(+)-*carvone* [185]. New transition metal catalyzed reactions are applied to construct the eight-membered B ring of *taxol* [186].

Phosgenation reactions are applied to a variety of synthetic targets. They play a

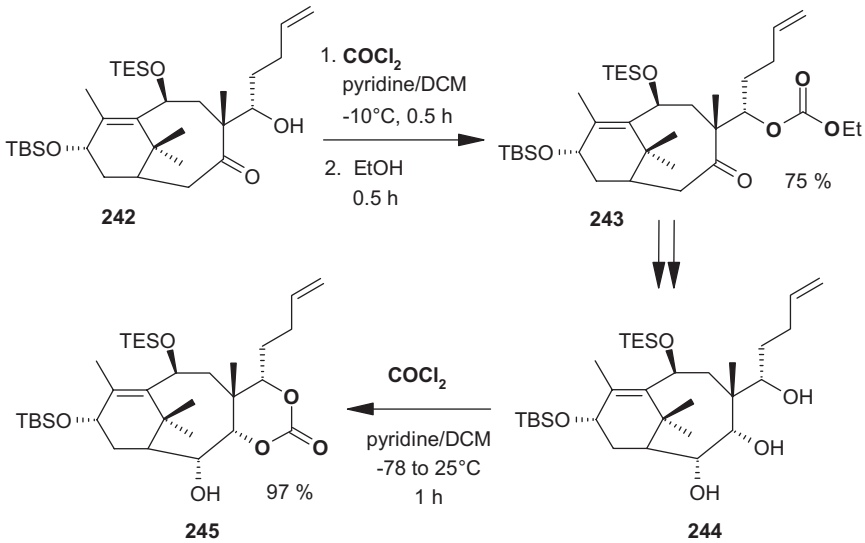


Taxol 241

part in syntheses of *taxol*, both total and semisynthetic, as well as in various modifications of *taxol*, particularly its C-2 analogues. Phosgenation reactions are also important in making *taxol* water-soluble as well as in the construction of *taxol* prodrugs. Several of the following reactions have already been presented in Chapter 4 in the context of forming functional groups using specific reagents in various phosgenation reactions.

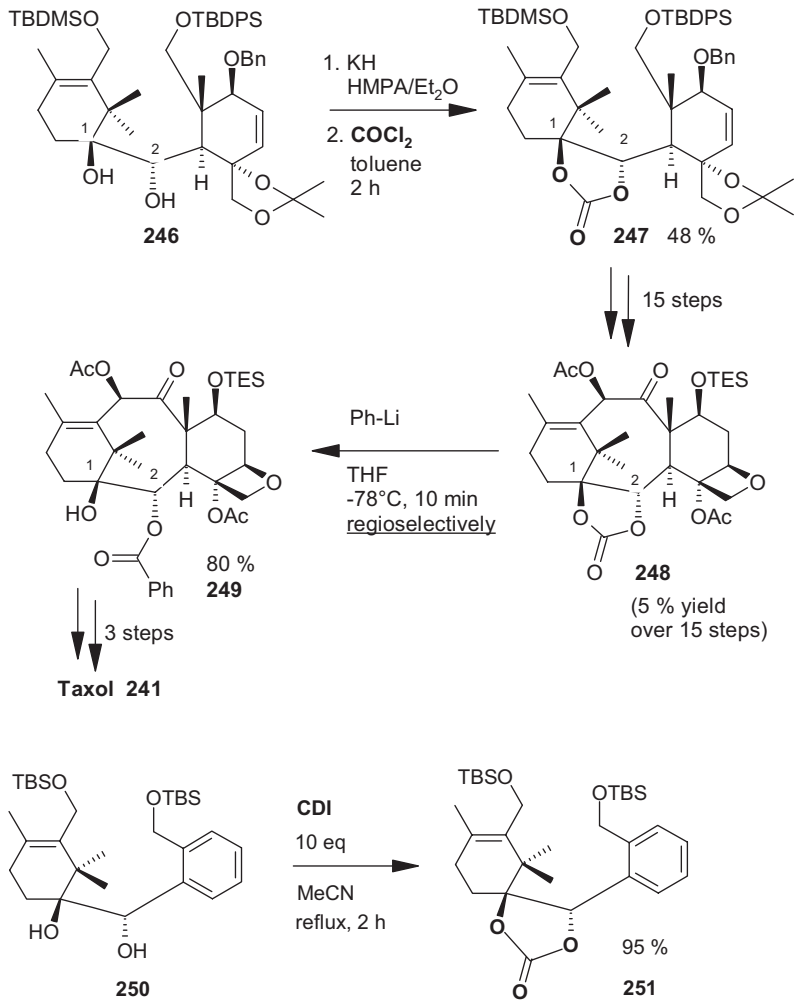
5.2.1 Total Synthesis Approaches

During the first total synthesis of *taxol* by Holton [179], a sequence of *phosgenation reactions* was performed in forming both a carbonate **243** and a cyclocarbonate **245** with **phosgene**. The cyclocarbonylation of the triol **244** with **phosgene** is regioselective and yields the six-membered ring **245**.

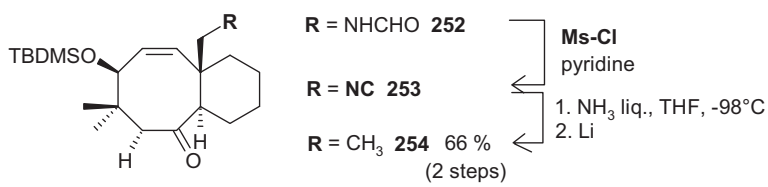


Nicolaou's approach to the total synthesis of *taxol* [182] employed **phosgene** to form the 1,2-cyclocarbonate **247** from **246** at the taxane scaffold as a protective group for the next 15 steps. Then, a regioselective ring-opening reaction with phenyllithium elegantly afforded the 2-*O*-benzoyl derivative **249** from **248**. A further three steps led to *taxol* **241**.

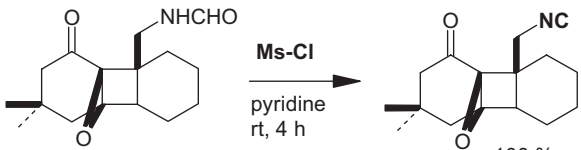
A cyclocarbonylation reaction akin to **246** → **247**, forming **251** from **250**, was accomplished with **CDI** in a taxoid synthesis by Nicolaou [187].



Mesyl chloride has been employed in the construction of the taxinine AB ring system [187] as well as of the taxane BC substructure [188]. The stereoselective construction of the taxinine AB system through a novel *tandem aldol–Payne rearrangement annulation* involves dehydration of the formamide **252** with **mesyl chloride** to give **253**, followed by reductive cleavage of the isocyano function in **253** to afford **254** [188].



Stereoselective construction of the *taxane BC* substructure requires an intermediate isocyano function in **256**. Intermediate **256** is obtained in 100% yield by dehydration of the formamide **255** with **mesyl chloride** [189].

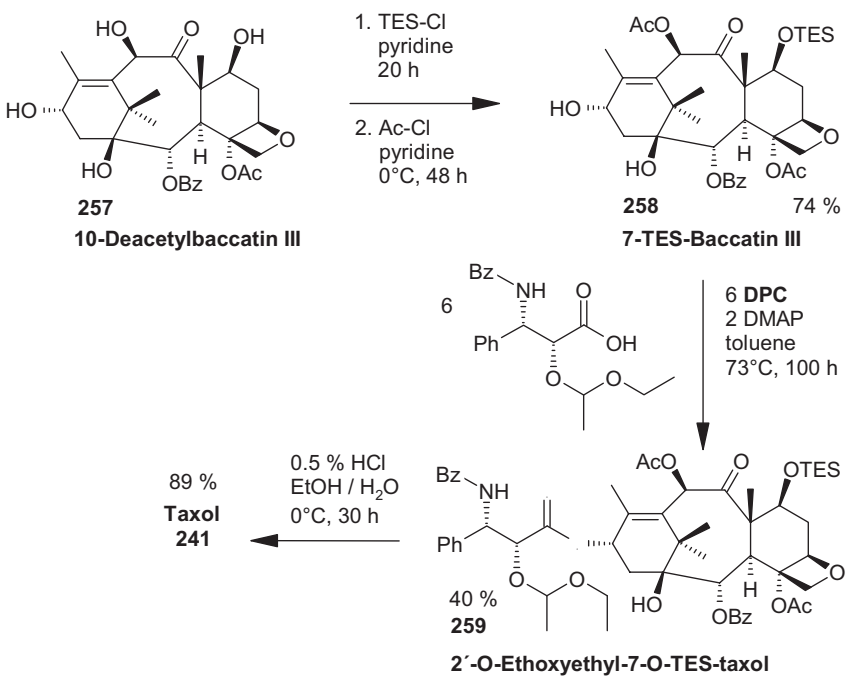


255 **256**

5.2.2

Semisynthetic Approaches

Some approaches for the semisynthesis of *taxol* are based on relatively economically priced *10-deacetylbaccatin III*, obtained from leaves of the European yew *Taxus baccata*. The leaves are able to regenerate by growing again, whereas removal of the bark of the Pacific yew *Taxus brevifolia*, which contains *taxol*, kills the tree. The semisyntheses of Denis and Greene from 1988 [190] and 1994 [191] are discussed here. *10-Deacetylbaccatin III* **257** is first protected at the 7-position with a triethylsilyl residue and acetylated at the 10-position with acetyl chloride. The resulting 7-TES-baccatin III **258** is coupled with *O*-protected *N*-benzoyl-3-phenylisoserine using a sixfold excess of **dipyridyl carbonate** (**DPC**) to afford 2′-*O*-ethoxyethyl-7-TES-taxol **259**, which is deprotected with 0.5% hydrochloric acid to afford *taxol* **241** [190].



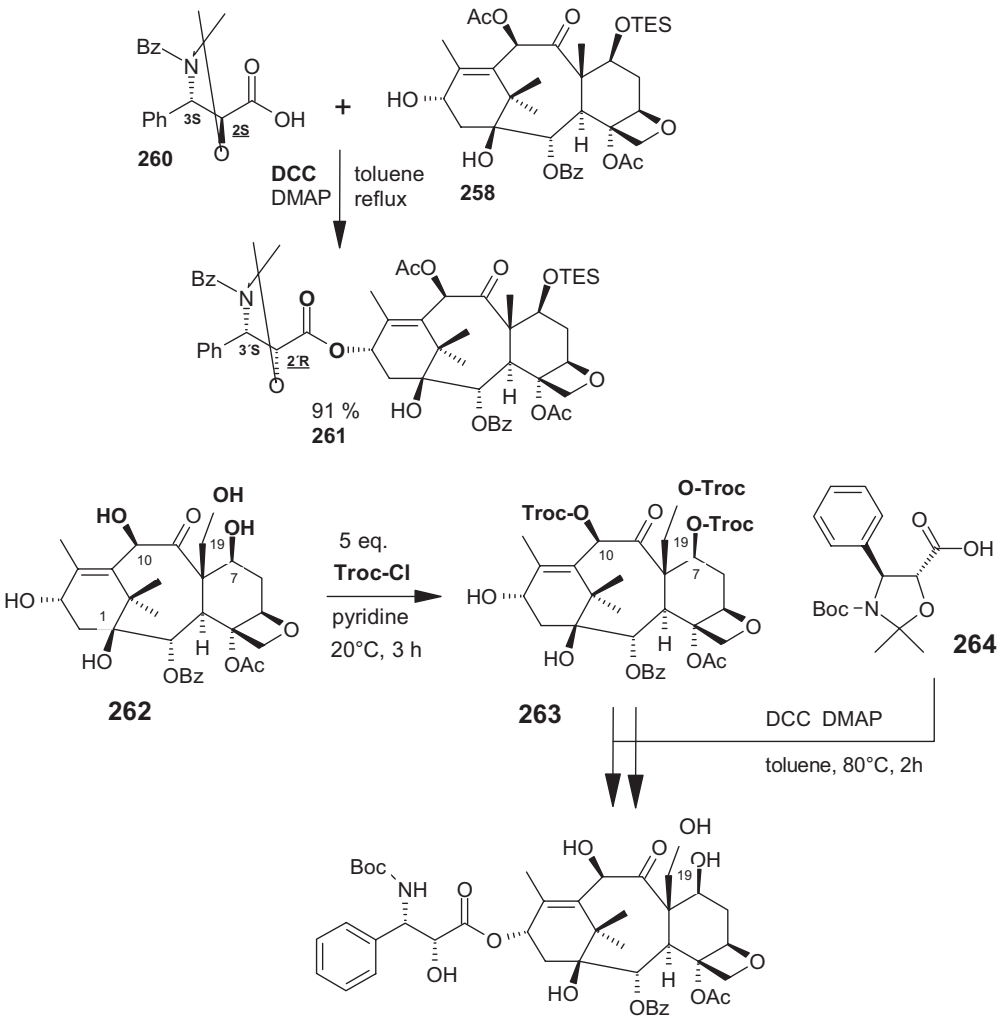
257
10-Deacetylbaccatin III

258
7-TES-Baccatin III

259
2´-O-Ethoxyethyl-7-O-TES-taxol

A substantially better yield in the coupling step can be achieved using differently protected coupling partners (*N*,*O*-protection with an isopropylidene residue), in particular (2*S*)-2-*O*-3-*N*-isopropylidene-*N*-benzoyl-3-phenylisoserine **260**, which has the "wrong" configuration at C-2. Coupling of **260** with 7-TES-baccatin III **258** using **DCC**/DMAP leads to complete epimerization at C-2 of **260** affording (2′*R*)-2′-*O*-3′-*N*-isopropylidene-7-TES-taxol **261** in 91% (!) yield [191].

2,2,2-Trichloroethyl chloroformate (**Troc-Cl**) has been used for the *O*-protection of the C-7, C-10, and C-19 positions of 10-deacetyl-19-hydroxybaccatin III **262**, a novel baccatin derivative which is reacted with the *N*-Boc-3-phenylisoserine **264** in the presence of **DCC**/DMAP to form, after further steps, the novel 19-hydroxy-docetaxel **265** [192]. The analogue **265** exhibits a high level of in vitro cytotoxicity

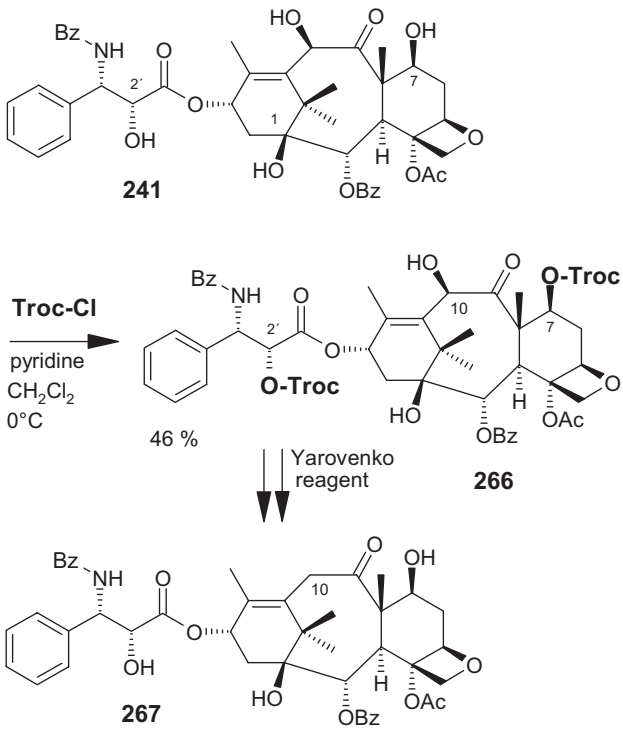


and thus the results demonstrate that chemical modifications at C-19 can be made without significant loss of biological activity.

5.2.3 Modifications of Taxol

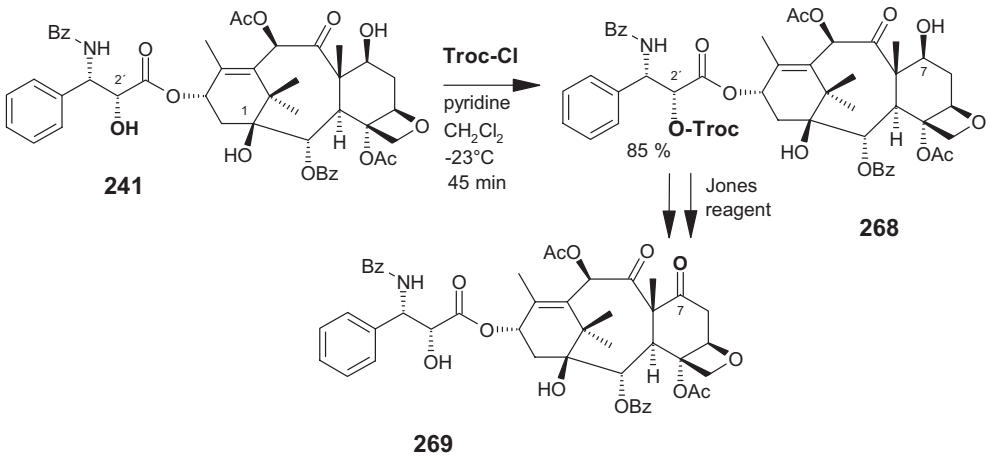
Modifications of *taxol* by manipulation of specific functional groups on the entire system can be performed by treatment with the appropriate reagents.

10-Deoxytaxol **267** is prepared from taxol **241** in four steps. Dehydration of the alcohol group at C-10 requires protection of the hydroxy functions at C-2′ and C-7, which is accomplished with **Troc-Cl**, affording the corresponding 2,2,2-trichloroethyl carbonate **266** [193].

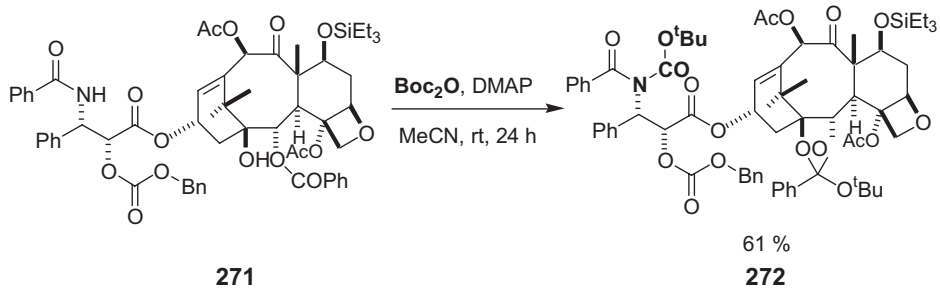


Oxidation of taxol **241** with Jones' reagent yields 7-oxotaxol, 2′,7-dioxotaxol, or 2′-oxo-7-acetyl taxol. In order to selectively obtain 7-oxotaxol **269**, it is necessary to block the C-2′ hydroxy function of **241**, which is accomplished using the Troc group, introduced with **Troc-Cl**, to afford *2′-O-Troc-taxol* **268** [194].

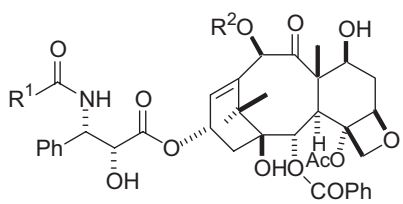
Protection of the amidic nitrogen with **di-*tert*-butyl dicarbonate** (**Boc_2O**) to afford **272**, as part of an efficient and regioselective method for the *N*-debenzoylation of *taxol* **241** to 10-acetyldocetaxel and to *Docetaxel* **270**, has been reported [195]. *Taxol* and its semisynthetic analogue *Docetaxel* (*Taxotere*®) are among the most important new antitumor agents of last decade.



241 268 269



271 272



Taxol	R^1 = Ph, R^2 = Ac, **241**
Docetaxel	R^1 = ^{t}BuO, R^2 = H, **270**

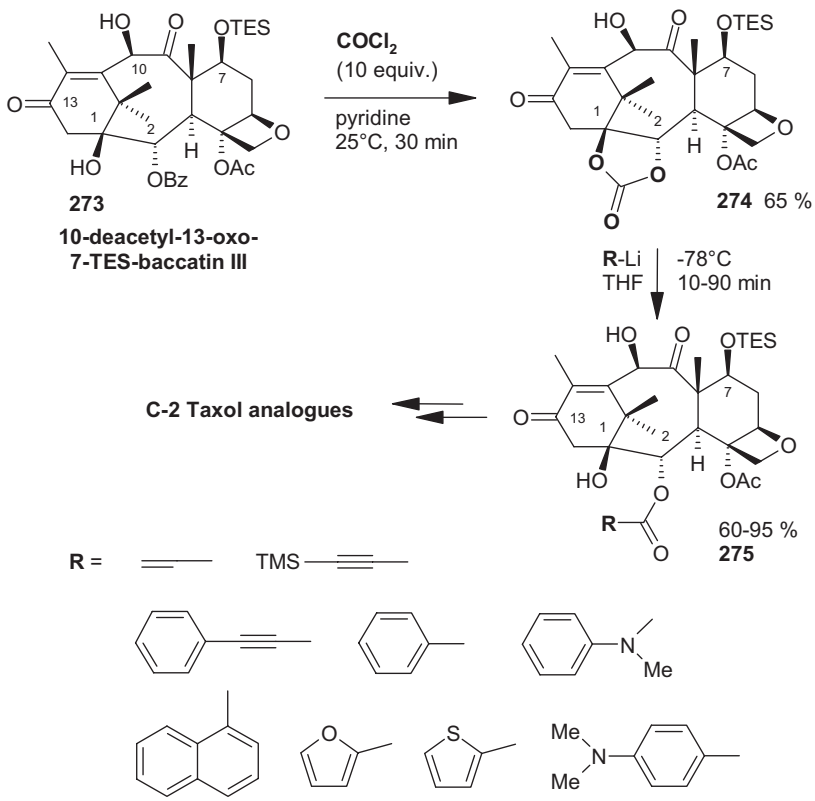
Deprotection and further selective *N*-debenzoylation of **272** to afford **270** are accomplished by treatment with magnesium methoxide in methanol [195].

The design and synthesis by solid-phase methods of a *combinatorial chemistry library* of C-7 acyl, C-10 acyl, and C-7,10 diacyl analogues of paclitaxel (*taxol*) has been described [196]. In this connection, a patent application on *"Methods and useful intermediates for paclitaxel [taxol] synthesis from C-7,10 di-Cbz 10-deacetylbaccatin III"* is worthy of mention [197].

5.2.4
C-2 Analogues of Taxol

The observation in the total synthesis of *taxol* by Nicolaou [182] (see Section 5.2.1) that the 1,2-cyclocarbonate **248** can be opened strictly regioselectively with phenyllithium to give **249** in good yield, led to consideration as to whether the reaction of **248** with other nucleophiles would provide easy access to other C-2 analogues.

As a result, Nicolaou developed a preparative method for converting *10-deacetyl-13-oxo-7-TES-baccatin III* **273** (available from naturally occurring *10-deacetyl-baccatin III*) into *10-deacetyl-13-oxo-7-TES-baccatin III 1,2-cyclocarbonate* **274** with **phosgene** [198]. The latter can be ring-opened chemoselectively and regioselectively by various nucleophiles **R**Li to yield C-2 analogues **275**, which are reduced at C-13 and coupled with the requisite side chain to give C-2 *taxol* analogues [199].

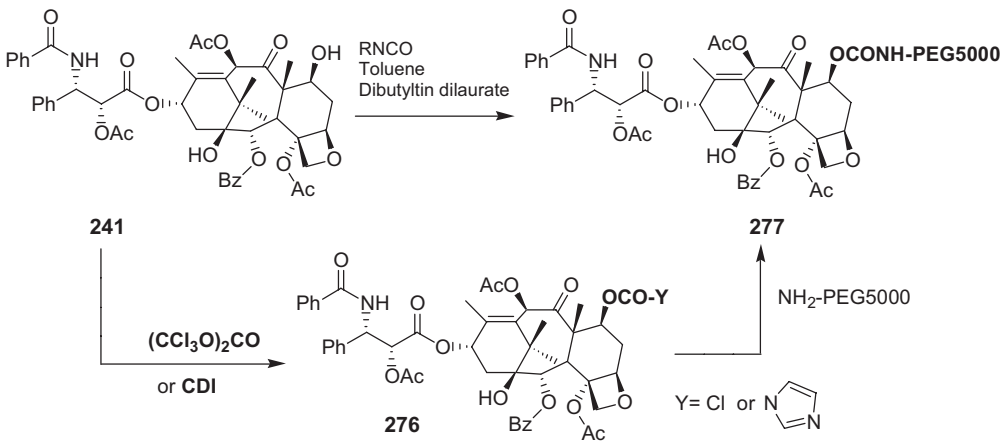


5.2.5
Water-Soluble Prodrugs

To achieve high bioavailability of *taxol*, it needs to be highly soluble in water, but, in fact, it suffers from extremely low solubility in water ($< 5 \times 10^{-6}$ M). Thus, *taxol*

is applied clinically in a mixture of Cremaphor (a polyoxyethylated castor oil) and ethanol. Unfortunately, this formulation often induces hypersensitivity reactions. A water-soluble form of *taxol* could completely obviate these problems and both expand its usage and dramatically improve its pharmacological profile [200]. Of tremendous potential are *taxol* derivatives in which the C-2′ and C-7 hydroxyl groups are engaged in a functional group that collapses upon *in vivo* activation, releasing *taxol*. Conjugates of this type are termed prodrugs. Successful application of these compounds requires both hydrophilic (for formulation) and lipophilic (for therapy) properties [200].

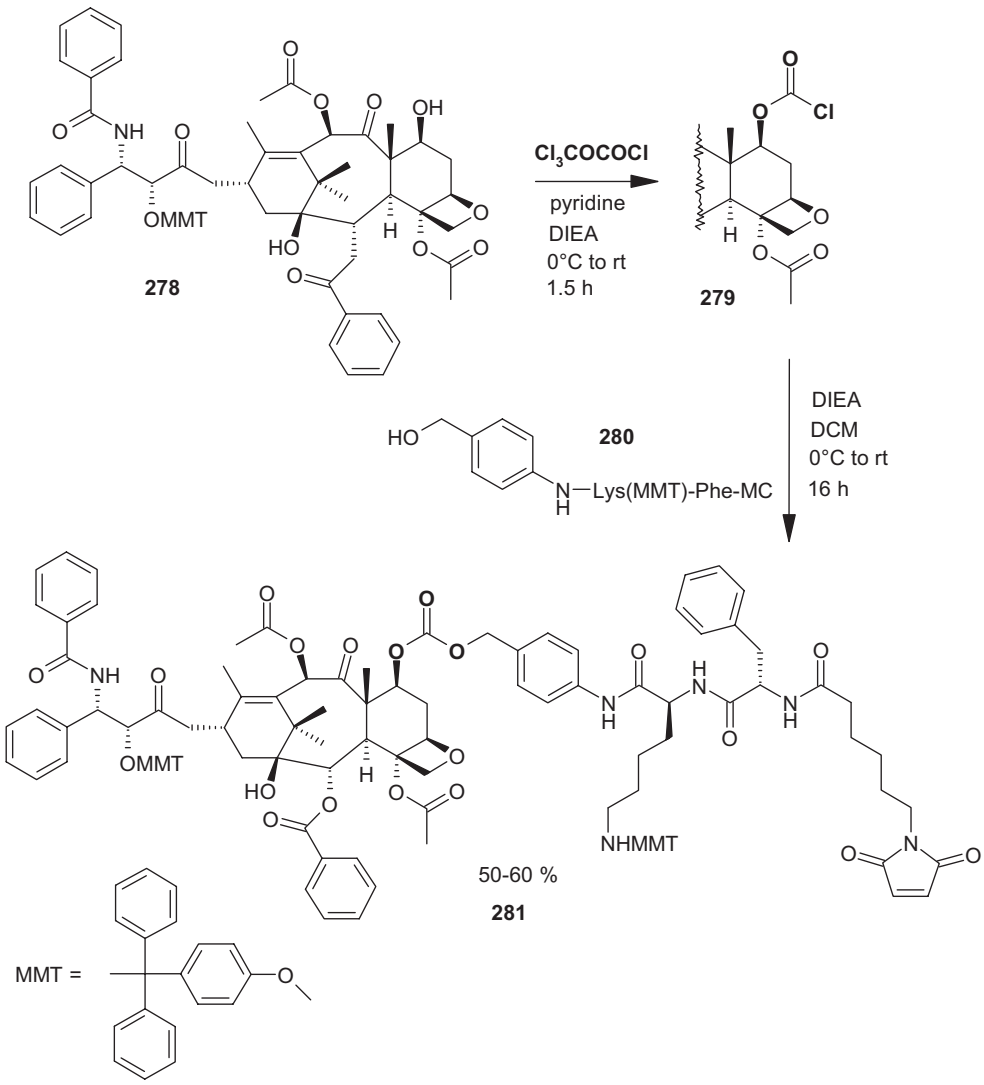
This was realized by coupling *taxol* **241** (acetylated at C-2′) through C-7, via carbonate or carbamate linkages, with polyethyleneglycol PEG 5000 to form **277** [201]. Couplings were accomplished with **triphosgene** or **CDI** via formates **276** (Y = Cl, imidazolyl). Another synthesis of water-soluble prodrugs bonded to PEG is given in [202].



A sophisticated approach involves the attachment of a series of alternating hydrophilic and lipophilic moieties at the C-7-O position of *taxol* to give the prodrug **281**. *Taxol* derivative **278**, blocked by an MMT residue at C-2′, is reacted with **diphosgene** to form the **chloroformate 279**. This is then reacted with the linkage-bearing dipeptide Lys-Phe **280**, the linker being *p*-aminobenzyl alcohol (PABA), and the amino group of Phe being derivatized with *N*-succinyl aminocapronic acid [203], thereby affording the highly water-soluble *taxol* prodrug **281**.

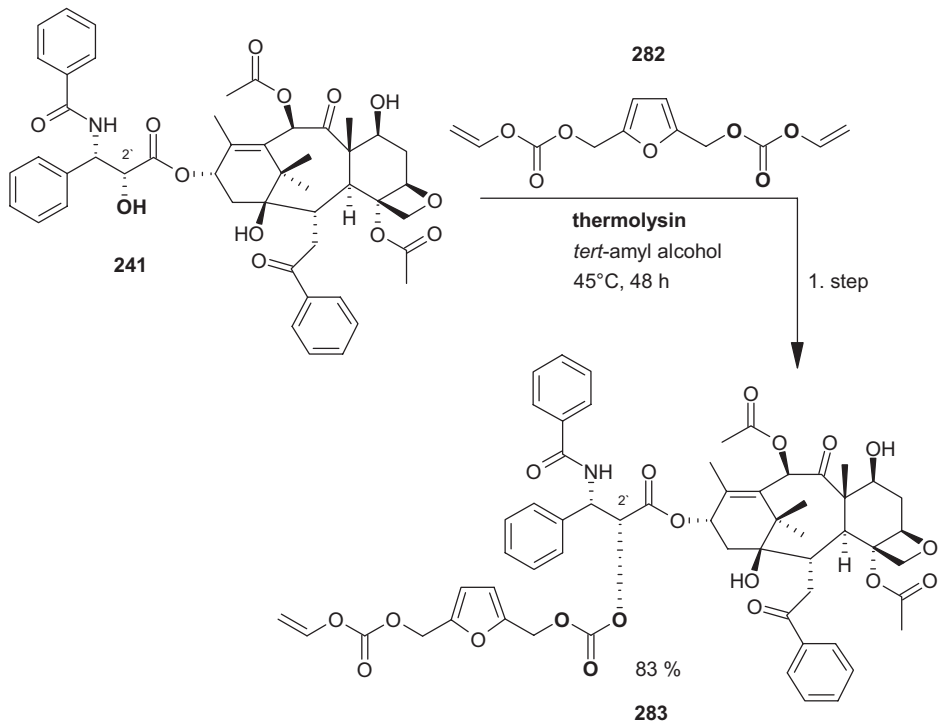
In another approach, the C-2′ position of *taxol* is the site of manipulation. Thus, a two-step enzymatic acylation in organic solvents has been employed to synthesize water-soluble *taxol (paclitaxel)* derivatives. In the first step, *taxol* **241** is reacted with the bifunctional acylating reagent **282**, as catalyzed by **thermolysin** (from *Bacillus thermoproteolyticus rokko*), to give the activated acyl derivative **283**. This is then used as a complex acyl donor in the second step [204].

The possibilities of detoxifying chemotherapeutics and of targeting drugs specifically to tumors have been investigated using taxol inclusion complexes with a cyclodextrin dimer [205].



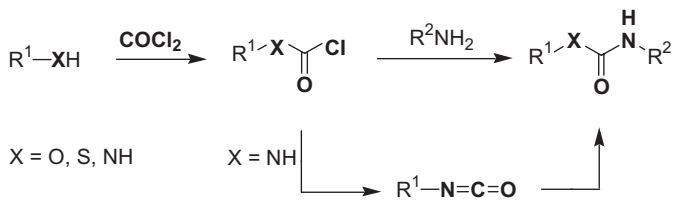
5.3
Syntheses of Agrochemicals with Phosgene and Derivatives

The carbamate and urea derivatives used as pesticides are commonly prepared with **phosgene**. The substituted ureas are mainly used as *herbicides*, while carbamates are used as *insecticides* and *acaricides*. It is estimated that 93% of all carbamates and 92% of all urea-based herbicides on the U.S. market are commercially synthesized with phosgene [206]. Of the substituted ureas, *Monuron* and *Diuron* are the most important pesticides in volume terms, and of the carbamates, *Carbaryl* (*Sevin*) is the single most important chemical. *Eptam* (*S*-ethyl-*N*,*N*-dipropyl



thiocarbamate) is an example of a range of selective thiocarbamate herbicides that can be derived from **phosgene**.

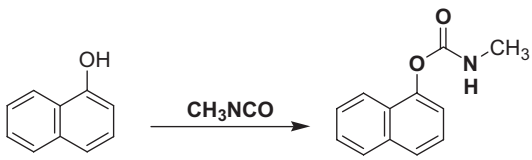
These products are made in a two-stage process by reacting **phosgene** with an alcohol, thiol, or amine to give a **chloroformate**, **thiochloroformate**, **carbamoyl chloride**, or **isocyanate**, which is then combined with an amine to give carbamates (X = O), thiocarbamates (X = S), or ureas (X = NH).



Monoisocyanates prepared by aminolysis of **phosgene** are predominantly used as intermediates in the manufacture of agricultural products such as herbicides and insecticides [207, 208]. The commercially used aliphatic **isocyanates** include methyl, propyl, isopropyl, butyl, isobutyl, octadecyl, and cyclohexyl isocyanate. The aromatic isocyanates used as building blocks for agricultural chemicals include phenyl isocyanate and halogen-substituted phenyl isocyanates.

The accident involving **methyl isocyanate** (**MIC**) in Bhopal, India (1984) has

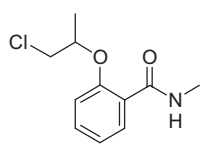
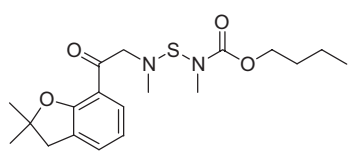
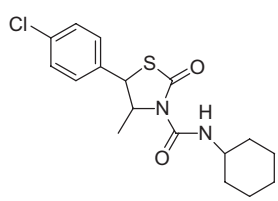
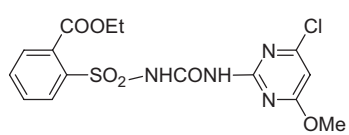
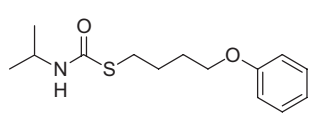
changed many process and manufacturing strategies regarding the storage and use of *low-boiling aliphatic isocyanates*. Formerly, the Union Carbide broad spectrum contact insecticide *Sevin* (*N-methyl-1-naphthyl carbamate*, **284**) was prepared by the addition of 1-naphthol to **MIC** (for the synthesis of other carbamates with **isocyanates**, see Section 4.3.2).



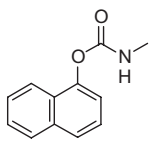
284

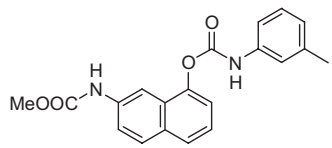
Table 5.1 shows examples of various classes of compounds having pesticide activity with potential **isocyanate** intermediates.

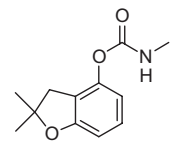
Tab. 5.1. Pesticide products with potential **isocyanate** intermediates.

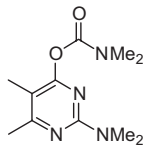
Chemical Type	*Structure*	*Type of Pesticide*
Carbamate		Insecticide/Nematicide
Carbamate		Insecticide/Nematicide
Urea		Insecticide
Sulfonyl urea		Herbicide
Thiocarbamate		Insecticide

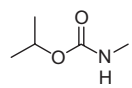
Selected important *carbamate*, *thiocarbamate*, and *urea herbicides* and their chemical structures are presented below.

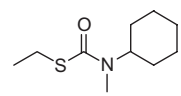

Carbaryl

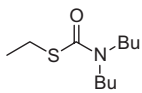

Phenmedipham

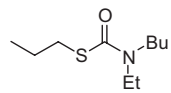

Carbofuran

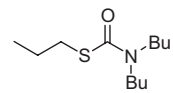

Pyrimicarb

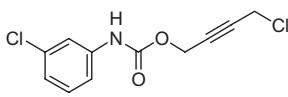

Propham

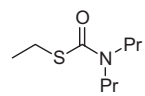

Cycloate

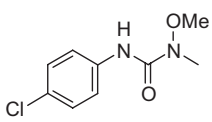

Butylate

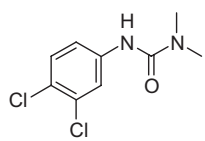

Pebulate

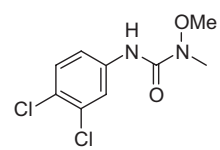

Vernolate

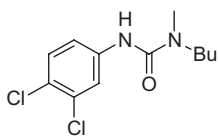

Barban

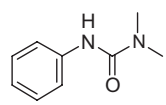

Eptam

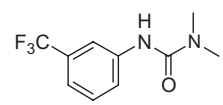

Monuron

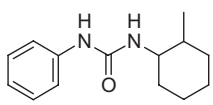

Diuron

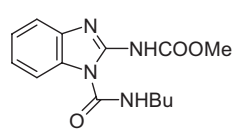

Linuron

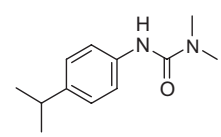

Neburon


Fenuron

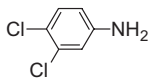
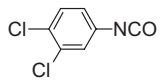
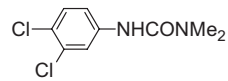
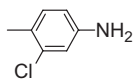
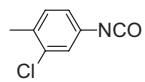
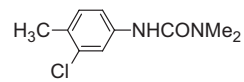
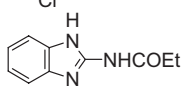
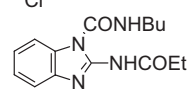
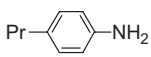
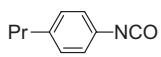
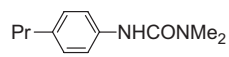
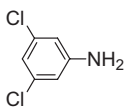
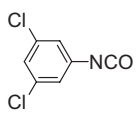
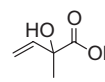
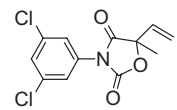
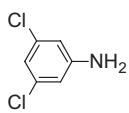
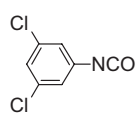
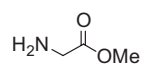
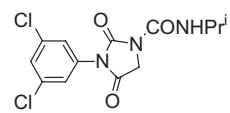
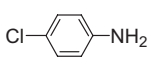
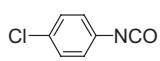
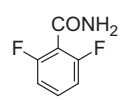
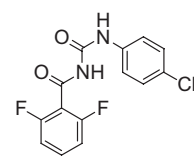
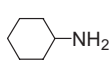
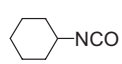
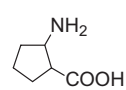
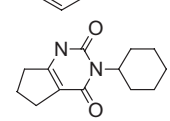
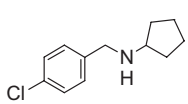
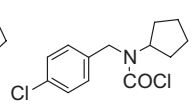
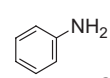
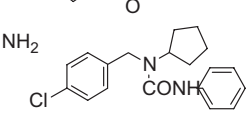
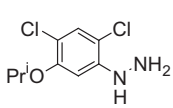
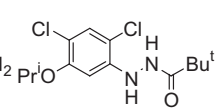
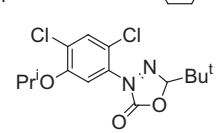
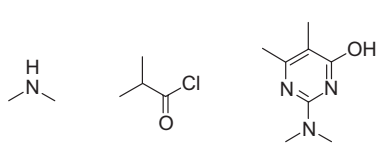
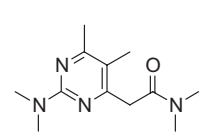
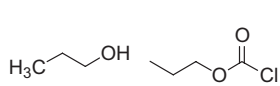
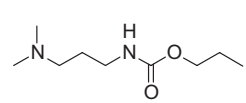
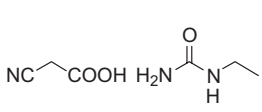
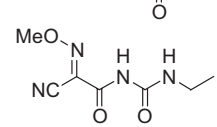

Fluometuron


Siduron


Benomyl


Isoproturon

Tab. 5.2. Main synthetic components of some crop protection products.

Raw Material A	*Phosgenation Intermediate*	*Raw material B*	*Agro-Product*	*Commercial Name Cas Reg no*
		Me_2NH		Diuron [330-54-1]
		Me_2NH		Chlortoluron [15545-48-9]
	n-BuNCO	MeOCOCl		Benomyl [17804-35-7]
		Me_2NH		Isoproturon [34123-59-6]
				Vinclozolin [50471-44-8]
				Iprodione [36734-19-7]
				Diflubenzuron [35367-38-5]
				Lenacil [2164-08-1]
				Pencycuron [66063-05-6]
		Bu^tCOCl		Oxadiazon Ronstar [19666-30-9]
				Pirimicarb [23103-98-2]
				Propamocarb [24579-73-5]
	HNO_2 Me_2SO_4			Cymoxanyl [57966-95-7]

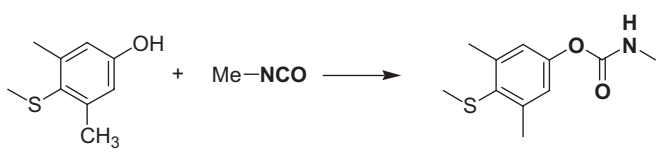
Following the above general synthetic scheme, the majority of crop protection products are made from the starting substrate (''raw material A'', Table 5.2) by ''activating'' it through a **phosgenation** process to give an **isocyanate**, **chloroformate**, or **carbamoyl chloride** as a ''phosgenation intermediate'', followed by addition of ''raw material B'' to form the desired ''agro product''.

Aromatic and aliphatic **isocyanates** are the key intermediates. Table 5.3 lists a number of pesticides with structures suggestive of an **isocyanate** intermediate, but which are probably not necessarily synthesized by employing a purchased **isocyanate**.

A series of fungicides are prepared with **isocyanates**. Addition of oximes **285** to **MIC** is the main process stage for the manufacture of *N*-methyl carbamate insecticides such as *Aldicarb*, *Methomyl*, *Oxamyl*, *and Thiopanox*.

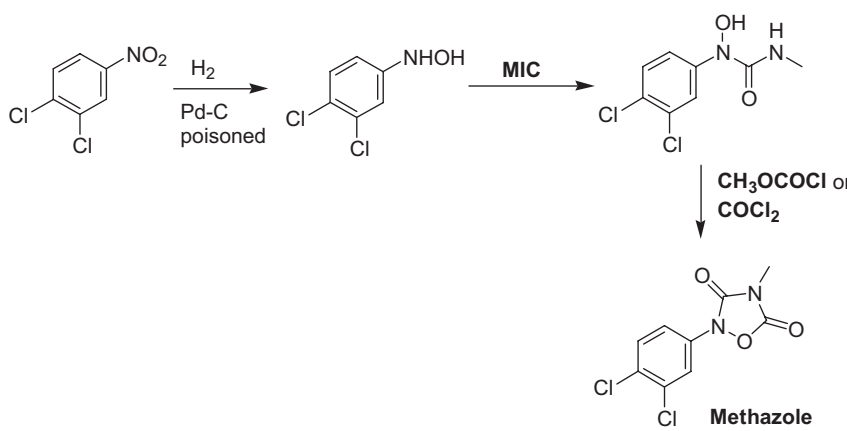
285 **Methomyl**

Addition of substituted phenol **286** to **MIC** generates *Methiocarb*. *Mexacarbate*, *Promecarb*, *Propoxur*, and *Trimethacarb* are produced in a similar fashion.



286 **Methiocarb**

The herbicide *Methazole* was traditionally manufactured by the addition of 3,4-dichlorophenyl hydroxylamine to **MIC**, followed by treatment with **methyl chloroformate** or **phosgene** and cyclization.

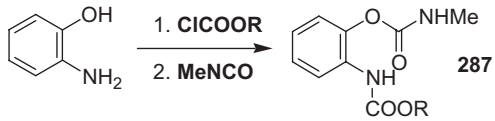


Methazole

Tab. 5.3. Pesticides suggestive of alkyl or aryl **isocyanate** precursors.

Common Name	*Potential Isocyanate or Phosgene Derivative Precursor*	*Remarks*
Aminocarb	Methyl isocyanate	Insecticide
Aldicarb (Temik)	Methyl isocyanate	Insecticide
Bendiocarb (Ficam)	Methyl isocyanate	Nematocide
Tebuthiuron	Methyl isocyanate	Herbicide
Formetanate	Methyl isocyanate	Acaricide
Carbaryl (Sevin)	Methyl isocyanate	Broad spectrum contact insecticide
Carbofuran (Furadan)	Methyl isocyanate	Systemic insecticide, Nematocide
Methomyl (Lannate)	Methyl isocyanate	Contact insecticide
Propoxur (Baygon)	Methyl isocyanate	Insecticide
Formetanate	Methyl isocyanate	Acaricide
Methiocarb	Methyl isocyanate	Insecticide
Desmedipham	Ethyl isocyanate	Herbicide
Cymoxanyl	Ethyl isocyanate	Urea fungicide
Benomyl (Benlate)	*n*-Butyl isocyanate	Urea fungicide
Bromacil (Hyvar)	*sec*-Butyl isocyanate	Carboxamide, Herbicide
Terbacil	*t*-Butyl isocyanate	Substituted uracil
Hexazinone (Lenacil)	Cyclohexyl isocyanate	Herbicide
Fenuron	Phenyl isocyanate	Herbicide
Propham	Phenyl isocyanate	Not made by isocyanate route
Siduron (Tupersan)	Phenyl isocyanate	Herbicide
Pencycuron	Phenyl isocyanate	Urea fungicide
Monuron TCA (Telvar)	4-Chlorophenyl isocyanate	Herbicide
Barban (Carbone)	3-Chlorophenyl isocyanate	Selective herbicide
Chlorpropham	3-Chlorophenyl isocyanate	Herbicide
Phenmedipham	3-Tolyl isocyanate	Herbicide
Diflubenzuron	4-Chlorophenyl isocyanate	Herbicide
Monolinuron	4-Chlorophenyl isocyanate	Herbicide
Chloroxuron	4-Chlorophenoxyphenyl isocyanate	Herbicide
Fluometuron (Cotoran)	3-Trifluoromethylphenyl isocyanate	Herbicide
Isoproturon	4-Isopropylphenyl isocyanate	Herbicide
Metobromuron	4-Bromophenyl isocyanate	Herbicide
Diuron (Telvar)	3,4-Dichlorophenyl isocyanate	Herbicide
Linuron (Lorox)	3,4-Dichlorophenyl isocyanate	Herbicide
Neburon	3,4-Dichlorophenyl isocyanate	Herbicide
Chlortoluron	3-Chloro-4-methylphenyl isocyanate	Herbicide
Vinclozolin	3,5-Dichlorophenyl isocyanate	Fungicide
Iprodione	3,5-Dichlorophenyl isocyanate	Fungicide
Chlorbromuron	3-Chloro-4-bromophenyl isocyanate	Herbicide
Oxadiazon	Pivaloyl chloride	Herbicide
Propamocarb	*n*-Propyl chloroformate	Carbamic fungicide
Pirimicarb	Dimethylamino carbamoyl chloride	Carbamic insecticide
Triasulfuron	Sulfonyl isocyanate	Herbicide
Chlorimuron	Carboxyethylbenzosulfonyl isocyanate	Herbicide

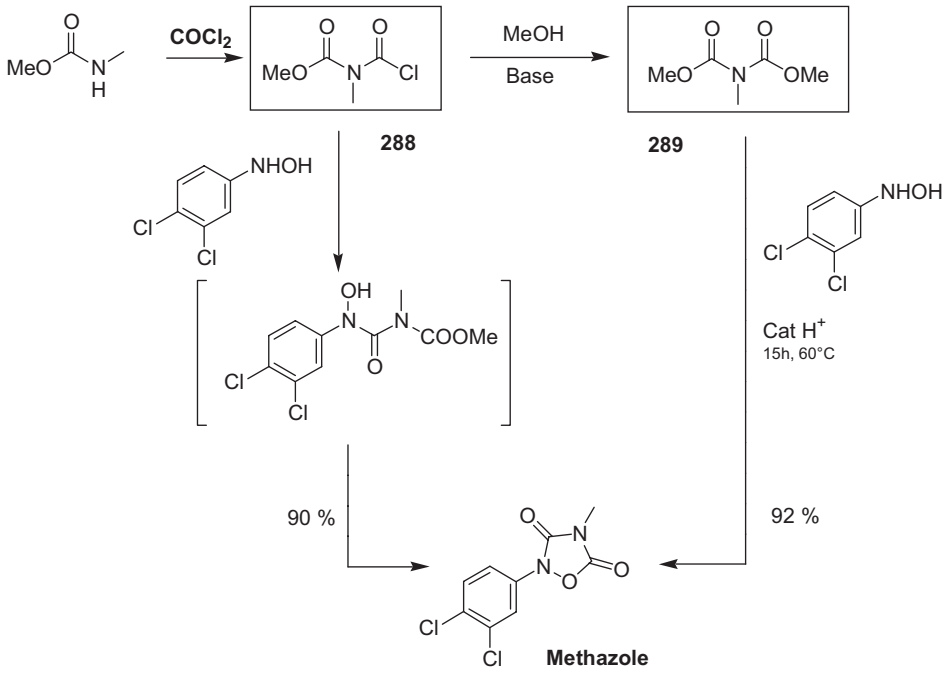
N-Alkylcarbamates substituted with a derivative of carbamic or carbonic acid (pyrocatechol carbonates) in the *ortho* position show fungicidal and phytocidal activity. For example, esters **287** have been prepared by treating *o*-aminophenol sequentially with **chloroformate** and **MIC** [209].



R = lower alkyl, 2-MeC_6H_4, 2-ClC_6H_4,
1-naphthyl, N=CMe_2, N=CPhMe

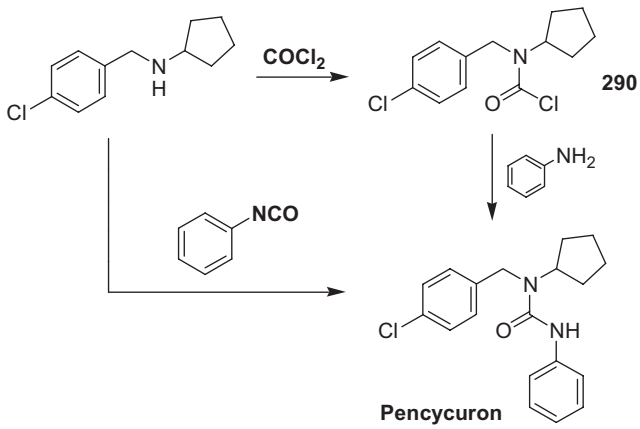
The urea and carbamate derivatives can often be produced by alternative routes avoiding the manufacture and handling of isocyanates. The Du Pont process of methylamine carboxylation with **carbon monoxide** to give *N*-methylformamide, followed by oxidation to **methyl isocyanate** and further in situ conversion of the isocyanate to the less volatile derivatives, is only one example of a safer route to pesticides.

Safer synthetic alternatives avoiding handling of the extremely hazardous **methyl isocyanate** (**MIC**) have been investigated [210]. Two intermediates gave interesting results. *N*-Methyl carbamoyl chloride **288** exhibits a high level of toxicity and decomposes to methyl isocyanate on heating, very slowly when pure, more rapidly and quantitatively in presence of nucleophile. *N*-Methyl dicarbamate **289** is a low-

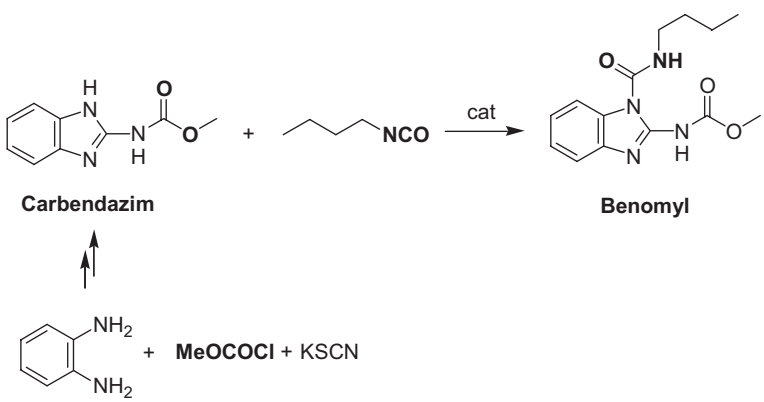


melting, stable solid, which has been used to produce *Methazole* in high yield and under mild conditions.

The urea fungicide *Pencycuron* can be prepared by aminolysis of carbamoyl chloride **290** derived from *N*-cyclopentyl-*N*-4-chlorobenzylamine. The alternative route involves addition of the secondary amine to **phenyl isocyanate**.

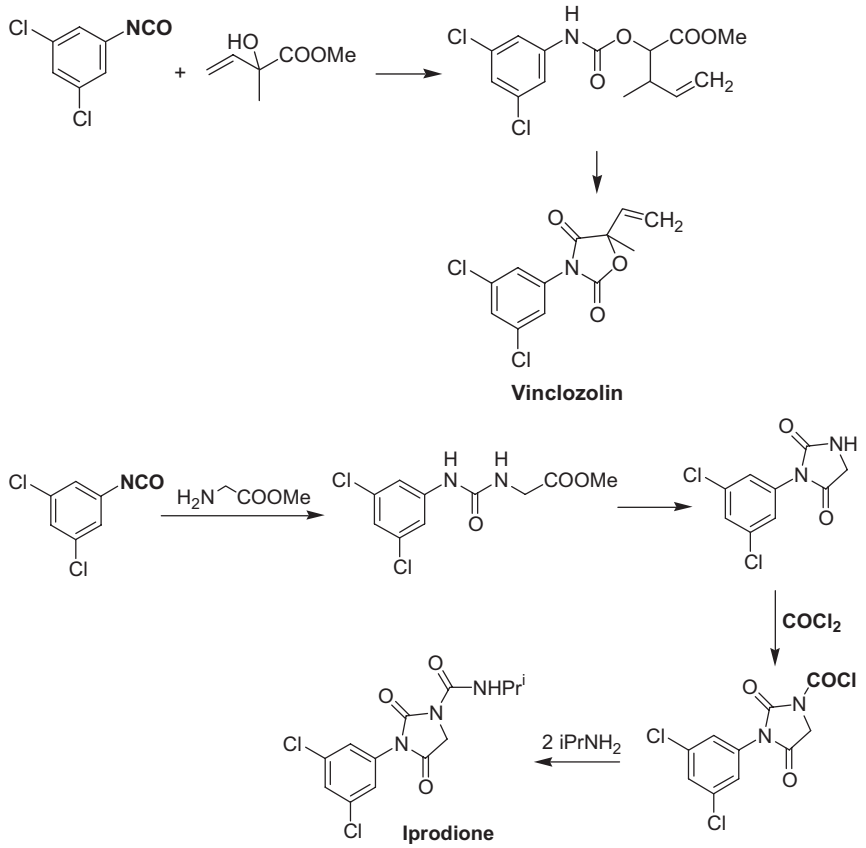


The urea fungicide *Benomyl* is prepared with ***n*-butyl isocyanate** starting from the amidine-carboxamide *Carbendazim*.

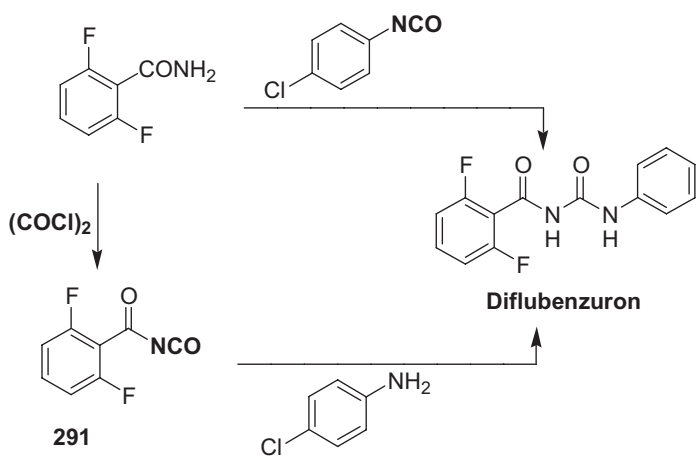


The fungicide *Vinclozolin*, a cyclic carbamate, is prepared with **3,5-dichlorophenyl isocyanate**.

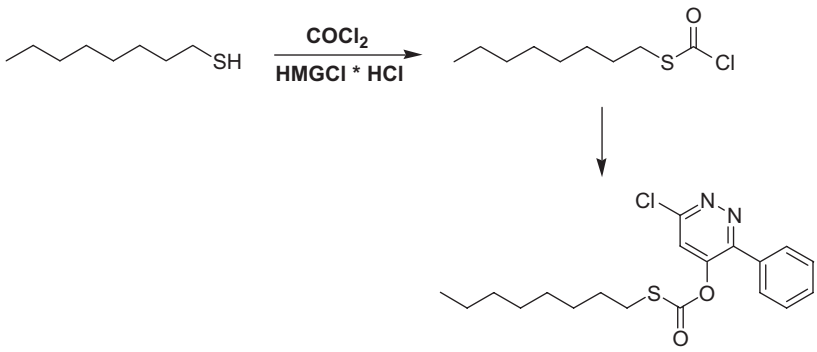
3,5-Dichlorophenyl isocyanate is also the starting material for the synthesis of the fungicide *Iprodione*.



Two synthetic routes have been reported for the preparation of the herbicide *Diflubenzuron*. Addition of 2,6-difluorobenzamide to **4-chlorophenyl isocyanate** is an equivalent route to the synthesis of acyl isocyanate **291** and subsequent addition of 4-chloroaniline.

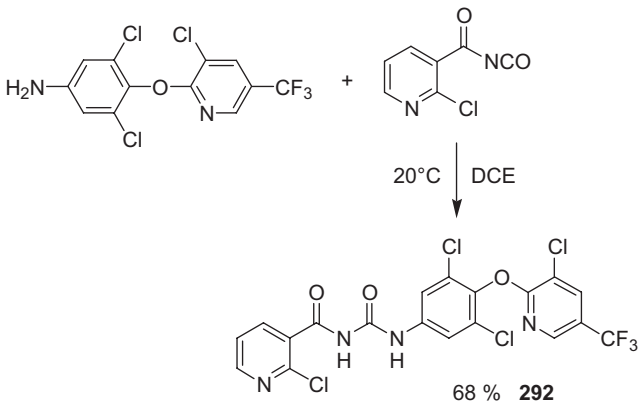


An intense research effort was dedicated to finding new synthetic routes and catalysts or improved processes for obtaining carbamates and ureas, avoiding the hazardous **phosgenation** conditions. For example, SNPE reported the use of hexamethylguanidinium chloride hydrochloride (**HMGCl·HCl**) as a catalyst, which is soluble during the reaction, but insoluble after its completion and thus can be removed by simple filtration, for the synthesis of high quality ***n*-octyl thiochloroformate**. This thiochloroformate is a useful intermediate in the manufacture of the herbicide *Pyridate* (*Lentagran*®, Chemie-Linz AG) [211].



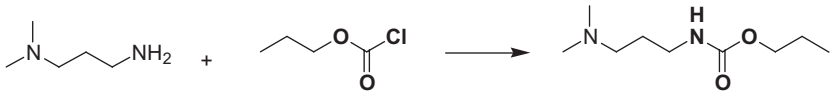
Pyridate

2-Chloronicotinyl isocyanate has been used to prepare interesting new insecticides such as **292**, which are effective against larvae, especially from lepidoptera [212, 213].



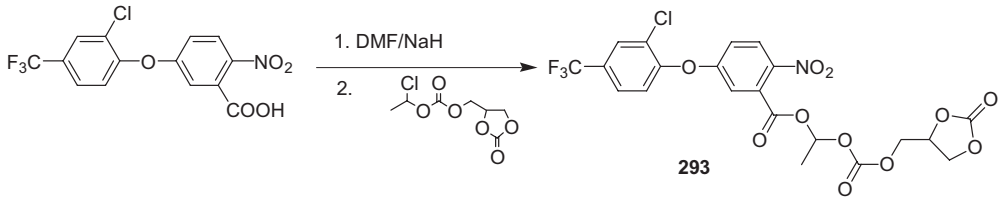
68 % **292**

Chloroformates are valuable raw materials for a series of crop protection agents. The carbamic fungicide *Propamocarb* is prepared with ***n*-propyl chloroformate**.

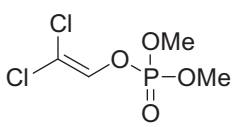


Propamocarb

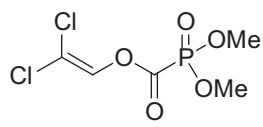
A proherbicide of *Acifluorfen* **293** [214] has been prepared with a **1-chloroalkyl carbonate**, obtained by reaction of the appropriate **1-chloroalkyl chloroformate** with glycerol carbonate.



2,2-Dichlorovinyl chloroformate (for a preparation, see Section 4.2.1 "Chloroformylation"), the key intermediate for the preparation of the phosphonato ester **294**, which is assumed to exhibit interesting insecticidal properties by analogy with the well-known insecticide *Dichlorvos*, was synthesized from chloral and **phosgene** in the presence of reusable "naked chloride ions" and subsequent dechlorination with Zn [215].

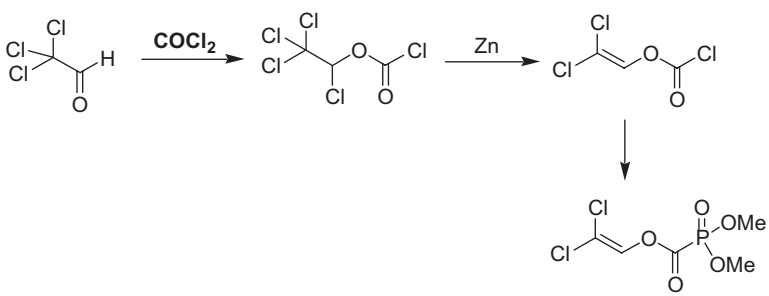


Dichlorvos



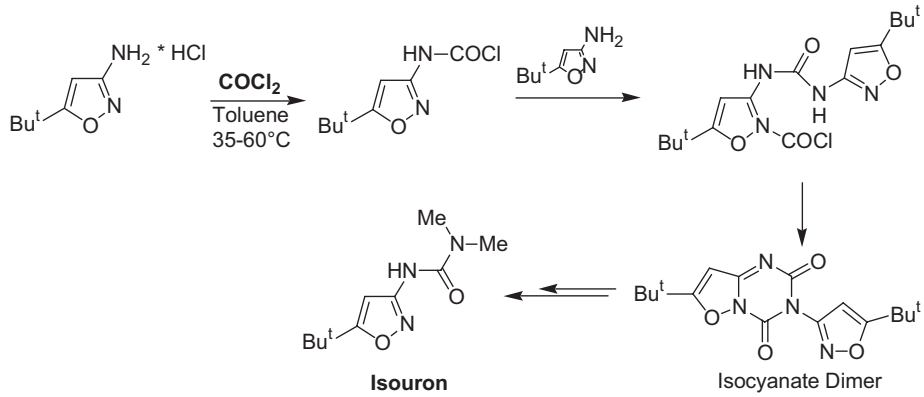
294

Phosphonato ester from
Arbuzov reaction of
2,2-dichlorovinyl chloroformate

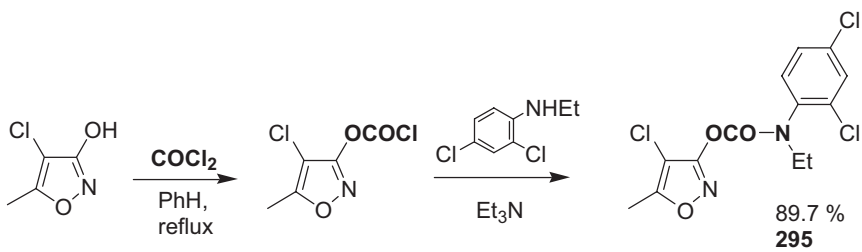


The **phosgenation** of a substituted isoxazolamine hydrochloride does not afford the expected free isocyanate but a peculiar dimer according to the following scheme.

This dimer reacts as two molecules of free **5-*tert*-butyl-isoxazolyl-3-isocyanate** with secondary amines or with alcohols to give the corresponding ureas or carbamates. These are useful as agrochemicals or as intermediates for fine chemicals, e.g. 3-(5-*tert*-butylisoxazolyl)-1,1-dimethyl urea (common name *Isouron*), which is useful as a herbicide for sugar cane and other crops [216].



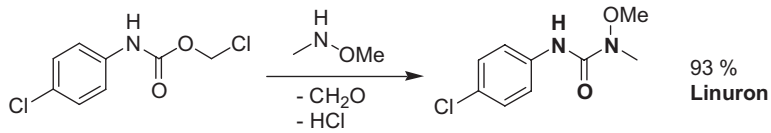
Herbicidal and plant growth-regulating *N*-carbamoylisoxazolone derivatives have been prepared from 3-hydroxyisoxazoles by treatment with **phosgene** and secondary amines or with the corresponding carbamate [217]. The carbamate **295** was prepared from 4-chloro-5-methyl-3-hydroxyisoxazole by refluxing with **phosgene** in a solvent (benzene), followed by treatment with *N*-ethyl-2,4-dichloroaniline for 4 h at room temperature in the presence of triethylamine.



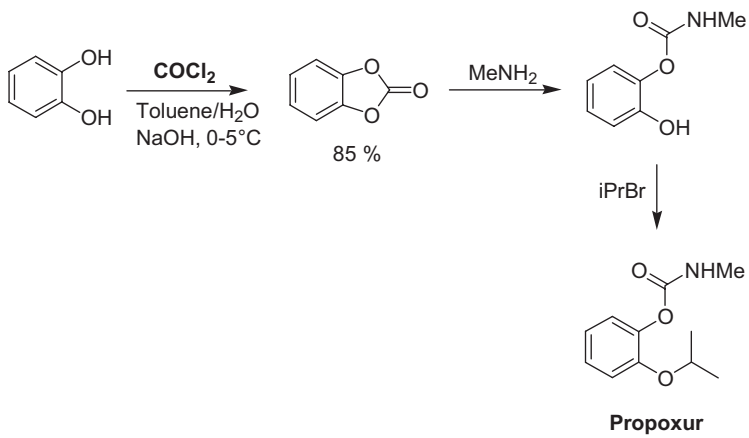
295 showed herbicidal and plant growth-retarding activities in pre- and post-emergence treatments of a wide variety of weeds. The compounds of this family were particularly effective against weeds of the *Poaceae* family; they showed high herbicidal activity towards manna grass and also retarded the growth of lawn grasses.

The same authors studied the synthesis of 2-alkoxy-5-*n*-propyl- or 2-alkoxy-5-*sec*-butylphenyl methylcarbamates as active intermediates for insecticides [218]. This involved phosgenation of the substituted phenol, followed by aminolysis of the formed **chloroformate** with monomethylamine. As already discussed, methylcarbamates can also be synthesized by reacting the appropriate phenol with **methyl isocyanate**. Thus, 2-isopropoxy-5-*sec*-butylphenyl chloroformate was synthesized by treating 2-isopropoxy-5-*sec*-butylphenol with **phosgene**. The product was reacted with monomethylamine to obtain the desired 2-isopropoxy-5-*sec*-butylphenyl methylcarbamate. Similarly, 2-*sec*-butoxy-5-*sec*-butylphenyl methylcarbamate, 2-isopropoxy-5-*n*-propylphenyl methylcarbamate, and 2-*sec*-butoxy-5-*n*-propylphenyl methylcarbamate were also synthesized.

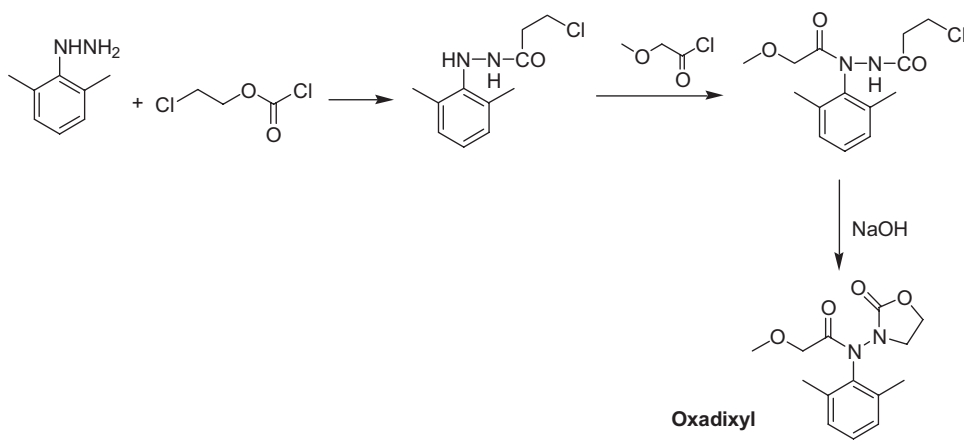
1-Chloroalkyl carbamates, prepared with **phosgene** (see Section 4.3.2 "Carbamates"), react with hard nucleophiles such as methoxymethyl amine to afford known ureas such as the herbicide *Linuron* [219].



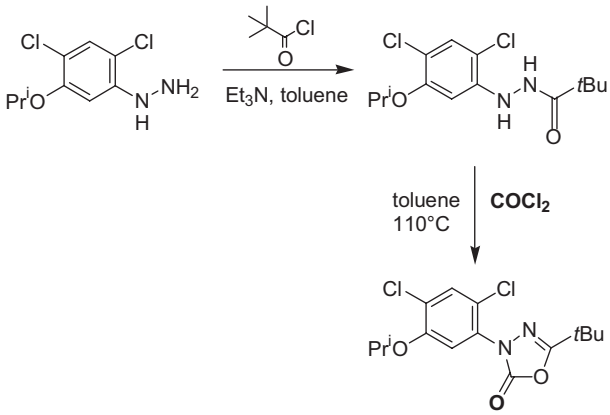
Phosgenation of catechol affords ***o*-phenylene carbonate**, which is the key starting material for the preparation of the insecticide *Propoxur* [220].



An industrial process for the preparation of the systemic fungicide *Oxadixyl* has been disclosed by Sandoz [221].

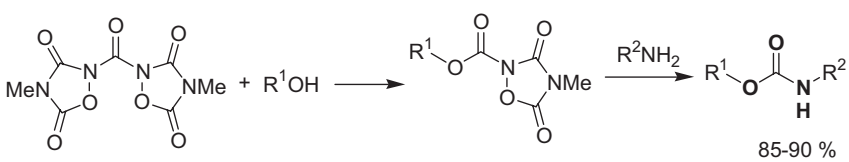


Pivaloyl chloride is a key starting material for the preparation of many pesticides, such as the selective herbicide *Oxadiazon*, prepared according to a process disclosed by Rhône-Poulenc [222]. **Phosgene** reacts with the intermediate hydrazide to afford the 1,3,4-oxadiazolinone.

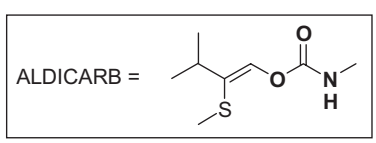


Oxadiazon

2,2′-Carbonyl-bis(3,5-dioxo-4-methyl-1,2,4-dioxazolidine) (acronym: **COMODD**), a symmetrical non-hygroscopic equivalent of **1,1′-carbonyldiimidazole** (**CDI**) [223], has been employed for the synthesis of the insecticide *Aldicarb* in 85% yield, avoiding use of the noxious isocyanate [224] and following a proven general reaction route for this phosgene equivalent.



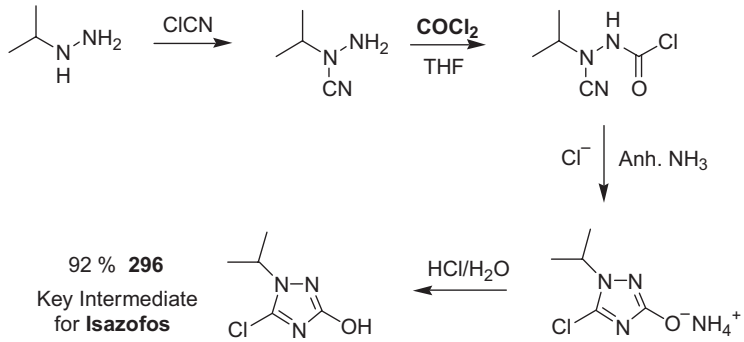
COMODD



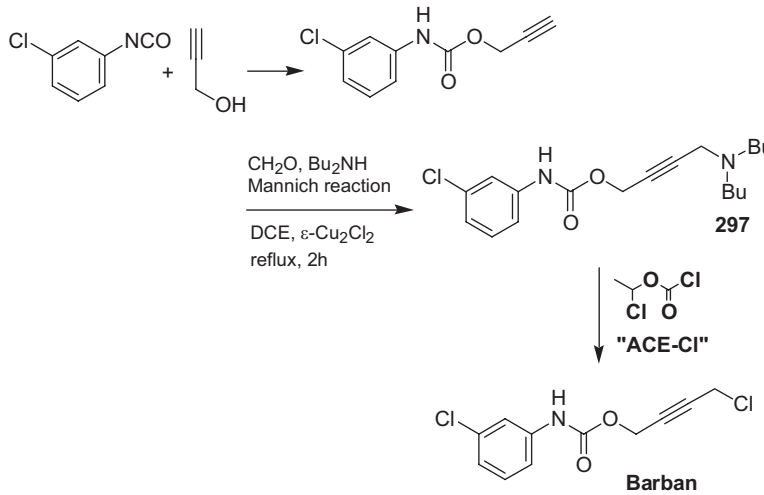
The reaction of **phosgene** with cyanohydrazines to yield 3-hydroxy-5-chloro-1,2,4-triazoles has been applied in the synthesis of the key intermediate **296** in the production of the soil-applied nematocide *Isazofos* [225].

An alternative synthetic route to the above intermediate **296**, avoiding the extremely noxious *cyanogen chloride*, has also been disclosed [226].

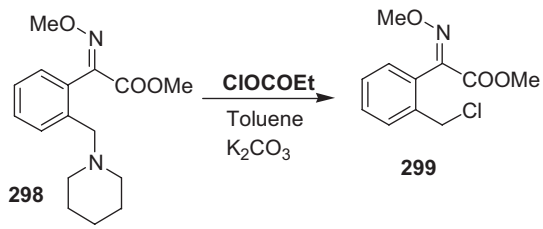
α-**Chloroethyl chloroformate** ("**ACE-Cl**", see Section 4.7.2) has been successfully used for the selective *N*-dealkylation of tertiary alkylamine intermediate **297** in a



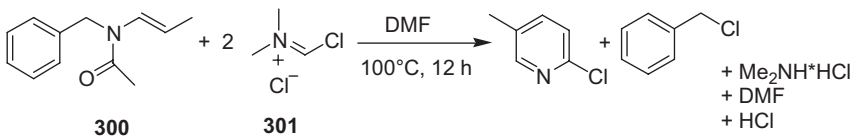
novel and safe synthesis of the herbicide *Barban*, used for the control of wild oats [227].



N-Dealkylation (*N*-debenzylation) of tertiary amines with **phosgene** or **phosgene equivalents** has also been employed by a recently disclosed process for the preparation of *o*-(chloromethyl)phenylacetic acid derivatives, which are important intermediates for the preparation of microbicides. *o*-Chloromethylphenylacetic acid derivatives **299** were prepared by reacting the benzylamine **298** with an **alkyl chloroformate** or **phosgene** in the absence of water [228].

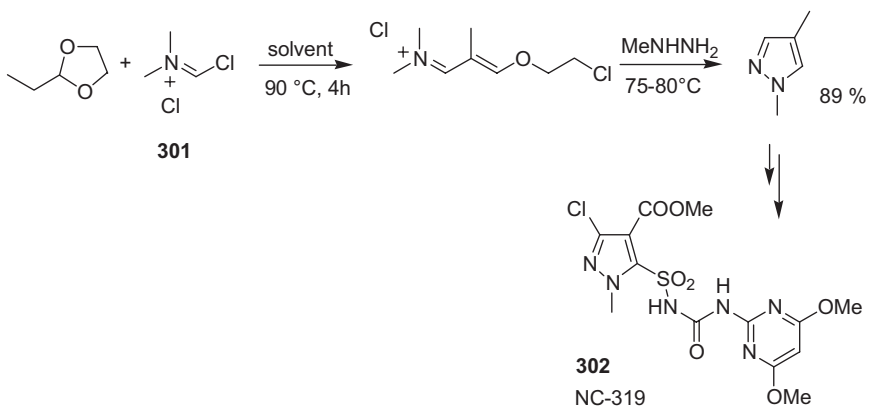


5-Substituted 2-chloropyridines, useful intermediates for the synthesis of valuable insecticides, have been prepared by **Vilsmeier formylation** of substituted enamides **300** and subsequent *N*-debenzylation [229, 230].



300 **301**

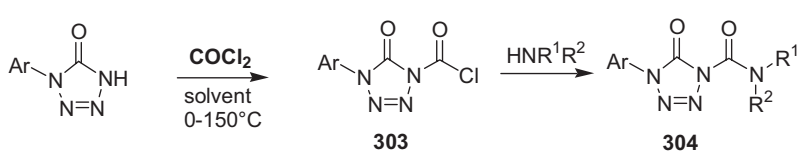
The modified reaction of **Vilsmeier salt 301** with acetals has been employed for a new synthesis of 1,4-dimethylpyrazole [231]. Chlorination of 1,4-dimethylpyrazole with chlorine in 1,2-dichloroethane affords 3,5-dichloro-1,4-dimethylpyrazole in high yield [232], the key starting material for the synthesis of *pyrazolesulfonyl urea* **302**, useful as broad spectrum, pre- and early post-emergence herbicides such as **NC-319** [233].



301

302
NC-319

Herbicidally active 1-aryl-4-carbamoyl-tetrazolinones **304** were recently obtained by reacting 1-aryl-tetrazolinones with **phosgene** in the presence of a solvent at 0–150 °C, and then reacting the resulting (novel) 1-aryl-4-chlorocarbonyl-tetrazolinones **303** with amines in the presence of a solvent, and, where appropriate, in the presence of a further basic compound, at −20 to +100 °C [234].

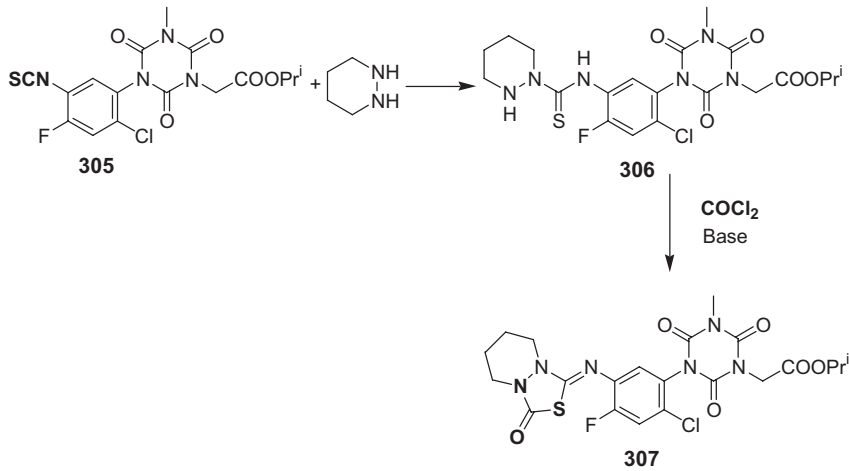


303 **304**

R^1, R^2 = alkyl, alkenyl, alkynyl, alcoxy
Ar = phenyl,naphtyl

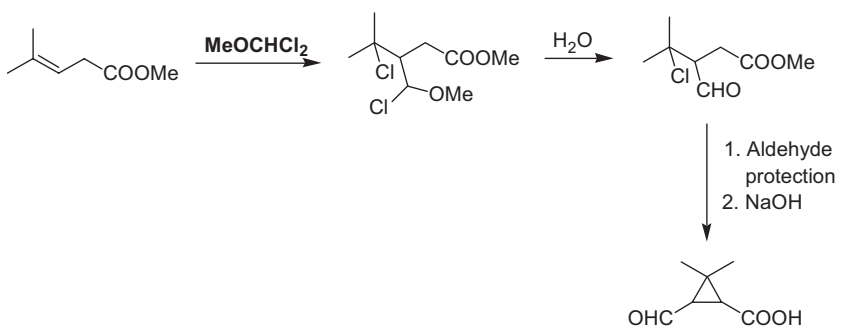
Thriotrone herbicidal agents **307** having substituted cyanuric structures [e.g. 1-(3-

heterocyclylphenyl)-*s*-triazine-2,4,6-oxo] and showing 100% efficacy against, e.g., common lambsquarters in a pre-emergence test, were prepared by reacting an isothiocyanate **305** with a hydrazine followed by reaction of the resulting intermediate **306** with **phosgene** or a phosgene equivalent in the presence of a base [235].

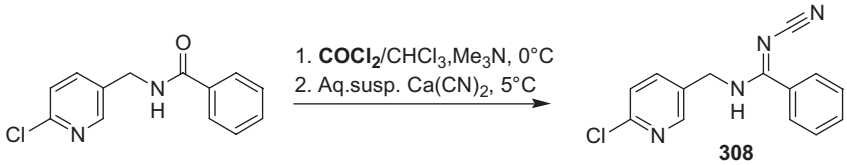


A similar cyclocarbonylation reaction of a thiourea to a thiazetidinone was described in Section 4.3.2 ''Carbamates''.

The addition reaction of the phosgene equivalent **1,1-dichloromethyl methyl ether** (**Chloromyl**®) to alkenes to afford *β*-chlorinated aldehydes has been used for the preparation of pyrethroid intermediates [236, 237].

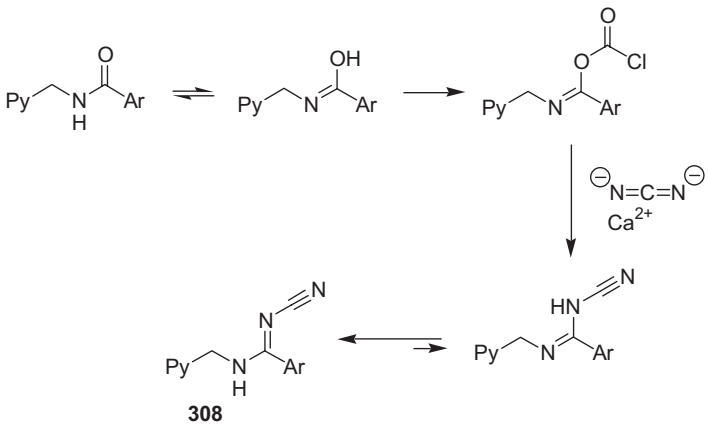


N-Cyanoamidines, such as N^1-(6-chloro-3-pyridyl)methyl-N^2-cyanobenzamidine **308**, which are precursors of insecticides, can be prepared by treatment of 3-(benzamidomethyl)-6-chloropyridine with electrophilic agents (e.g. **phosgene** in a solvent) in the presence of tertiary amines (Me_3N) at 0 °C, followed by treatment with an aq. suspension of $Ca(CN)_2$ at 5 °C for 1 h. The yield in the case of **308** was 44% [238].



308
44 %

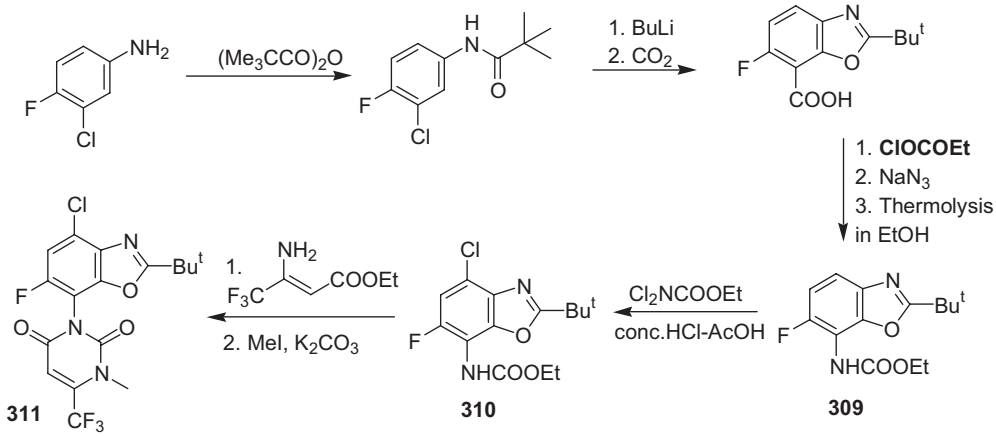
Activation of the amidol to promote nucleophilic attack by the cyanamide ion is the most likely mechanism of the reaction.

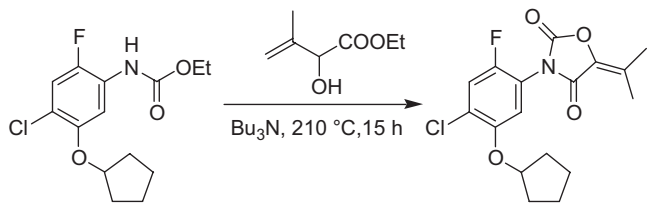


Herbicidal 3-(substituted benzoxazol-7-yl)- and 3-(substituted benzothiazol-7-yl)-1-substituted-6-trifluoromethyl-2,4-(1*H*,3*H*)pyrimidinediones and the methods of using them to control undesired plant growth have been disclosed, as have the novel intermediates used in their preparation [239].

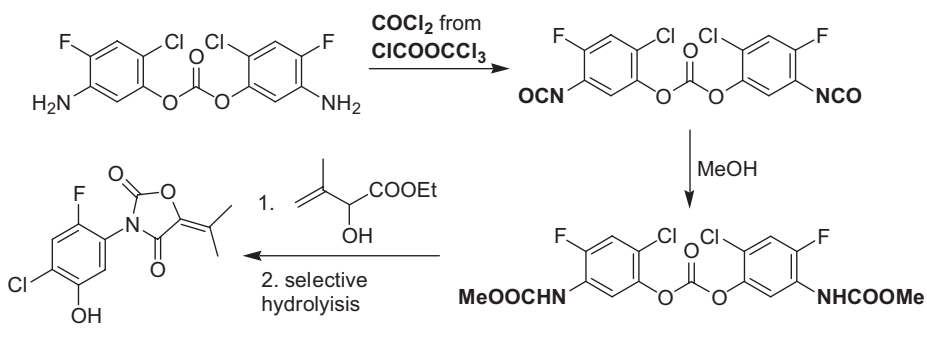
For example, 3-chloro-4-fluoroaniline was reacted with trimethylacetic anhydride to give the corresponding amide, which was lithiated with BuLi and treated with carbon dioxide to give 2-(*tert*-butyl)-6-fluorobenzoxazole-7-carboxylic acid. The acid was treated with **ethyl chloroformate** and then sodium azide to give the acyl azide, which was thermolyzed in refluxing EtOH to give the benzoxazole carbamate derivative **309**. This was chlorinated with *N*,*N*-dichlorourethane in concentrated HCl/AcOH to give **310**, which underwent cyclocondensation with ethyl trifluoroamino crotonate and then *N*-methylation with methyl iodide and K_2CO_3 to give the desired 3-(substituted benzoxazol-7-yl)-2,4-(1*H*,3*H*)pyrimidinedione **311**.

A large-scale cyclization reaction of carbamates with functionalized butenoates, starting from carbamates prepared without phosgene, for the efficient preparation of 3-(substituted phenyl)-5-isopropylidene-1,3-oxazolidine-2,4-dione derivatives (azalactones) having potent herbicidal activity, has been described in a patent application [240]. By reacting an *N*-(substituted phenyl)carbamate **312** with a 2-hydroxy-3-alkenoic acid ester (for example, ethyl 2-hydroxy-3-methyl-3-butenoate) or a 3-alkoxy-2-hydroxyalkanoic acid ester, at 210 °C for 15 h, azalactone **313** was formed in 71.5% yield.

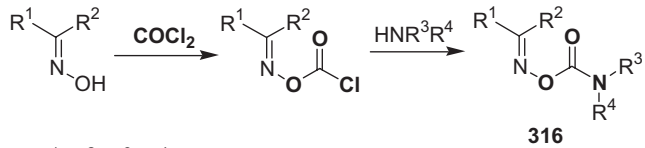




The same authors described a process for the preparation of substituted fluorophenol-1,3-oxazolidine-2,4-dione derivatives, which are important intermediates for producing herbicidal compounds [241]. Their synthesis starts from a **diisocyanato** bis(fluorophenyl)carbonate, prepared by reacting the corresponding diamine with **phosgene** or a phosgene equivalent (**phosgene** gas by decomposition of **diphosgene**) at 100 °C. The **diisocyanate** is then reacted with methanol in the presence of a base to give the dicarbamate carbonate **314** in 85% yield. (Fluorophenyl)oxazolidinedione derivative **315** was prepared by cyclization and selective hydrolysis of **314**.



Phenyl ketoxime carbamates, which are useful as selective herbicides, were prepared by treating a phenyl ketoxime with either a base and a **carbamoyl halide** or **phosgene** and a substituted amine. Field tests demonstrating the efficacy of emulsions of **316** as pre- and post-emergence herbicides in the presence of *Loium perenne* (*English ryegrass*), *Avena sativa* (oats), *Beta vulgaris* (beet), and *Sinapis alba* (mustard) have been reported [242].

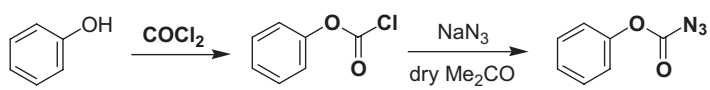


316

R^1, R^2, R^3, R^4 = Ph, Me, allyl, allyl
2-$MeOC_6H_4$, Me, Me, Me
2-$O_2NC_6H_4$, Me, Me, Me
Ph, Me, *i*Pr, *i*Pr

Organic **azidoformates**, $R(O_2CN_3)_n$, exhibit high biological activity and are useful as fungicides and bacteriocides [243]. Such compounds are prepared by the reaction of a cyclic **organic haloformate** with an azide (see Chapter 4). The haloformate is prepared by passing **phosgene** through a solution of a hydroxy-substituted cyclic hydrocarbon and heating the solution to reflux.

NaN_3 was added to a solution of **317** in dry acetone. The resulting mixture was stirred under reflux for 2 h to yield **318**.



317 **318**

The compounds (p-$N_3CO_2C_6H_4)_2CMe_2$ (75.4%), [3,5,4-$Cl_2(N_3CO_2)C_6H_2]_2CMe_2$, and 1-naphthyl azidoformate (100%) were prepared in a similar manner.

5.4
Topics in Polymer Synthesis

The main uses of phosgene are in the production of *isocyanates* and *polycarbonates*. Whilst not involving any new chemistry (as far as phosgene is concerned), the scope for preparation of new polymeric materials is enormous, if not infinite.

5.4.1
Polyurethanes

The production of isocyanates represents the major output. Reaction of diisocyanates with polyhydroxylic compounds is the basis of polyurethane manufacture

and has been extensively reviewed in the literature [244–247]. Some recent data on new urethane polymeric materials are presented below.

Substituted 4,4′-methylenebis(3-chloro-2-alkylphenyl isocyanate)s, prepared with **phosgene**, form isocyanate prepolymers useful for producing polyurea–polyurethanes with high chemical resistance and good thermal stability, and for conversion to polyether–polyurea–polyurethane elastomers [248].

Methylenediphenyldicarbamate-based aromatic polycarbamate mixtures, useful for preparing polyurethanes, are prepared by nitration of diphenylmethane and reaction of the resulting dinitrodiphenylmethane-based mixtures with hydroxyl-containing organic compounds and **carbon monoxide** in presence of a catalyst [249].

Aromatic urethanes, useful as starting materials for polymethylene polyphenyl polyisocyanates, are prepared by treating aromatic nitro compounds with hydroxyl-containing organic compounds and **CO** in the presence of platinum group catalysts and promoters comprising Lewis acids and <0.5 mol (per 1 g-ion of anion of the Lewis acids) of N-containing heteroaromatic bidentate ligands [250]. Urethanes, useful for the preparation of polyurethanes, are prepared by the reaction of alcohols and **CO** with organic nitro compounds in the presence of a Cu catalyst. For example, pressurizing a mixture of nitrobenzene, $CuCl_2 \cdot 2H_2O$, EtOH, and pyridine (promoter) with **CO** to 1000 psig at room temperature and stirring at 180 °C for 4 h gave a 76% conversion of nitrobenzene to ethyl phenylcarbamate (90% selectivity) [251]. A method for manufacturing aromatic urethanes involving a process for producing *N*,*N*-disubstituted ureas using **carbon monoxide** in the presence of a catalyst and a solvent is described in a European patent [252].

Polyurethane leather substitute and nylon-6 melt-coated vinyl fabrics were treated with **elastomeric polycarbonates**, such as polytetramethylene glycol–bisphenol A–**phosgene** polymer, poly(ethylene adipate)–4,4′-dihydroxydiphenylmethane–**phosgene** polymer, or ethylene bis(*p*-hydroxybenzoate)–polytetramethylene glycol–**phosgene** polymer to give products with improved abrasion resistance and flexural strength [253].

Nematic polyurethanes derived from 4,4′-dihydroxybiphenyl and 4,4′-bipiperidine, ethylene-4,4′-bipiperidine, or trimethylene-4,4′-bipiperidine have been reported [254]. 4,4′-Bipiperidine, 1,2-bis(4-piperidinyl)ethane, and 1,3-bis(4-piperidinyl)propane were condensed with the **dichloroformates** of *p*-phenylene, 2-methyl-1,4-phenylene, or 2,5-biphenylylene. Furthermore, two copolyurethanes were prepared either by mixing 4,4′-bipiperidine and 1,2-bis(4-piperidinyl)ethane or by mixing the **dichloroformates** of *p*-phenylene and 2,5-biphenylene. The polyurethanes derived from hydroquinone or methylhydroquinone were semicrystalline polymers with a short-term thermostability up to 310 °C. The **polyurethanes** derived from phenylhydroquinone were amorphous with a thermostability up to 360 °C. The homo- and co-polyurethanes containing 4,4′-biphenylylene units formed a smectic layer structure in the solid state and a nematic melt above the melting point [254].

A new method for the synthesis of linear, film- and fibre-forming polyurethanes free of allophanate branches and cross-links, by reacting activated diol bis(carbonate)s with diamines, has also been reported [255].

Thermoplastic, light-stable polyurethanes derived from caprolactone polyesters and diamines have been prepared by interfacial polycondensation of diamines with polyester diol bis(chloroformate)s. The effects of varying the molecular weight of the polyester diol and varying the diol initiator, as well as of methyl substituents on the caprolactone rings used to prepare the polyester, and of the diamine structure, have been determined. The polyester diol bis(chloroformate)s were prepared by ring-opening of ε-caprolactone or methyl ε-caprolactone in the presence of 1,4-butanediol, 1,3-butanediol, 2-butene-1,4-diol, trimethylolpropane monoallyl ether, or neopentyl glycol, followed by **phosgenation** [256].

A *phosgene-free process* for preparing urethane and carbonate monomers and polymers has been reported [257]. The process involves reaction of **CO_2** with amines (e.g. 4,4′-methylenebis(cyclohexylamine)), alcohols, or amino alcohols in the presence of an amidine- or guanidine-type base (e.g. *N*-cyclohexyl-*N*′,*N*′,*N*″,*N*″-tetraethylguanidine), followed by treatment of the resulting ammonium carbamate or carbonate salt with a primary or secondary hydrocarbyl halide of a specified structure in a polar, aprotic solvent (e.g. *N*-methylpyrrolidinone). When hydrocarbyl dihalides or -polyhalides are used in the second step, polyurethanes and polycarbonates are formed.

5.4.2
Polyketones, Polyureas

Besides the aforementioned urethane polymers, **phosgene** may also be used to prepare polymers via the C=O linkage, such as polyketones, polyureas, etc. For example, the preparation of aromatic polyether–polyketones by a two-stage Friedel–Crafts polycondensation has been reported. A monomer system comprising an aromatic **dicarboxylic acid chloride** (or **phosgene**)/polynuclear arene mixture or a polynuclear aromatic **carboxylic acid chloride** containing a hydrogen atom amenable to electrophilic substitution is mixed with a Lewis acid, a Lewis base (optional), and an inert solvent. The mixture is partially polymerized in a first reaction zone, and then passed through a second reaction zone along with an inert solvent or an inert gas-saturated inert solvent to complete the polymerization without fouling of the polymerization reactor. This method has been used for the polymerization of terephthaloyl chloride with 4,4′-diphenoxybenzophenone [258]. A poly(arylene ether ketone) is prepared by polymerizing a polynuclear aromatic monomer bearing both an **acid halide** function and an active hydrogen atom, or by co-polymerizing **phosgene** or an aromatic **diacid dihalide** with a polynuclear aromatic monomer having two active hydrogen atoms, in the presence of a Lewis acid and, optionally, a controlling agent (especially a Lewis base) and/or a non-protic diluent. A thermally stable, linear polymer is obtained, which has a high molecular weight and is largely free of pendant groups resulting from *ortho*-substitution of *para*-linked aromatic rings in the polymer backbone [259].

A process for the preparation of aryl polyether–polyketones by electrophilic polymerization has been disclosed [260]. The polymers, having excellent high-temperature resistance, are prepared by the reaction of carboxylic acid halides in

the presence of Lewis acids and, optionally, Lewis bases in inert solvents. This process obviates the use of the phosgene monomer. Thus, a mixture of $AlCl_3$, dimethylsulfone, benzoyl chloride, **oxalyl chloride**, and 4,4′-diphenoxybenzophenone in dichloromethane was subjected to the polymerization conditions, producing a polymer having a good inherent viscosity.

5.4.3 Polycarbonates

Phosgene is an important raw material for *polycarbonate resins*, a class of polymers for which world capacity has reached 1.5 million MT, corresponding to a yearly phosgene consumption of over 0.6 MT. The production of polycarbonates, predominately the aromatic carbonates derived from bisphenol A, represents the second largest area of phosgene usage and is probably the fastest growing area. The polycarbonate market is one of the most buoyant sectors in the polymer industry, at least in volume terms, and over the past decade demand has expanded rapidly at more than 10% per annum [261]. Growth is likely to continue to be strong, as new markets and applications (ranging from baby bottles to the digital versatile disc, DVD) are found for this high-clarity engineering polymer [262].

Research activity in the field of new polymeric materials based on advanced polycarbonates for *optical recording media* is very intense, as reflected in the recent patent literature. For example, aromatic polycarbonates based on the 4,4′-dihydroxyphenyl-2,2-propane–**phosgene** copolymer have been prepared as fire-resistant thermoplastic resin compositions with good heat and impact resistance and good moldability [263]. Polycarbonates, as substrates for *optical recording media*, have been prepared by reacting **phosgene** with a diphenol (e.g. bisphenol A) and a *p*-C6-30 group substituted phenol blocking agent (e.g. *p-tert*-octylphenol) [264]. *Digital video disk* substrates containing polycarbonate–polyorganosiloxane materials have also been reported [265]. Polycarbonate-type fire-proofing agents for thermoplastic resins with low nitrogen content, useful for polycarbonates, poly(butylene terephthalate), PET, polyarylates, etc., consist of halo-substituted polycarbonates and, optionally, siloxane copolymers (e.g. 2,2-bis(4-hydroxy-3,5-dibromophenyl)propane–**phosgene** copolymer) [266]. 1,1-Bis(4-hydroxyphenyl)-3,3,5-trimethylcyclohexane was reacted with **phosgene**, and then with C_{20} alkyl-substituted phenol, to give an aromatic polycarbonate terminated by an alkylphenol polymer, useful for the manufacture of *optical disks* [267]. Transparent polycarbonate–styrene polymer blends are used for *optical devices*. Injection moldings of a 60:40 blend of bisphenol A–1-phenyl-1,1-bis(4-hydroxyphenyl)ethane–**phosgene** copolymer and Styrol HF 10 were found to have a light transmittance of 89% and a low birefringence [268]. *High-birefringence polycarbonates* are prepared from dihydric phenols and **phosgene**. Thus, the addition of mercaptoacetic acid (10 g) to a solution of *o*-phenylphenol in acetone at 60 °C, followed by passage of a stream of gaseous hydrogen chloride through the mixture for 36 h gave 2,2-bis(3-phenyl-4-hydroxyphenyl)propane. **Phosgenation** in the presence of a molecular weight regulator (e.g. *p-t*-butylphenol) gave a polycarbonate of high birefringence [269].

High molecular weight, light-stabilizing compounds for imparting improved resistance to ultraviolet radiation to **polycarbonate**-based polymers are prepared by interfacial condensation of **phosgene** or its derivatives or **carbonate esters** with bisphenol derivatives [270].

Thermoplastic molding compositions, containing aminomethyl-substituted poly(phenylene ethers), epoxy group containing ethylene copolymers, and *aromatic polycarbonates*, have been produced [271].

2,2-Bis(4′-hydroxyphenyl)propane, **diphenyl carbonate**, and polyethylene glycol monooctadecyl ether were treated in the presence of 4-*N*,*N*-dimethylaminopyridine at 180–270 °C for 3 h to give an aromatic polycarbonate terminated with polyethylene glycol monoalkyl ether groups with an average molecular weight of 51,200 [272].

Transparent aromatic polycarbonate compositions useful for automobile, electrical, and electronic parts, and as building materials, have been prepared by blowing **phosgene** into a mixture containing bisphenol A at −20 °C over 60 min, and emulsifying with 1:20 (mol) *m*-hydroxybenzyl alcohol-ε-caprolactone reaction product [273].

Electrophotographic photoreceptors based on *polycarbonate resins* have been prepared by treating aromatic dioxy compounds with **phosgene** [274]. Electrophotographic photoconductors containing fluorine-bearing polycarbonate binders have also been prepared from bisphenol A, **phosgene**, and 1,1,1,3,3,3-hexafluoro-2,2-bis(4-hydroxyphenyl)propane [275].

Polycarbonates are prepared from a mixture of bisphenols and **phosgene**, and are used as *heat-resistant cores for optical fibres* [276].

Polymers from hydroxy-substituted fatty acids or esters, derived from fats and oils and bifunctional compounds, have been reported [277]. The fat- and glyceridic oil-derived monomers used represent an inexpensive and readily obtainable monomer source for the preparation of condensation polymers from hydroxy- or amino-substituted fatty acids (e.g. 12-hydroxystearic acid) with difunctional compounds (e.g. diamines, polyamines, amino alcohols, diols, polyols, **diacid chlorides**, **diisocyanates**, **phosgene**, etc.).

High-fluidity polycarbonates with molecular weights of 10,000–30,000 have been prepared from dihydroxy aromatic compounds, carbonate precursors (e.g. **phosgene**; **aryl**, **alkyl**, or **benzylic esters** of **carbonic acid**, or **chloroformyl**-capped polycarbonate oligomers), and phenol-amidic compounds. Thus, for example, *N*-pivaloyl-*p*-hydroxyaniline, bisphenol A, and **phosgene** were polymerized to give such a *high-fluidity polycarbonate* [278]. Aromatic polyester–polycarbonates with improved flow properties are manufactured from diphenols, terephthalic acid and/or isophthalic acid, and **phosgene** by standard interfacial polycondensation and using a phenol with a branched alkyl substituent as a chain-terminating agent [279].

The manufacture of *copolycarbonate resins with good fluidity* and mold-releasing properties, based on bivalent biphenols and prepared with **phosgene**, have also been reported [280].

Polycarbonates exhibiting improved heat resistance are prepared with **phosgene** from diphenol containing disubstituted phenylene radicals by polymerizing a poly-

carbonate precursor. A polymer prepared in this way had an intrinsic viscosity (in $CHCl_3$ at 25 °C) of 0.87 dL/g, a 45:55 head-to-head:head-to-tail microstructure, and a glass temperature of 173–174 °C [281].

Blends of polypropylene short fibres and a pulp of poly(4,4′-dioxydiphenyl-2,2-propane carbonate) or 2,2-bis(4-hydroxy-3,5-dibromophenyl)propane-bis(4-hydroxyphenyl)propane–**phosgene** copolymer have been used to prepare paper substitutes useful as insulators for high-voltage cables [282].

Modified polycarbonates, proposed as protective coatings for glass, and the effect of modifying additives on the properties of polycarbonates, have been discussed [283]. In preparing polycarbonates from 1,1-bis(4-hydroxyphenyl)cyclohexane and **phosgene**, partial substitution of **phosgene** by $(ClCOCH_2SiMe_2)_2O$ or $(ClCO{\cdot}CH_2CH_2OCH_2SiMe_2)_2O$ led to copolymers having improved water- and alkali-resistance and good adhesion to glass.

Azidoformates have also been applied to polymeric substrates. Polymeric and non-polymeric compounds, $p\text{-}RC_6H_4NEt(CH_2)_2OCON_3$, useful as azo dyes or oil-, laundry-, and waterproofing agents for polyamide and polyester fibres, have been manufactured by treatment of a variety of **chloroformates** (prepared in situ with **phosgene**) with sodium azide [284].

Polycarbonates bearing imido terminal groups have been prepared by treating a mixture of dihydroxy-terminated compounds with **phosgene** and a chain-terminating agent containing a substituted imido group. Thus, **phosgene** was added to a mixture of *p*-maleimidobenzoic acid, pyridine, and dichloromethane, 2,2-bis(4-hydroxyphenyl)propane was then added, and the mixture was stirred. Additional **phosgene** was added, followed by 6 N hydrochloric acid, to give the *imido-terminated polycarbonate* [285].

The effect of tertiary amines and quaternary ammonium salts on the interfacial polycondensation of 2,2-di-(4-hydroxyphenyl)propane and **phosgene** has been studied [286]. The rate of polymerization of $(4\text{-}HOC_6H_4)_2CMe_2$ with **phosgene** in alkali solution is accelerated by the addition of Et_3N, $PhNEt_2$, $PhN(CH_2Ph)_2$, $PhCH_2NEt_3Cl$, or triethyloctadecylammonium chloride. These compounds not only act as surface-active agents promoting polymerization at the interface between the aqueous alkali and organic phases, but also form solution salts, which react further with the growing polycarbonate in the aqueous phase away from the interface. Addition of these compounds increases the molecular weight of the polycarbonates.

Cyclic carbonic acid derivatives, useful as copolymerization components for the preparation of polycarbonates, are obtained by treating a polyol such as a trimethylolalkane (e.g. trimethylolpropane) with a carbonic acid derivative such as a **dialkyl carbonate** (e.g. diethyl carbonate). They can be copolymerized with other organic carbonates at 150–240 °C and 0.001–10 mbar to give insoluble, cross-linked polycarbonates, which can be depolymerized at 240–320 °C and 0.001–2 mbar [287].

The polymerization of trimethylene carbonate (1,3-dioxan-2-one) with complexation catalysts has been discussed [288]. The bulk polymerization of trimethylene carbonate was conducted at 90, 120, and 150 °C in the presence of initiators. In

contrast to similar polymerizations of ethylene carbonate, ether groups were never found. However, all polycarbonates have CH_2OH end-groups. Furthermore, methyl carbonate, acetate, 2-ethylhexanoate, and stearate end-groups were found. Cyclic oligomers were not detectable in gel-permeation chromatograms of the reaction mixtures, and IR spectra were indicative of complexation of the carbonyl group by the initiators.

Block polycarbonate–siloxanes are prepared by *interfacial polymerization* of bisphenols and siloxanes bearing terminal hydroxyaryl groups of specified structure with carbonic acid derivatives. Thus, interfacial polymerization of a hydroxyaryl-terminated siloxane [prepared by heating an AcO-terminated dimethyl siloxane (d.p. 80) with 4,4′-dihydroxybenzophenone and K_2CO_3 in chlorobenzene at 100 °C] with **phosgene** gave a block polycarbonate–siloxane [289]. *Polycarbonates* and mixed polycarbonates based on di-(4-hydroxyphenyl) oxide have been obtained by the *interfacial polycondensation* of $(4\text{-}HOC_6H_4)_2O$ with $Me_2C(C_6H_4OH\text{-}4)_2$, $(4\text{-}HOC_6H_4)_2S$, $(4\text{-}HOC_6H_4)_2SO_2$, or $(3,5\text{-}Br_2\text{-}4\text{-}HOC_6H_2)_2O$ and **phosgene** [290]. *Polycarbonates* and mixed polycarbonates based on 1,2-bis(4-hydroxyphenyl)ethane and 1,2-bis(4-hydroxy-3,5-dibromophenyl)ethane have been prepared at 20 °C with 0.2 mol-% triethylamine as catalyst by polycondensation of **phosgene** with $(p\text{-}HOC_6H_4CH_2)_2$ in dichloromethane in the presence of aq. NaOH, with 1,2-bis(3,5-dibromo-4-hydroxyphenyl)ethane in dichloroethane, or with bisphenol A in dichloromethane. These polymerizations occur at *the organic/aqueous interface* [291].

Carbonic acid esters are, depending on their molecular weight and structure, rather viscous, colorless or yellow oils, low-melting waxes, or high-melting resins. The liquid and wax-like esters can be used as lubricants or lubricant additives, while the solid esters can be dissolved in suitable organic compounds, e.g. polychlorobiphenyl or phosphoric acid esters. These esters can be prepared by the action of **phosgene** on diols in the presence of acid acceptors. For example, a bis(chloroformate) can be prepared from 1 mol of a diol and 2 mol of **phosgene** and then reacted with excess diol or substituted alcohol in the presence of an acid acceptor, e.g. K_2CO_3. Similarly, carbonic acid esters can be prepared by ester interchange of dialkyl or diaryl carbonates with diols or mixtures of excess diols with substituted alcohols. For example, **diaryl carbonates**, especially diphenyl carbonate (**DPhC**), are used in ester exchanges without a catalyst. The water-soluble carbonic acid esters are especially useful as lubricants for textile machinery, since they can easily be washed out of textiles [292]. They also have good biodegradability. The esters are useful as metalworking lubricants. They can be used in pure form or dissolved in suitable solvents. For example, a 5% aqueous solution of a polycarbonate based on tetraethylene glycol (mol. wt. 854) is useful for the drilling of holes in steel and for finishing Al. The water-insoluble carbonic acid esters are also useful as lubricants for deep drawing and for the forming of sheets and profiles. The water-soluble polycarbonate of tetraethylene glycol is an excellent aid in the chipless forming of metal workpieces. Liquid carbonic acid esters, e.g. *polypropylene glycol polycarbonate* and their mixtures with, e.g., ester oils or mineral oils, are particularly useful as hydraulic fluids because of their good lubricating properties and very low compressabilities.

High molecular weight polycarbonates are prepared without using phosgene by melt polycondensation of dihydric phenols with **carbonic acid diesters** using carboxylic acids (e.g. phenylacetic acid) and electron-donating amines (e.g. 2-methylimidazole) as catalysts [293].

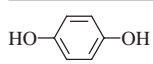
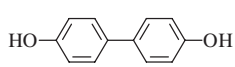
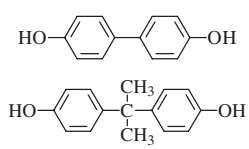
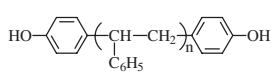
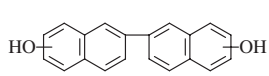
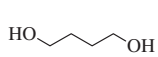
Starting from 2,2′,6,6′-tetrabromobisphenol A and/or 2,2′,6,6′-tetrachlorobisphenol A, heat- and light-resistant *aromatic poly(ester carbonate)s* have been prepared with the **acid chloride** of terephthalic or the **diphenyl ester** of 2,5-dichloroterephthalic acid and **diphenyl carbonate** (**DPhC**) or **phosgene** [294].

Poly(ester carbonate)s with low birefringences and small photoelastic coefficients have been prepared by mixing a solution of 1,1-bis(3-methyl-4-hydroxyphenyl)-cyclohexane in 2 N aq. NaOH and a solution of phthaloyl dichloride in dichloromethane, adding a solution of an **phosgene** oligomer in dichloromethane and 7% aqueous triethylamine, allowing the mixture to react for 5 min, adding additional oligomer solution and PTBP, reacting for a further 40 min, and quenching with **phenyl chloroformate** [295].

Polycarbonates and *polythiocarbonates* from **phosgene** and **thiophosgene**, respectively, have been prepared from diphenols with chlorinated aromatic side groups under phase-transfer conditions using several quaternary ammonium and phosphonium salts and dichloromethane as solvent. The effect of varying the catalyst and of the structure of the diphenol was studied [296].

Phosgene equivalents and their substitutes have found many applications in the synthesis of polycarbonates. Table 5.4 lists some examples employing **triphosgene**.

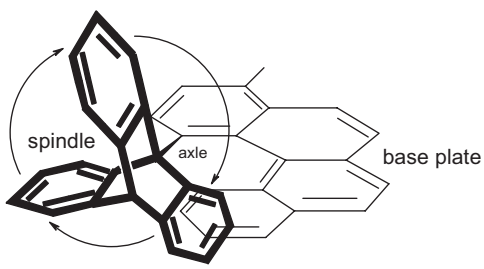
Tab. 5.4. Polycarbonates from **triphosgene** and dihydroxylic compounds [297].

Dihydroxylic Compound	*Reaction Conditions*	*Polymer*	*Refs.*
	triphosgene/CH_2Cl_2; 1 N NaOH	Thermotropic polycarbonates	298
	triphosgene/CH_2Cl_2; 1 N NaOH	Thermotropic polycarbonates	298, 299
	triphosgene/1 N NaOH/CH_2Cl_2	Polycarbonate/styrene/acrylonitrile copolymer	300, 301
	triphosgene/CH_2Cl_2/Py	Functionalized polystyrene	302
Brominated diphenol-polystyrene	triphosgene/CH_2Cl_2/Py	Block copolymer	303
	triphosgene/water/KOH, reflux	Thermolabile polymer	304
	triphosgene/Py/toluene	Wax-type polymer	305

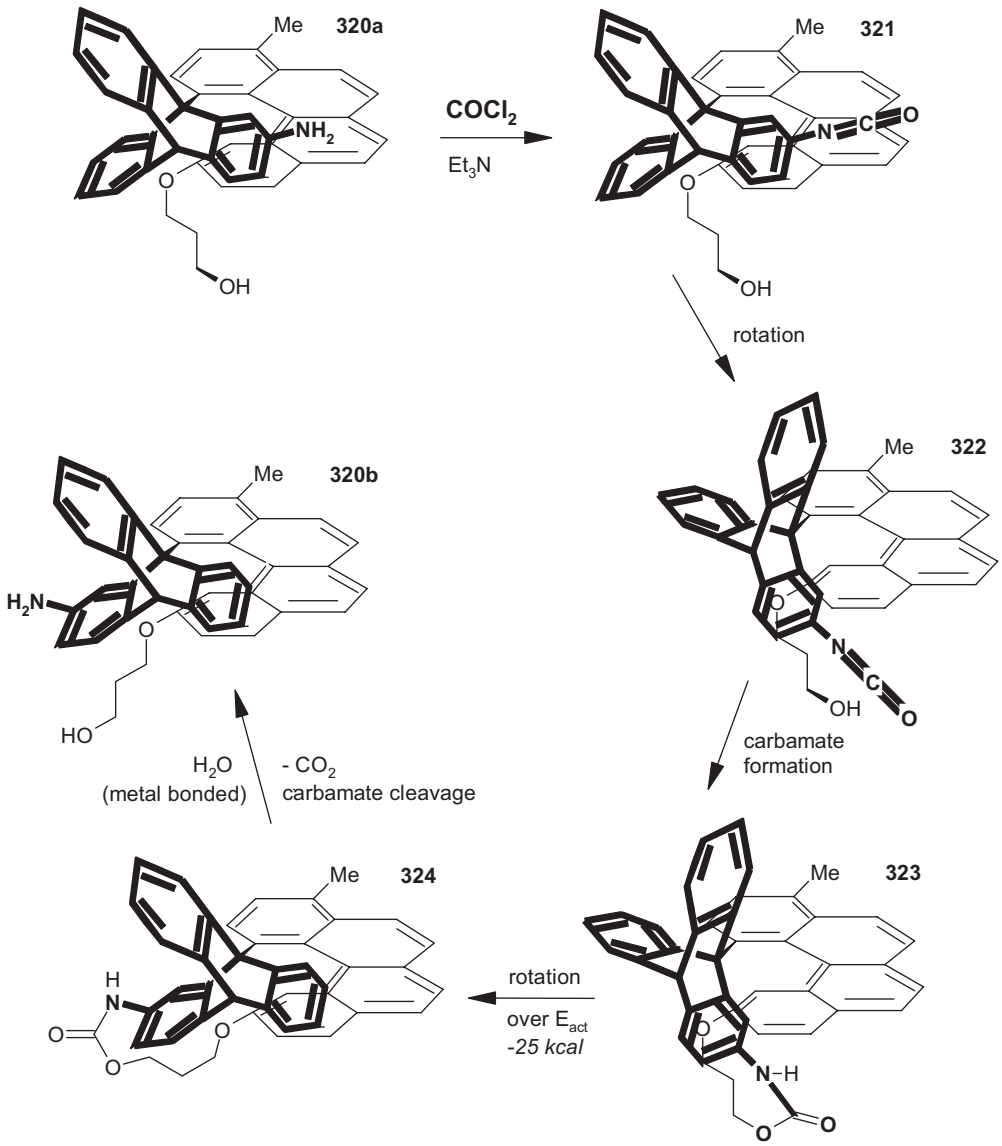
5.5
The Molecular Motor

It is not common to use a gaseous poison like **phosgene** to fuel a motor, but it is a reality. Devised by Kelly at Boston in 1999, it led to the world's first *molecular motor*, **319**, sometimes called the *Boston motor* [306–309]. It consists of just *78 atoms* (**320**) and has a spindle of triptycene, which rotates about a carbon–carbon single bond as an axle between the triptycene and a helicene as a base plate. The triptycene can only rotate in a clockwise direction because the chiral helicene acts like a friction or back-pedaling brake shaped in an asymmetric skew. Chirality is the reason for the unidirectional rotation.

The thermodynamics is outlined in the reaction sequence **320a** → **320b**. Molecule **320a** is one of three low-energy rotational isomers (rotamers) and has a rather high rotational energy barrier of about 25 kcal mol^{-1} (caused by the friction brake of the helicene; the barrier to rotation about a typical C–C single bond is only 3–5 kcal mol^{-1}). Rotamer **320a** is activated by reaction with **phosgene** (*4 atoms*) to give the isocyanate **321** via a carbamoyl chloride. Isocyanate **321** is chemically prepared to react with the alcohol function of the hydroxypropyl ether chain attached to the helicene, but in the rotational ground state **321** the isocyanate and the alcohol group are too far apart to interact. However, in the event of a clockwise rotation of the triptycene to **322** (as opposed to an anti-clockwise rotation, which would take the reacting groups further apart and prevent the essential carbamate formation), the isocyanate and alcohol groups are brought sufficiently close to react, such that carbamate **323** can be formed. In this way, the triptycene is irreversibly trapped in a relatively high-energy conformation (E_{act}) about the triptycene–helicene axle. Ambient thermal energy then drives the exoergic unidirectional rotation from **323** to **324** releasing 25 kcal mol^{-1} (E_{act}). Finally, the carbamate function in **324** is cleaved with water to give **320b**, thereby completing the chemically driven rotation of **320a** to **320b**, which is the second low-energy rotamer. Hydrolysis of the carbamate group in **324** is accelerated by a relative rate enhancement of 2×10^4 using metal-bonded water or hydroxide as the nucleophile [310].



319
Molecular Motor



Since **phosgene** enters into the motor as a high-energy molecule (**320a** → **321**) and leaves it as the low-energy molecule CO_2 (**324** → **320b**), it fulfils the characteristics of a fuel.

Although this *molecular motor* does not achieve continuous and fast rotation, the design principles may prove relevant for a better understanding of biological *molecular motors* producing unidirectional rotary motion.

A *molecular motor* with unidirectional rotation driven by *visible light* has been described [311]. Hereby the rotor is donor-acceptor substituted by dimethylamino- and nitro-groups.

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6
Evaluation of Phosgenation Reactions

6.1
Criteria for Selecting a Reagent

Whenever a phosgenation reaction has to be performed, one first has to consider whether a safe phosgene equivalent or substitute can be used, or whether phosgene itself is required. What are the criteria for making this decision?

It should first be ascertained whether one is trying a new synthesis (research) or developing a procedure for a recurrent preparation (R&D) or a production. In the first case, attention should be focussed (under the prevailing conditions) on gaining *access* to the desired product as *simply* and as *rapidly* as possible, and *in sufficient amount*. The **phosgenation reagent** should be selected accordingly – often it could be **phosgene** due to reasons of chemical character (see below). In other cases, choice of the reagent depends on other assessment criteria as listed below.

6.1.1
Preparative Criteria

A second class of criteria for choosing an appropriate reagent is based on *chemical properties* such as *reactivity*, *selectivity*, and *yield*, as well as *reaction time*, *handling*, *work-up*, *purity*, and, last but not least, *costs* (see also Chapter 3). These preparative criteria are more reaction-dependent and can be optimized either by modifying the reaction or by selecting an appropriate reagent. They are less dependent on equipment or infrastructure.

Criterion: *yield*

This is the primary criterion in that it gives an indication of the degree of success of the chosen chemistry. *Yield* is a complex criterion, comprising a lot of parameters, such as *reactivity*, *selectivity*, reaction time, and product stability, as well as *environmental impact* (possibly caused by unwanted or unknown by-products), and is very sensitive to any alteration of these.

Criterion: *reactivity*

As shown in Table 3.1 in Chapter 3, **phosgene** is 19 times more reactive than **diphosgene** and 170 times more reactive than **triphosgene** [1], the main phosgene

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equivalent. Therefore, reactions with **phosgene** can be carried out under much milder conditions than those with **triphosgene**. Compounds will react faster and at lower temperatures (often at −78 °C), causing less thermal strain, and thus preserving sensitive moieties (if the ratio of the temperature dependence of the reaction to that of the side-reaction is >1) – a weighty argument when considering valuable compounds.

Criterion: *handling*

Phosgene itself is a toxic gas, which is inconvenient to weigh or to add to a reaction mixture. Easiest to handle are liquids, which can be added directly through a dropping funnel. This is the case with **diphosgene**, **chloroformates**, **DMC**, **TFAA**, **triflic anhydride**, **thionyl chloride**, **TsCl**, and **phosphoryl chloride** as the most important reagents. Solids generally have to be dissolved before addition to a reaction mixture, but can easily be weighed; most of the phosgene substitutes belong to this group, **triphosgene**, **CDI**, **DSC**, **DPhC**, **DPC**, **NPC**, **phosphorus pentoxide**, **CyCl**, **pyBOP**, **DCC**, **CDC**, and the **Burgess reagent** being the most important.

Criterion: *work-up*

Table 3.2 in Chapter 3 shows the most important **phosgenation reagents** with their bp and mp. The highly volatile reagents are, of course, the gases **phosgene**, **carbon monoxide**, and **carbon dioxide**. With limitations, the liquids **TFAA**, **triflic anhydride**, **DMC**, **thionyl chloride**, and **phosphoryl chloride** can also be evaporated from reaction mixtures. The other reagents are non-volatile. The removal of excess phosgenation reagent is often problematic during the work-up of a reaction mixture. The purification of products requires an extra distillation or recrystallization step. The above mentioned **phosgenation reagents** can be largely separated from the products by evaporation, but only **phosgene** can be separated easily and quantitatively by evaporation or stripping with nitrogen.

Another method used to remove phosgene substitutes from the desired products is to destroy them with appropriate nucleophiles such as water or alcohols. This method can, of course, only be applied when the product is insensitive to these nucleophiles, as is the case for carbamates, carbonates, ureas, cyanides, isocyanides, and alkyl chlorides. Chloroformates, carbamoyl chlorides, isocyanates, acyl chlorides, *N*-carboxylic anhydrides, and carbodiimides, on the other hand, cannot be purified by this method. Consequently, a synthesis of these compounds using **phosgene** is worthy of consideration.

6.1.2 Extrinsic Criteria

Safety, *health concerns* (represented in this context as *toxicity*), and *environmental impact* are a third class of criteria in assessing the suitability of a reagent selected on the basis of the above chemical criteria. These extrinsic criteria are inextricably linked with the laboratory equipment and the infrastructure of the place of work. This may mean that a specific reagent can be used without any problem in labo-

ratory A, whereas the same reagent may not be applied at all in laboratory B due to different configurations of the laboratories.

Criterion: *safety*

As **phosgene** is a highly toxic gas, it is seen from the safety viewpoint as a high-risk compound, which, where possible, should be substituted by appropriate equivalents such as **diphosgene**, or much better, **triphosgene**, both of which perform most of the reactions of phosgene. All other phosgenation reagents only substitute phosgenation reactions in part, but all equivalents and substitutes are liquids or solids and thus avoid the problem of quantifying and introducing a toxic gas. This problem has recently been solved by the process of *safety phosgenation*, in which *gaseous* **phosgene** is generated from a definite amount of *solid* **triphosgene** in an absolutely controlled way with an adjustable flow rate. In this way, **phosgene** is produced only in amounts that are immediately consumed by the phosgenation reaction [2]. This process is described in more detail in Section 7.1.

Criterion: *toxicity*

Because phosgenation reagents all are high-energy compounds and thus very reactive, most of them are toxic. Toxicity becomes increasingly dangerous the greater the volatility of the reagent. The property of volatility is expressed in terms of *vapor pressure*, and the values for some phosgenation reagents are shown in Table 3.3 in Chapter 3. It is instructive to compare, for example, the vapor pressures at room temperature of gaseous **phosgene** (1400 Torr), liquid **diphosgene** (10 Torr), and solid **triphosgene** (0.15 Torr). The ratio of *vapor pressures* **phosgene**/**triphosgene** is nearly 10000! Other important volatile phosgenation reagents, such as **chloroformates**, **TFAA**, **triflic anhydride**, **thionyl chloride**, and **phosphoryl chloride**, are also highly toxic.

A regulation indicating the maximum permissible airborne concentration of a dangerous compound in a place of work over 8 hours a day is enforced on the basis of threshold limiting values (TLVs). These are collected in lists and a selection of TLVs of **phosgenation reagents** is given in Table 3.4 in Chapter 3.

Criterion: *environmental impact*

Regarding *environmental impact*, some phosgene substitutes are more problematic than **phosgene**. Phosgene itself is decomposed by moisture to give hydrochloric acid and carbon dioxide, whereas, for example, **thionyl chloride** decomposes under the same conditions to give hydrochloric acid and sulfur dioxide. While hydrochloric acid can easily be removed by water or amines, and carbon dioxide is harmless, sulfur dioxide will significantly pollute the air and cannot be removed by simple methods. Similar problems may arise from **DPhC** with phenol, from **CDI** with imidazole, or from **DPC** with 2-hydroxypyridine if these are not recycled. Trifluoroacetic acid from **TFAA** and trifluoromethanesulfonic acid from **triflic anhydride** also have severe environmental impact. Pentafluorophenol, which is released from pentafluorophenyl active esters in peptide coupling, is too stable in waste and thus the pentafluorophenyl group has been replaced by the *p*-chlorotetrafluoro-

phenyl group; the reagent used to prepare the corresponding ''active'' ester is **di-*p*-chlorotetrafluorophenyl carbonate** (see Section 4.3.3.2).

6.1.3 Deductions

Each of these criteria is determined by its intrinsic value, although among several criteria, one ''leading'' criterion generally predominates. Nevertheless, by adjusting the criteria with respect to each other, the optimal **phosgenation reagent** can be selected.

6.2 Comparison of Reagents in Phosgenation Reactions

In the following, the same or similar phosgenation reactions with various **phosgenation reagents** are compared with regard to certain criteria. They are presented in the order of Chapter 4.

6.2.1 Criteria for Comparison of Phosgenation Reagents

Yield is still the primary criterion in chemistry because, indirectly, it contains some other preparative criteria such as *reactivity* and *selectivity*, and also has a significant bearing on *costs*. Therefore, *yield* will be the ''leading'' criterion in our comparison of same and similar reactions accomplished with various **phosgenation reagents**. Further criteria to be taken into consideration are *purity*, *handling*, and *work-up*, as well as *safety*, *toxicity*, and *environmental impact*.

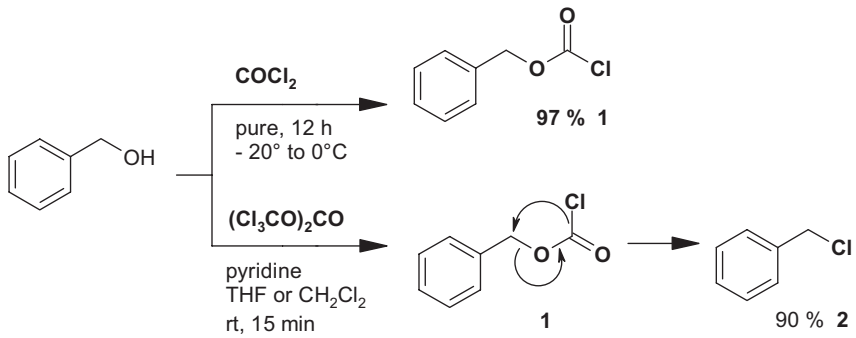
6.2.2 Phosgenation Reactions

6.2.2.1 Chlorocarbonylation

For chlorocarbonylations, only **phosgene**, **diphosgene**, and **triphosgene** are able to react with alcohols to afford the desired products, namely chloroformates and carbamoyl chlorides (see Section 4.2).

Benzyl chloroformate 1

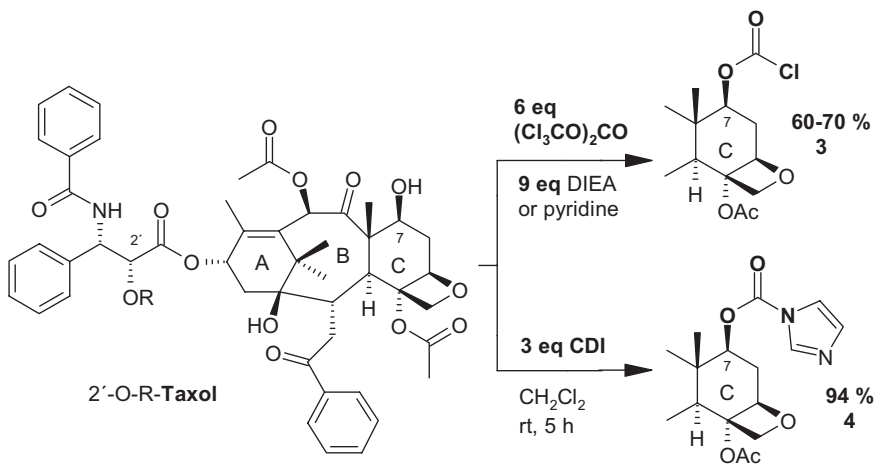
To begin our comparison of **phosgenation reagents**, an example is presented in which a marked influence of reaction conditions on product formation is observed. Benzyl chloroformate (Z–Cl) **1** can be prepared from benzyl alcohol with either **phosgene** (for a *safe source*, see Chapter 7) [4] or **triphosgene** [5]. Reaction with **phosgene** at −20 to 0 °C without a base proceeds extremely well in the desired manner to afford **1** in high **purity** and, even after distillation, in a high *yield* of 97% without the occurrence of benzyl chloride **2** [4] (see Section 4.2.1).



Benzyl alcohol does not react with **triphosgene** at the low temperatures used in the above example in the absence of a base. On reacting benzyl alcohol with **triphosgene** at room temperature in the presence of pyridine, only benzyl chloride is isolated. Chloroformate **1** is formed initially, and if the alcohol is activated, as in the case of benzyl alcohol, decomposition ensues under these conditions, generating benzyl chloride in 90% yield [5]. (If the alcohol is not activated, decomposition will not occur.) Optimizations aimed at achieving higher yields of chloroformate **1** from the reaction of benzyl alcohol with **triphosgene** *without a base* led to a maximum of 15% of **1** besides **2** [4].

2′-*O*-R-Taxol-7-chloroformate 3 and 2′-R-taxol-7-oxycarbonyl imidazole 4

Comparing the formation of chloroformate **3** with **triphosgene** and of oxycarbonyl imidazole **4** with **CDI**, respectively, as activated intermediates for the preparation of carbamates at *7-O-taxol* shows that, under similar reaction conditions, **CDI** yields better results than **triphosgene** [6] (see Section 4.2.1).



Reaction of 2′-*O*-R-*taxol* with **triphosgene** requires a six-fold excess of the reagent and at least a nine-fold excess of base providing a 60–70% yield of **3**, which is

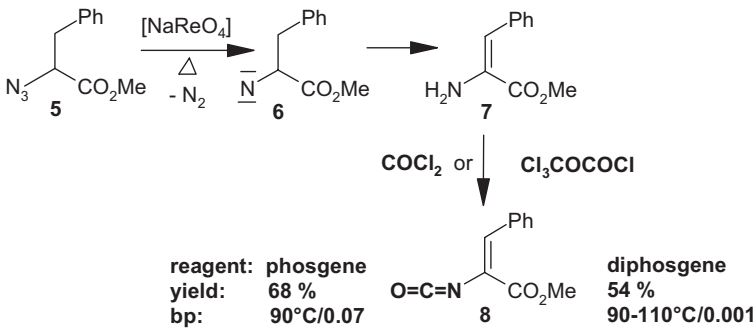
rather sensitive towards water. In contrast, reaction of 2′-*O*-R-*taxol* with **CDI** (three-fold excess) needs no base and the resulting product can be washed several times with water during *work-up* to afford **4** in 94% *yield* and in a high state of *purity* [6].

6.2.2.2 Carbonylation

(See Section 4.3 for isocyanates, carbamates, carbonates, ureas, and reactions with binucleophiles).

Methyl 2-isocyanato-3-phenyl-2-propenoate 8

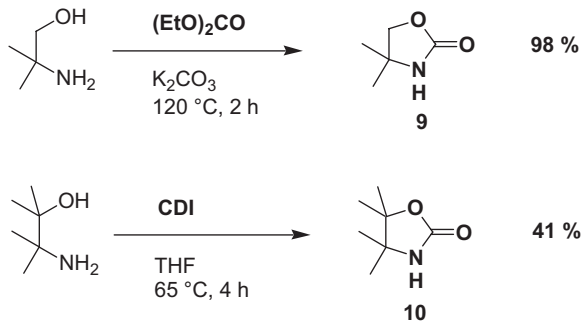
An impressive example, where purification presents severe problems according to whether **phosgene** (for a *safe source*, see Chapter 7) or **diphosgene** is used as the carbonylating reagent, is given by the preparation of methyl 2-isocyanato-3-phenyl-2-propenoate **8** [7]. The azido group in compound **5** is thermally decomposed under catalysis by sodium perrhenate to afford nitrene **6**. Nitrene **6** then undergoes a hydride shift to give **7**, which is reacted with either **phosgene** or **diphosgene** to afford the isocyanate **8**.



Isocyanate **8** is obtained in 54% *yield* using **diphosgene**. Distillation provides a boiling region of 90–110 °C at 0.001 Torr, which means that the compound is of low *purity*. Using **phosgene**, however, there is a sharp bp of 90 °C at 0.07 Torr, and the *yield* is 68%. In this case, "**phosgene** is distinctly superior to **diphosgene**" (as stated by Effenberger in [7]). To maximize the yield, an excess of diphosgene was required; evidently, this excess could not be adequately removed by distillation, whereas excess phosgene is easily evaporated and the product **8** thus prepared is *pure* and distils with a sharp bp in a significantly better yield (see Section 4.3.1.3).

4,4-Dimethyl-2-oxazolidinone 9 and 4,4,5,5-tetramethyl-2-oxazolidinone 10

The similar compounds 4,4-dimethyl-2-oxazolidinone **9** and 4,4,5,5-tetramethyl-2-oxazolidinone **10** have been prepared by cyclocarbonylation of the corresponding amino alcohols with either **diethyl carbonate** [8] or **CDI** [8, 9] as carbonylation reagents (see also Section 4.3.2.4).

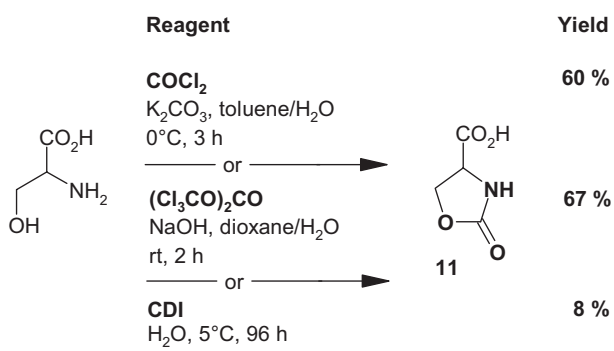


Carbonylation with **diethyl carbonate** provides substantially better results (98% *yield* of **9**) than the comparable reaction with **CDI** (41% *yield* of **10**), although this is likely to be due in part to the presence of the two additional methyl groups in the latter case. Beyond this, the *toxicity* of diethyl carbonate (TLV of the related **DMC** is 200 ppm; see Table 3.4, Chapter 3) is relatively low and *work-up* is easy [9], but the thermal strain (reaction temperature of 120 °C) on the reactants is considerable. This fact would come to prominence if more sensitive groups were to be present in the substrate molecule. In such cases, a reagent of higher energy would be appropriate instead of high temperature conditions.

4-Carboxyoxazolidin-2-one 11

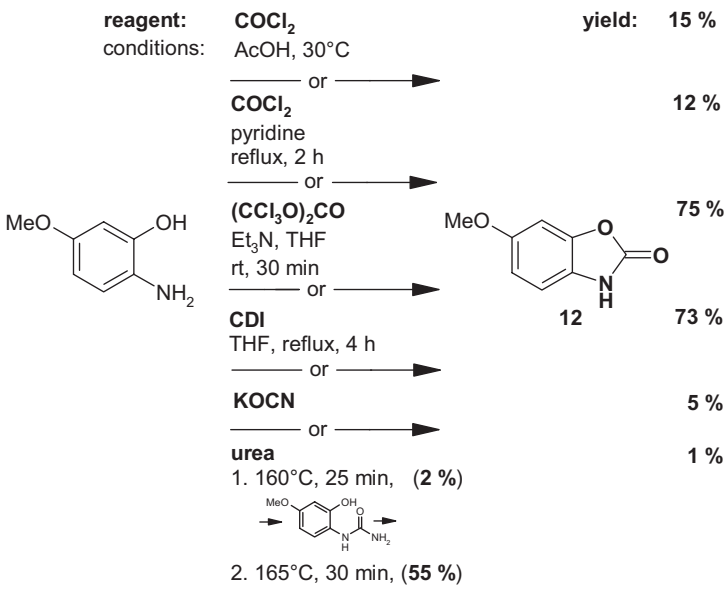
The oxazolidinone from the amino acid serine has been prepared with either **phosgene** (for a *safe source*, see Chapter 7) [10], **triphosgene** [11], or **CDI** [12]. The phosgene-based reagents afford useful *yields* of **11** of 60% and 67%, respectively, but **CDI** provides only an 8% *yield* (see also Section 4.3.2.4).

The reasons as to why **CDI** gives poor results (likewise with threonine; only with cysteine does it give satisfactory results) are not clear, as reaction conditions such as temperature and time have obviously been adapted to the relative reactivities of the phosgenation reagents. It is possible that the reaction medium is not sufficiently basic for reaction of the alcohol function with the intermediate imidazolyl aminocarbonyl group.



MBOA, 6-methoxy-2-oxo-2,3-dihydrobenzoxazole 12

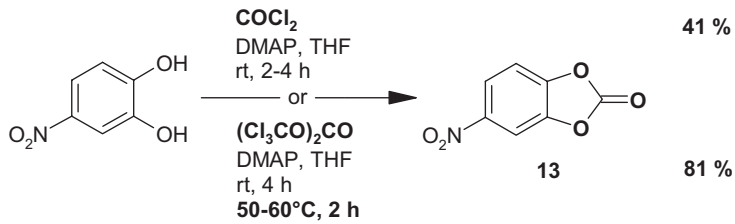
MBOA **12**, the resistance factor of wheat against fungi and insects, has been prepared by various methods from 2-amino-5-methoxyphenol using either **phosgene** (for a safe source, see Chapter 7) [13, 14], **triphosgene** [15], **CDI** [16], **potassium cyanate** [17], or **urea** [18]. Good *yields* of **12** were obtained with **triphosgene** (75%) and **CDI** (73%), whereas **phosgene** (15% or 12%), **potassium cyanate** (5%), and **urea** (1%) were unsatisfactory.



The two cyclocarbonylations of the aminophenol with **phosgene** (in either AcOH [13] or pyridine [14]) afford only poor *yields*, probably due to the occurrence of side reactions between the highly activated aminophenol and the very reactive **phosgene**. These results, coupled with the high *toxicity* of gaseous phosgene, make these syntheses unsuitable for the production of **12**. On the other hand, harmless **urea** provides an even worse *yield* of **12** of 1.1%. With urea, **12** is formed by way of a two-step synthesis; in the first step, 4-methoxy-2-hydroxyphenyl urea is formed in just 2% *yield*, whereas the second step, its intramolecular cyclization by pyrolysis, affords **12** in 55% *yield*. This is an instructive example, in that heat-powered (160–165 °C) reactions are largely unselective and are accompanied by a significant amount of by-products, making them totally inapplicable for the production of **11**. **Triphosgene**, which has only 1/170th of the *reactivity* of **phosgene** (see Table 3.1 in Chapter 3), and **CDI**, which has a similar *reactivity* as triphosgene, afford **12** in good *yields* of 75% and 73%, respectively (see also Section 4.3.2.4).

***o*-(4-Nitrophenylene) carbonate 13**

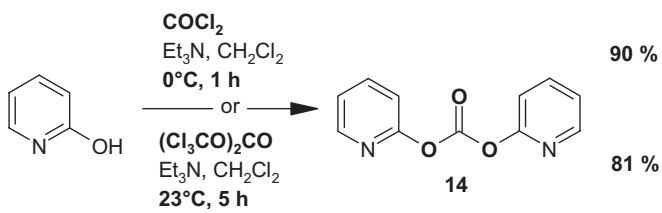
Cyclocarbonylation of 4-nitrocatechol forming *o*-(4-nitrophenylene) carbonate (**NPC**) **13** has been accomplished with either **phosgene** (for a *safe source*, see Chapter 7) or **triphosgene** [19].



Conditions and *work-up* of these two carbonylation reactions were the same, except for the additional heating of the reaction mixture with **triphosgene** for 2 h; *yields* of **13** were 41% and 81%, respectively. A substantial increase in the *yield* for the reaction with **triphosgene** is thus observed (see Sections 4.3.3.2 and 4.3.3.4).

Di-2-pyridyl carbonate 14

In contrast, the generation of di-2-pyridyl carbonate (**DPC**) **14** proceeds equally effectively using either **phosgene** (for a *safe source*, see Chapter 7) [20] or **triphosgene** [21], affording **14** in *yields* of 90% and 81%, respectively (see Sections 4.3.3.2 and 4.3.3.4).



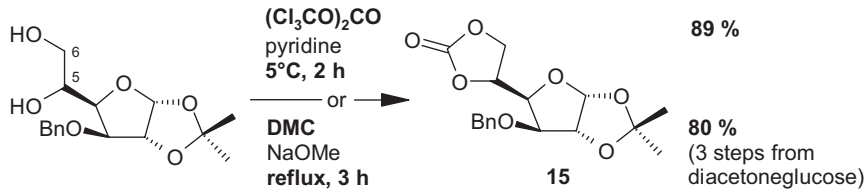
The different *reactivities* of the two reagents are offset by the respective reaction conditions used, specifically a five-fold increase in the reaction time and an increase in the reaction temperature from 0 to 23 °C (corresponding to 2.3 units of 10 °C increments). The latter causes an increase of *reactivity* by roughly a factor of 5–12 (assuming an increase of activity by a generally accepted factor of two- to three-fold for each increment of 10 °C). Multiplying this by the five-fold longer reaction time results in an estimated overall increase of *reactivity* of about **25**- to **60-fold** on going from **triphosgene** to **phosgene**.

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose-5,6-carbonate 15

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose-5,6-carbonate **15** has been prepared from the corresponding 5,6-diol with **triphosgene** [22] (see Section 4.3.3.4), and from the corresponding 5,6-isopropylidene derivative over three steps with **dimethyl carbonate** (**DMC**) [23] (see Section 4.3.3.7).

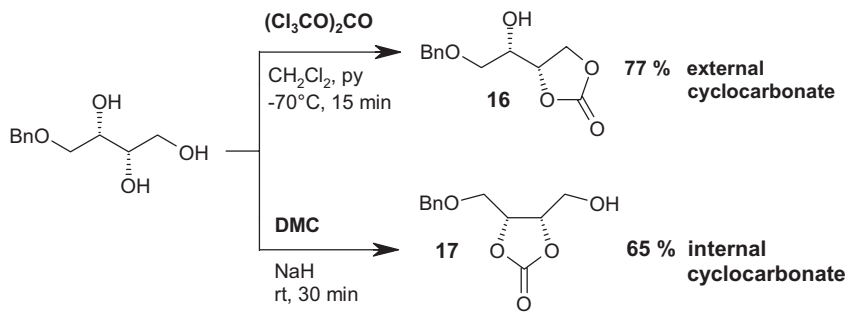
Yields of **15** by both reactions are good (89% and 80%, respectively) and comparable, even though the yield given for the carbonylation with **DMC** is based on three steps. *Safety* requirements are met, although **DMC** is rather volatile (bp 90 °C, compared with a mp of 80 °C for **triphosgene**; the *vapor pressure* of **DMC** is 100

Torr at 37 °C, compared with 0.15 Torr at 20 °C for **triphosgene**; see Tables 3.2 and 3.3, Chapter 3). DMC is of low *toxicity* (a TLV of 200 ppm, as compared with 0.1 ppm for **phosgene** possibly arising from the **triphosgene**; see Table 3.4, Chapter 3). The reaction temperature of about 90 °C (bp of **DMC**) is also acceptable. Both reactions are useful, although *handling* and *work-up* are easier with **DMC**.



(2*S*,3*S*)-4-Benzyloxy-1,2,3-butanetriol 1,2-cyclic carbonate 16 and (2*S*,3*S*)-4-benzyloxy-1,2,3-butanetriol 2,3-cyclic carbonate 17

In some cases, different **phosgenation reagents** can show different selectivities towards certain substrates. Thus, (2*S*,3*S*)-4-benzyloxy-1,2,3-butanetriol reacts with **triphosgene** in the presence of pyridine to form solely the five-membered *external* (2*S*,3*S*)-4-benzyloxy-1,2,3-butanetriol 1,2-cyclic carbonate **16** in 77% *yield*, whereas reaction of the 1,2,3-triol with **DMC** affords the five-membered *internal* (2*S*,3*S*)-4-benzyloxy-1,2,3-butanetriol 2,3-cyclic carbonate **17** in 65% *yield* [24] (see also Section 4.3.5.3).



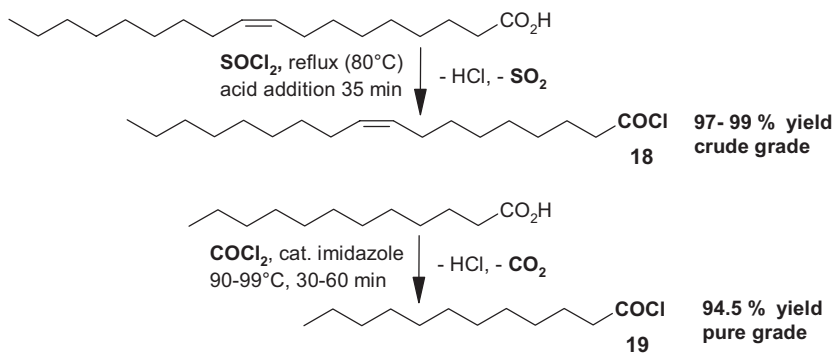
6.2.2.3 Chlorination

(See Section 4.4)

Oleoyl chloride 18 and lauroyl chloride 19

The conversion of long-chain carboxylic acids into their carboxylic chlorides using excess **thionyl chloride** is a standard method. Thus, oleoyl chloride **18** has been prepared in *yields* of 97–99% (crude material) from oleic acid by refluxing with **thionyl chloride** [25]. An equivalent alternative method is the reaction of a fatty acid with **phosgene** (for a *safe source*, see Chapter 7). In this way, lauroyl chloride

19 has been produced from lauric acid in 94.5% yield (distilled product) [26] (see Section 4.4.2.1).



Both reactions proceed very well, affording excellent *yields* of fatty acid chlorides under similar reaction conditions (temperature and time). In contrast to excess gaseous **phosgene**, which can be removed easily, the removal of excess **thionyl chloride** requires reduced pressure.

As regards *safety* considerations, it should be noted that **thionyl chloride** is refluxed prior to addition of the fatty acid, whereas **phosgene** is passed in with the complete amount of fatty acid already being available.

Toxicities (see Table 3.4, Chapter 3) are both high, with TLVs of 1 ppm for **thionyl chloride** and of 0.1 ppm for **phosgene**, respectively.

Here, a key factor in selecting the appropriate method is the *environmental impact* of the by-products. Both reactions release hydrogen chloride, which can easily be removed by a scrubber filled with aqueous sodium hydroxide. The scrubber also decomposes traces of **phosgene**. In contrast to the reaction with **phosgene**, which liberates harmless carbon dioxide as a second by-product, **thionyl chloride** releases gaseous sulfur dioxide, which significantly burdens the environment, and cannot be removed by simple methods.

The TLV of sulfur dioxide is 2 ppm [3] while that of carbon dioxide is 5000 ppm (see Table 3.4, Chapter 3). Because of the *high toxicity* and substantial *environmental impact* of the sulfur dioxide released in the reaction with **thionyl chloride**, **phosgene** is the superior reagent in this instance.

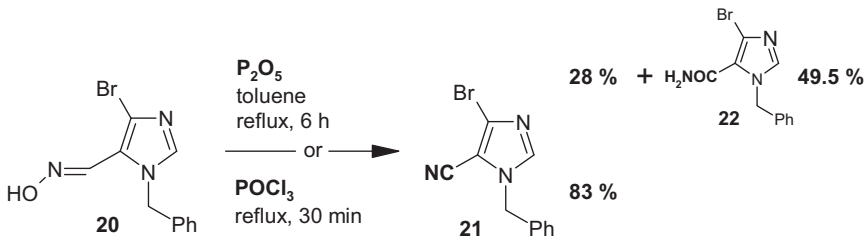
6.2.2.4 Dehydration

Phosgenation reagents used for dehydration reactions are particularly varied and sometimes produce by-products that are difficult to remove (see Section 4.5).

1-Benzyl-4-bromo-5-cyanoimidazole 21

An often used method to produce cyano compounds from carboxaldoximes and carboxamides is to dehydrate them with **phosphorus pentoxide**, which is a very low-priced reagent. In this way, 1-benzyl-4-bromo-5-cyanoimidazole **21** was prepared in 28% *yield* from **20**, although, surprisingly, the product was accompanied

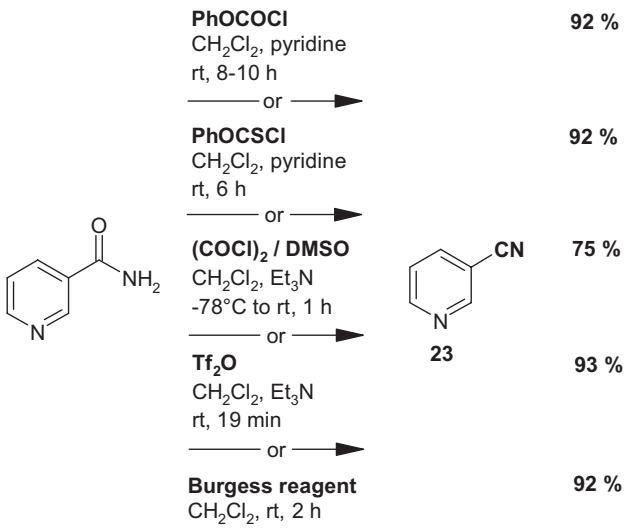
by 49.5% of the corresponding amide **22**, which did not react further [27]. In contrast, **phosphoryl chloride**, another low-priced reagent, reacted with the carboxaldoxime **20** to form the nitrile **21** in 83% *yield* [27] (see Section 4.5.1.1).



It is remarkable that **phosphorus pentoxide** did not react further with the carboxamide by-product, especially in view of the fact that this reaction is otherwise a standard method for preparing nitriles. This illustrates the point that even proven standard methods cannot be applied in all cases.

3-Cyanopyridine 23

3-Cyanopyridine **23** has been prepared from nicotinic amide by several methods, in good to excellent *yield* in each case. As dehydration reagents, **phenyl chloroformate** [28], **phenyl chlorothionoformate** [29], **oxalyl chloride**/**DMSO** [30], **triflic anhydride** [31], and the **Burgess reagent** [32] have been used, giving yields of **23** of 92%, 92%, 75%, 93%, and 92%, respectively.



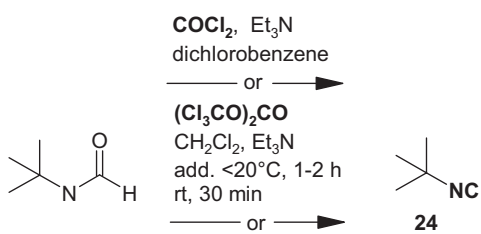
The reactions with the two **chloroformates** require rather long reaction times (6–10 h), whereas those with **triflic anhydride**, under **Swern** conditions, and with the

Burgess reagent are complete within 0.3–2 h. With the exception of the **Burgess reagent**, which is a solid (mp 80 °C), all the other reagents are *highly toxic* liquids (the *toxicity* of chloroformates is similar to that of phosgene; see Table 3.4, Chapter 3), particularly **oxalyl chloride**, which is also volatile (bp 63 °C).

On this basis, the **Burgess reagent** should be preferred, but it is a high-priced reagent, and thus its use is limited to valuable substrates (see Section 4.5.1.1).

tert-Butyl isocyanide 24

tert-Butyl isocyanide **24** has been produced from *tert*-butylformamide by three methods, using either **phosgene** (for a *safe source*, see Chapter 7) [33], **triphosgene** [34], or **phosphoryl chloride** [35].



	yield	bp [°C]	scale [g]	scale [mol]
$COCl_2$, Et_3N, dichlorobenzene	82 %	90-92	1000	10
$(Cl_3CO)_2CO$, CH_2Cl_2, Et_3N, add. <20°C, 1-2 h, rt, 30 min	88 %	90	100	1
$POCl_3$, pyridine, pentane, 60°C, 15 min	60 %	93-95	20	0.2

Yields of **24** obtained with **phosgene** and **triphosgene** are 82% and 88%, respectively, and are thus significantly higher than that achieved with **phosphoryl chloride** (60%). Indeed, phosgene-based reagents generally give the best results in preparations of isocyanides [36]. *Work-up* of isocyanides is usually carried out by the addition of water, whereby excess phosgenation reagents are decomposed. Therefore, solid **triphosgene** is superior to *gaseous* **phosgene** on grounds of *safety*. Applying phosgene-based reagents, scale-up (for example, from 100 g to 1 kg) does not present a problem, and *yields* remain constant.

In contrast, isocyanide-forming reactions involving **phosphoryl chloride** are remarkably dependent on the scale of the approach. Whereas the method (**phosphoryl chloride** in conjunction with either pyridine, triethylamine, or, particularly for phenyl isocyanides, diisopropylamine) works well with <0.1 mol formamide, giving isocyanides in *yields* of 56–93%, on a larger scale the *yields* decrease considerably, because insoluble polyphosphates increasingly precipitate upon neutralizing the reaction mixtures with solutions of aqueous alkali, and these greatly hamper the separation of the organic and aqueous phases [37].

Similar results have been described in relation to the synthesis of 1-cyclohexenyl isocyanide; Armstrong stated that: "... **triphosgene** as a dehydrating agent was superior to the **phosphorus oxychloride** called for by Ugi" [38].

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7
Materials and Resources for Phosgenation Reagents

Most of the phosgene equivalents and substitutes are commercially available, albeit at widely varying costs, whereas **phosgene** itself is subject to restrictions. For those phosgene substitutes that are not available, procedures or references for their preparation are given herein. In some phosgenation reactions, the role of phosgene is played by rather simple, ordinary chemicals, which can be found in any catalogue of fine chemicals and hence need not be mentioned further in this chapter.

7.1
Sources of Phosgene

Phosgene is nowadays produced in two ways, in stationary plants or special facilities that operate continuously producing 100s of kilograms up to 1,000s of tons a day, and in rather small amounts on a scale of grams to kilograms a day in bottles, lecture bottles, or dissolved in toluene. Recently, a process whereby **phosgene** is evolved from a safe precursor has been developed [1], which has also been applied in the form of cartridges for *safe phosgenations* [2].

7.1.1
Industrial Plants

Most of the annual worldwide consumption of 5–6 million tons of **phosgene** is produced from carbon monoxide and chlorine in the presence of a catalyst based on activated carbon (charcoal) in special plants. The process, the tetrachloromethane problem associated with it, and the approaches to solve it, are described in Section 2.1.

To provide **phosgene** *on the demand of consumer* by producing it on location, *Modular Phosgene Generators* are offered by *Davy Process Technology (DPT)*, Switzerland [3], in seven output sizes ranging from 3 kg/h up to 10,000 kg/h (Table 7.1). These *Modular Generators* produce **phosgene** from carbon monoxide and chlorine and consist of two sections, the intrinsic *phosgene generator* (see Scheme 2.3, Section 2.1) and a *safety absorption* module.

Phosgenations – A Handbook. L. Cotarca, H. Eckert

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Tab. 7.1. Modular phosgene generators from *Davy Process Technology (DPT)* [3].

Type	G/A 30	G/A 100	G/A 200	G/A 600	G/A 1200	G/A 2000	G/A 10000
Output [kg/h]	2–30	10–100	20–200	60–600	120–1,200	200–2,000	1,000–10,000

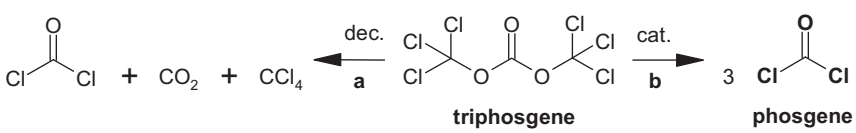
7.1.2 Safety Phosgenation

If the advantages of **phosgene** (such as high reactivity, high yields, and pure products; see the evaluation in Chapter 6) could be combined with the convenience of safe phosgene equivalents without any loss of potential reactivity, this would constitute a valuable method in preparative chemistry. This has been achieved through the method known as *"safety phosgenation"*.

7.1.2.1 The Process

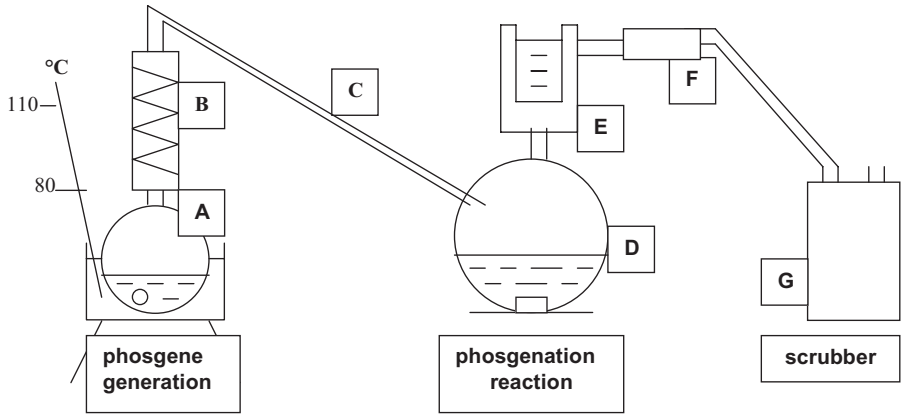
Triphosgene, as a safe precursor, is "depolymerized" into three equivalents of **phosgene** by a special catalyst in a *controlled* reaction [1, 4]. The process is patented worldwide by *Dr. Eckert GmbH* [1] (see also Chapter 2).

Triphosgene as a solid (mp 80 °C) is rather stable under most conditions. As a liquid, it decomposes according to route **a** (as does diphosgene) under several conditions, such as in the presence of metal salts, to give one equivalent each of phosgene, carbon dioxide, and tetrachloromethane. In the presence of catalysts based on special amines or imines, the decomposition takes an entirely different route, route **b**, forming three equivalents of **phosgene**. Route **a** is exothermic, whereas route **b** is endothermic and thus the rate of this decomposition can be controlled by heating from 80 to 110 °C. This temperature increment increases the rate of the **phosgene** generation threefold [2]. During the whole decomposition reaction, from start to finish, an absolutely constant **phosgene** stream is evolved at a pre-selected heating temperature. The reaction can be stopped immediately by cooling to below 80 °C, whereupon triphosgene crystallizes. Other catalytic systems work in a similar manner [5] (see Chapter 3).



dec. = decomposition catalyzed by metal salts, silica gel, etc., "dirt", heat (>150°C)
cat. = catalyst: "deactivated" amine or imine

The main advantage of the process lies in its *safety*. The generated **phosgene** is immediately consumed in the phosgenation reaction, and hence the actual amount



Scheme 7.1. *Safety Phosgenation* equipment with an *external* **phosgene** *source.*

of phosgene present in the whole facility at any given time is a diminutive fraction of the entire reagent; in fact, the maximum amount corresponds to the dead volume of the equipment. In this respect, the method is superior to all procedures in which **phosgene** is stored or is present in large excess. It is also superior to **phosgene** dissolved in toluene or other solvents, because in such protocols phosgene is present in excess at the beginning of the reaction, and in the case of spillage the entire amount of phosgene evaporates immediately.

The process of *safety phosgenation* is recommended by the *Accident Insurance of the German Chemical Industry* [6].

The process of *safety phosgenation* can be conducted in two ways.

7.1.2.2 External Phosgene Source

As depicted in Scheme 7.1 (*safety phosgenation* equipment), vessel **A**, containing **triphosgene** and the catalyst [2] without a solvent, is fitted at the top with a reflux condenser **B**, which is connected by a tube **C** to the reaction vessel **D** containing the well-stirred reaction mixture. Vessel **D** is fitted at the top with a dry-ice reflux condenser **E** (or a reflux condenser cooled to −20 °C by a cryostat). The outlet of the reflux condenser **E** is connected via a tube to a drying tube **F**, which, in turn, is connected to scrubber **G**, containing aqueous sodium hydroxide, which absorbs hydrogen chloride and traces of phosgene. **Phosgene** generation is initiated by heating vessel A with an oil bath at a pre-selected bath temperature between 80 and 110 °C as described above. The generation can be stopped immediately at any time by removing the oil bath and cooling, such that triphosgene crystallizes.

7.1.2.3 Cartridges for Safety Phosgenations

The method of *safety phosgenation/external* ***phosgene*** *source* described above (Section 7.1.2.2) has been performed with pre-packaged cartridges for the production of 10 mmol (1 g), 20 mmol (2 g), or 50 mmol (5 g) of **phosgene** from an equivalent amount of **triphosgene** [7, 8]. The cartridge consists of a small tube (length 10 cm,

diameter 1.6 cm), containing the aforementioned amounts of **triphosgene** and a bead of catalyst, sealed by a cap. This serves as a storage vessel. Before use, the cap is removed and the cartridge and reaction vessel are connected by a length of tubing with a gas-tight adapter. A dosimeter badge and paper for measuring phosgene dosage are also supplied. The cartridges are commercially available from Sigma-Aldrich [8] (Table 7.2). Instructions for their use are given in [2, 8] and can be retrieved from [2].

7.1.2.4 In situ Phosgene Source

The requisite amount of **triphosgene** to generate the desired amount of phosgene is placed in the reaction vessel, together with the catalyst for the "depolymerization" [1, 2, 5], the other reactants and reagents, and the solvent. (In contrast to solid **triphosgene**, in solution it is decomposed by the catalyst even at temperatures below its mp). As above, **phosgene** is released over a defined period. In the presence of certain nucleophiles, particularly certain amines (as reactants or scavengers), the **phosgene** might be released all at once. If this were the case, the method would operate as a usual phosgenation reaction, but the safety aspect of *safety phosgenation* would be somewhat reduced. Nevertheless, the method is advantageous in terms of its simple *handling*.

7.2 Sources of Phosgenation Reagents

Available **phosgenation reagents** for laboratory use are listed in Table 7.2. Some are commercially available, while preparative procedures for others are either given in the relevant section of Chapter 4 in this book, or in the literature. For the structures of all these phosgenation reagents, see Scheme 2.1, Chapter 2.

Phosgene can be obtained on a large scale from *Van De Mark* (now part of *SNPE*), located in Lockport, N.Y., who sell the gas on the merchant market.

Diphosgene can be obtained on a large scale from *Degussa*, UK, *Dona Fine Chemicals*, Poland, *Fabricolor Vus*, US, *Fine Organics*, UK, *Ubichem*, UK and Hungary, *VUOS*, Czech Republic, or *Vujin Organic Chemical Plant*, PR China.

Triphosgene can be obtained on a large scale from *Dr. Eckert GmbH* [2], Germany, *Ubichem*, UK and Hungary, or *Synergetica*, PR China/US.

7.3 Safety Precautions

The high toxicity of **phosgene** and several of its substitutes, as well as of some products (!) from phosgenation reactions such as *alkyl isocyanates* (see Table 3.4, Section 3.4), necessitates restrictive regulations about exposure to them. In this section, instructions are given with a view to obtaining maximum benefit from these synthetically highly valuable reagents with a minimum of hazard. A general

Tab. 7.2. Available **phosgenation reagents** for laboratory use from commercial sources [2, 8–10], or prepared as described in sections of Chapter 4 of this book [Sec.], or in the literature [11–13]. For the structures of all these phosgenation reagents, see Scheme 2.1, Chapter 2.

Phosgenation Reagents Phosgene, Equivalents and Substitutes	*CAS Reg. No.*	*Source*	*Order No.*
Phosgene, cartridges for safe phosgenation, 0.01 mol	32315-10-9 75-44-5	2	CDC0.01
Phosgene, cartridges for safe phosgenation, 0.02 mol	32315-10-9 75-44-5	8, 9 2	51,975-8 CDC0.02
Phosgene, cartridges for safe phosgenation, 0.05 mol	32315-10-9 75-44-5	8, 9 2	51,976-6 CDC0.05
Phosgene, cartridges for safe phosgenation, starter kit[a]	32315-10-9 75-44-5	8, 9	51,978-2
Phosgene, cylinder	75-44-5	10	79372
Phosgene, in toluene	75-44-5	10	79372
Diphosgene (trichloromethyl chloroformate)	503-38-8	10	23261
Triphosgene (bis(trichloromethyl) carbonate, **BTC**)	32315-10-9	9 11, 12	33,075-2
Oxalyl chloride	79-37-8	9	22,101-5
Boron tribromide	10294-33-4	9	20,220-7
Boron trichloride, in dichloromethane	10294-34-5	9	17,893-4
Phosphoryl chloride	10025-87-3	9	26,209-9
Phosphorus oxybromide	7789-59-5	9	37,694-9
Thionyl chloride	7719-09-7	9	23,046-4
Thionyl bromide	507-16-4	9	25,125-9
Phosphorus pentoxide	1314-56-3	9	25,605-6
Triphenylphosphine dibromide (dibromotriphenylphosphorane)	1034-39-5	9	27,094-6
Cyanuric chloride (**CyCl**), (2,4,6-trichloro-1,3,5-triazine)	108-77-0	9	C9,550-1
Trichloroacetyl chloride	76-02-8	9	15,159-9
Methanesulfonyl chloride (**MsCl**)	124-63-0	9	47,125-9
p-Toluenesulfonyl chloride, (tosyl chloride, **TsCl**)	98-59-9	9	24,087-7
Benzyl chloroformate	501-53-1	9	11,993-8
4-Nitrobenzyl chloroformate (**NZ–Cl**)	4457-32-3	9	22,280-1
Methyl chloroformate	79-22-1	9	M3,530-4
Ethyl chloroformate	541-41-3	9	18,589-2
1-Chloroethyl chloroformate	50893-53-3	9	30,148-5
Phenyl chloroformate	1885-14-9	9	16,752-5
Phenyl chlorothionoformate	1005-56-7	9	23,452-4
Bis(4-nitrophenyl) carbonate	5070-13-3	9 Sec. 4.3.3.2	16,169-1
Di-*t*-butyl dicarbonate (**Boc_2O**)	24424-99-5	9	20,524-9
Ethylene carbonate (**EC**)	96-49-1	9	53,555-9
Chloroethylene carbonate	3967-54-2	9	16,763-0
Nitrophenylene carbonate (**NPC**)	25859-54-5	Sec. 4.3.3.2	
Dimethyl carbonate (**DMC**)	616-38-6	9 Sec. 4.3.3.7 Sec. 4.3.3.8 Sec. 4.3.3.9	51,712-7

Tab. 7.2 *(continued)*

Phosgenation Reagents Phosgene, Equivalents and Substitutes	***CAS Reg. No.***	***Source***	***Order No.***
Diethyl carbonate	105-58-8	9	51,713-5
Diphenyl carbonate (**DPhC**)	102-09-0	9	D20,653-9
		Sec. 4.3.3.2	
		Sec. 4.3.3.7	
		Sec. 4.3.3.8	
Di-2-pyridyl carbonate (**DPC**)	1659-31-0	Sec. 4.3.3.2	
		Sec. 4.3.3.4	
Disuccinimidyl carbonate (**DSC**)	74124-79-1	9	22,582-7
		Sec. 4.3.3.4	
1,1-Carbonyldiimidazole (**CDI**)	530-62-1	9	11,553-3
1,1-Carbonyl-bis(2-methylimidazole)	13551-83-2	9	32,307-1
1,1-Carbonyl-bis(benzotriazole)	68985-05-7	9	51,297-4
Ethyl acetoacetate	141-97-9	9	24,070-2
Acetic anhydride	108-24-7	9	53,999-6
Isatoic anhydride	118-48-9	9	I-1,280-8
Trifluoroacetic acid anhydride (**TFAA**)	407-25-0	9	10,623-2
Trifluoromethanesulfonic anhydride (triflic anhydride, $\mathbf{Tf_2O}$)	358-23-6	9	17,617-6
1,1-Dichlorodimethyl ether	4885-02-3	9	D6,565-8
Dimethoxymethane (formaldehyde dimethylacetal, methylal)	7149-92-0	9	D13,465-1
Diethoxymethane	462-95-3	9	53,828-0
Phosgene iminium chloride (dichloromethylene)dimethylammonium chloride (Viehe's salt)	33842-02-3	9	16,287-6
(Chloromethylene)dimethylammonium chloride (Vilsmeier reagent)	3724-43-4	9	28,090-9
Pyridine–phosgene adduct 1-[2-(chloroformyl)-2-azacyclohexa-3,5-dienyl]pyridinium chloride (**2-DHPP**)	117371-69-4	13	
Benzotriazol-1-yloxytripyrrolidino phosphonium hexafluorophosphate (**PyBOP**)	128625-52-5	9	37,784-8
Benzotriazol-1-yloxy tris(dimethylamino) phosphonium hexafluorophosphate (**BOP**) (Castros reagent)	56602-33-6	9	22,608-4
Carbon monoxide, **CO**	630-08-0	9	29,511-6
Carbon dioxide, $\mathbf{CO_2}$	124-38-9	9	29,510-8
Trimethylsilyl isocyanate	1118-02-1	9	25,264-6
Chlorosulfonyl isocyanate	1189-71-5	9	14,266-2
(Methoxycarbonylsulfamoyl) triethylammonium betaine (**Burgess reagent**)	29684-56-8	9	36,548-3
1,3-Dicyclohexylcarbodiimide (**DCC**)	538-75-0	9	D8,000-2
		Sec. 4.5.3.1	
1,3-Diisopropylcarbodiimide	693-13-0	9	D12,540-7
1,3-Bis(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)carbodiimide [bis-4-(2,2-dimethyl-1,3-dioxolyl)methyl carbodiimide (**BDDC**)]	159390-26-8	9	48,212-9
		Sec. 4.5.3.2	

Tab. 7.2 *(continued)*

Phosgenation Reagents Phosgene, Equivalents and Substitutes	*CAS Reg. No.*	*Source*	*Order No.*
2-Chloro-1,3-dimethylimidazolium chloride (**CDC**)	125376-11-6	9	52,924-9
2-Chloro-1,3-dimethylimidazolium hexafluorophosphate	101385-69-7	9	42,033-6
2-Chloro-1,3-dimethylimidazolium tetrafluoroborate	153433-26-2	9	43,927-4
Diethyl azodicarboxylate (**DEAD**)	1972-28-7	9	56,311-0
Diphenylphosphoryl azide	26386-88-9	9	17,875-6
Dibutyltin oxide	818-08-6	9	18,308-3

[a] Contains one cartridge for Safe Phosgene Generation, 0.02 mol, one gas-tight adapter with tubing, one dosimeter badge + paper, and instructions.

overview on handling hazardous chemicals and disposal of chemical waste has been reported [15].

7.3.1 Material Safety Data Sheets

To ensure safe working, *material safety data sheets (MSDS)* have to be consulted, particularly for the **phosgenation reagents** listed in Table 3.2, where the relevant *risk and safety (R+S) phrases* are presented. Further information can be found in the appropriate section of the relevant MSDS.

A special report on **phosgene** toxicology and treatment is given in [14].

7.3.2 Some Practical Hints

The following practical hints should facilitate the planning and realization of syntheses involving *phosgenation reactions*, and are particularly aimed at the chemist not trained or experienced in the procedures.

1) Phosgenation reactions must be performed in an efficient hood.
2) Consult the MSDS and take the necessary precautions (protective clothing, gloves, eye protection, etc.).
3) Minimize the risk by choosing the appropriate method and the appropriate **phosgenation reagent** according to Chapter 6. Use progressive methods and tools!
4) Use dosimeters (if available) to measure the degree of exposure to high risk compounds (these could also be products such as alkyl isocyanates).
5) Regarding high risk compounds, make sure that excesses (and unreacted fractions) are decomposed in an appropriate manner.

6) Regarding high risk compounds, clean all of the reaction equipment that may have become contaminated while it is still in the hood; in no case remove the apparatus from the hood before decontamination of the high risk compounds.
7) Ethanol can often be used for a quick deactivation of all phosgene equivalents, including chloroformates, carbamoyl chlorides, isocyanates, and acyl chlorides.

7.4 References

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8
Monitoring Phosgene and Phosgene Substitutes: Analytical Methods

8.1
Phosgene Monitoring

Phosgene is said to be probably the most poisonous gas used in industry. However, *hydrogen selenide* is probably a more poisonous gas and *methyl isocyanate* is certainly a more poisonous vapor (bp 39 °C). *Bis(chloromethyl) ether* is more poisonous in the chronic sense (Occupational Exposure Limit, OEL, 1 ppb). Phosgene might, therefore, be more correctly described as the most poisonous gas used in any significant volume in industry [1].

Phosgene is primarily a lung irritant. Because of its low solubility in water, phosgene reacts only to a limited extent with the aqueous film on the mucous membranes, so most of the phosgene reaches the pulmonary alveoli. Here, it reacts with bases at the blood–air barrier, disturbing the gas exchange. **Phosgene** poisoning is often characterized by a delayed onset, which may occur hours after the initial exposure. Based on symptoms caused by low concentrations, the recommended threshold limit value (TLV) is set at 0.1 ppm. This standard was established for an eight-hour time-weighted average [2, 3]. **Phosgene** is an especially insidious material in that human detection levels (about 0.5–1 ppm) are above those considered safe (0.1 ppm). After repeated exposures, human detection levels are elevated. In addition, phosgene is heavier than air, and so it accumulates at floor level.

Irritation of the throat and eyes by **phosgene** occurs immediately at 3–4 ppm. Exposure to 20–30 ppm for as little as 1 min may cause severe irritation of the upper and lower respiratory tract [4, 5], with symptoms including burning throat, nausea, vomiting, chest pain, coughing, shortness of breath, and headache. Brief exposure to 50 ppm can be fatal within a few hours. Severe respiratory distress may not develop for 4–72 hours after exposure, at which point pulmonary edema progressing to pneumonia and cardiac failure may occur. **Phosgene** has not been found to be carcinogenic or to show reproductive or developmental toxicity in humans.

Operating areas are continuously monitored by a variety of alarm and shutdown systems. Operating personnel or others using areas where phosgene is employed usually wear *phosgene indicator badges* that change color upon exposure. An analysis

Phosgenations – A Handbook. L. Cotarca, H. Eckert

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of casualities among workers exposed to **phosgene** in the past, as well as the occupational hazard assessment of phosgene, have been reported [6–8].

8.1.1 Laboratory and Kilolab Handling and Monitoring of Phosgene

Because of its corrosivity and high acute toxicity, **phosgene** should be handled using the "basic prudent practices", supplemented by additional precautions for work with compounds of high toxicity. Laboratory personnel intending to use phosgene should be fully acquainted with its toxicity and reactivity, and the protective measures associated with this particular type of chemical. In addition, the workers' colleagues should be familiar with the hazards and the necessary rescue and first aid procedures.

Before starting laboratory work with **phosgene**, it is recommended that the individual is equipped with fresh-air breathing apparatus, a bottle of strong ammonia (or an alternative reagent) for leak testing, and a supply of 10% aqueous ammonia solution (or 15% sodium hydroxide solution) for decontamination purposes [1].

In particular, laboratory work with **phosgene** should be conducted in a suitably effective fume cupboard, and splash goggles and impermeable gloves should be worn at all times. It is advisable to attach detector tapes (such as filter papers previously dipped in a solution of 5% 4-(dimethylamino)benzaldehyde and 5% *N*,*N*-diethylaniline in ethanol) to the fume cupboard face. Any emission of phosgene may then be noted from the characteristic color change (yellow to blue). Notices should be placed nearby to warn that phosgene is being used. All gas bubblers, or other vessels, through which phosgene has been passed should be labeled so that other workers are not exposed to the residual phosgene unwittingly [1]. Flow rates of phosgene gas and amounts of liquid material should be kept to the minimum practical amount. Vacuum pumps should be protected by solid sodium hydroxide traps. In the laboratory, gaseous phosgene can be conveniently metered by calibrated flow meters of stainless steel construction; electronic mass flow meters are commercially available for applications where accurate readings are required. It has been found that flow meters suitable for use with chlorine may also be used, after calibration, to meter phosgene [1].

Containers of phosgene solutions should be stored in secondary containers, and phosgene cylinders should be stored in a cool, well-ventilated area separate from incompatible materials.

In the event of skin contact, immediately wash with soap and water and remove contaminated clothing. In the case of eye contact, promptly wash with copious amounts of water for 15 min (lifting upper and lower lids occasionally) and obtain medical attention. If phosgene is ingested, obtain medical attention immediately. If phosgene is inhaled, move the person to fresh air and seek medical attention at once.

In the case of an accidental release of phosgene gas, such as from a leaking cylinder or associated apparatus, evacuate the area and eliminate the source of the

leak if this can be done safely. Remove the cylinder to a fumehood or remote area if it cannot be shut off. In the event of a spill of a phosgene solution, soak up the solution with a spill pillow or absorbent material, place in an appropriate container, and dispose of properly. Full respiratory protection and protective clothing will be necessary in the event of a spill or release in a confined area.

Excess phosgene and waste material containing this substance should be immediately deactivated in the hood by treatment with ethanol or ethanolic ammonia. *Aqueous solutions of phosgene* should be treated in the fume cupboard with an excess of 10% aqueous ammonia (or 15% sodium hydroxide solution), and allowed to stand until all the phosgene has been neutralized before running to drain. Solutions of phosgene in water-immiscible solvents should be destroyed with ethanolic ammonia. Decontamination of rubber tubing should be carried out by immersion in aqueous ammonia prior to disposal in sealed plastic bags. An efficient way to destroy phosgene gas is to catalyze the hydrolysis reaction on a bed of charcoal over which an excess of water is passing.

To ensure accurate compliance with regulations concerning the laboratory handling of phosgene and the corresponding safety procedures, it is obligatory to consult the national legislations on this matter, such as the recent Toxic Substances Control Act (TSCA) of the United States, and the various National Laws based on the EEC Sixth Amendment (Dangerous Substances). The legislation and codes of practices affecting compressed gases in general (for the United Kingdom) have been described by the British Compressed Gases Association [1].

8.1.2
Handling and Monitoring of Phosgene in Large-Scale Chemical Processing Plants

Comprehensive safety precautions are essential in facilities in which **phosgene** is manufactured, stored, or processed in any way. Techniques to control occupational exposure to phosgene must be assessed, and major accidents should be prevented, literally, at all costs. These requirements are enforced by legislation in most industrial nations. Although the recommended practices are, in part and of necessity, of a general nature for working with toxic gases, it is imperative that these, or similar, practices are followed when working with phosgene. Personnel should be protected from liquid phosgene by protective clothing that is impervious to **phosgene**, and exposure to the gas in concentrations above the recommended limits should be prevented by the use of suitable gas masks or air respirators.

Owing to the poor warning properties of the gas to the human senses, automatic continuous monitors equipped with alarm systems are recommended. Skin and eye contact with phosgene should be avoided, but contaminated clothing should be removed immediately and decontamination effected by washing. Emergency showers should be provided in any facility in which phosgene is stored, used, or manufactured [9]. Personnel engaged in the handling of phosgene should be trained to recognize its odor and instructed in the application of protective measures and first aid and emergency procedures [10, 11]. In particular, personnel

should be made to appreciate the delayed effects following potentially lethal exposures to **phosgene**.

Requirements for safety and environmental protection in industrial processing using **phosgene** supplied *on demand of the consumer* by the implementation of 'dynamic' reactors for its production have been reported (see Section 2.1.2). The manufacture and delivery of phosgene to the users on demand, without intermediate storage, has made it possible to strongly reduce the quantities of phosgene contained within the plant. Confinement of the phosgene production, supply, and utilization equipment in a double envelope makes it possible to collect any leakage with ultimate destruction of the **phosgene** in specific installations [12, 13].

The following safety measures have been described for phosgene storage and handling in a plant environment [1].

- Phosgene storage and handling operations should be in a remote location from the rest of the plant.
- Phosgene storage rooms should be provided with an inspection window to permit viewing of the area without the need of entry.
- Ventilation switches and emergency protection equipment should be located outside the storage area in easily accessible locations, which would be uncontaminated in the event of an emergency.
- Where possible, phosgene should be generated on demand to avoid cylinder handling and phosgene storage.
- Phosgene gas should be used in preference to the liquid material.
- The phosgene storage area should be continuously vented to alkali scrubbers.
- A system of automatic analyzers should be employed to continuously monitor the ambient air and all phases of the operation.
- Alarms (audible, visual, and valve-closing) should be set to operate automatically when the concentration of phosgene reaches the sensored limit.
- Phosgene should be piped through a double-skinned conduit, such as a pipe within a pipe. The outer pipe should be continuously monitored for phosgene. Pipes containing phosgene should be distinctively marked.
- Where phosgene is stored in tanks, these should be of a double-shell construction. Bulk phosgene is preferably stored underground.
- Plant hardware that is exposed to phosgene should be composed of high quality stainless steel, or PTFE, as appropriate.
- An extensive preventative maintenance program should be operated to safeguard against leaks and equipment failure. Potential emission sources should be identified.
- An extensive training program should be implemented and a 'Phosgene Manual' should be available.
- Dosimeter badges should be worn by personnel who work in the phosgene area.
- An emergency/evacuation plan should be established and frequent drills executed.
- Before equipment is taken out of service, all lines must be purged of any phosgene.

8.2 Analytical Methods

The required analytical range of concentrations for the quantitative determination of **phosgene** may vary from the parts-per-trillion (ppt) level to virtually 100%. In particular, the low exposure limit value for phosgene in air recommended in some countries (e.g. Sweden, Italy, and Romania have adopted 0.05 ppm, the UK 0.02 ppm) emphasizes the requirement for sensitive, reliable, and specific methods for its detection. The following analytical methods are currently employed for the determination of phosgene:

1. Volumetric methods: acidimetry, iodometry
2. Gravimetric methods
3. Colorimetric methods: non-automatic (wet and dry techniques) and automatic
4. Argentometric methods
5. Chromatographic methods (gas chromatography and HPLC)
6. Spectrometric methods (IR, UV, MS, NMR, interferometry)
7. Light-scattering and particle detection
8. Electrical methods (electrochemical and electrical conductivity)

An important survey on the above methods is available [1]. The acidimetric method is not specific to **phosgene** and is based on reaction according to the following equation:

$$COCl_2 + 4\,[OH]^- \longrightarrow 2\,Cl^- + [CO_3]^{2-} + 2\,H_2O$$

The **phosgene** can thus be determined by a double-indicator titration, or by determining the chloride ion content of the solution.

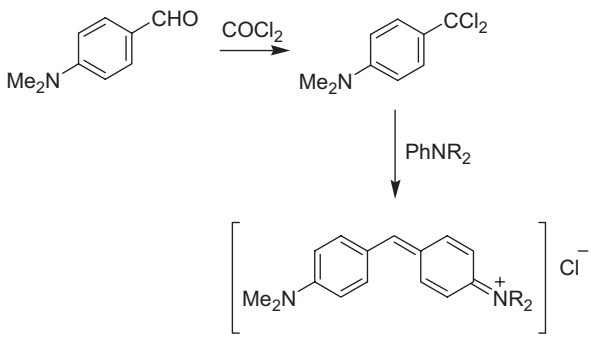
The oxidizing property of **phosgene** is employed for its determination by an iodometric technique:

$$COCl_2 + 2I^- \longrightarrow 2\,Cl^- + CO + I_2$$

A less accurate method is based on the quantitative formation of 1,3-diphenylurea upon passage of the phosgene-containing gas into a cold, saturated, aqueous solution of aniline according to the following equation:

$$COCl_2 + 4\,PhNH_2 \longrightarrow (PhNH)_2CO + 2\,[PhNH_3]Cl$$

The wet or dry colorimetric techniques are based on the reaction of **phosgene** with Harrison's reagent (a mixture of non-aqueous solutions of 4-(*N*,*N*-dimethylamino)-benzaldehyde and diphenylamine) yielding a yellow, orange, or brown color, according to the concentration. A more marked color change (yellow to blue) on exposure to phosgene is observed when *N*,*N*-dialkylanilines are coupled to the above aldehyde.



The one-time recommended standard (NIOSH) for the analysis of **phosgene** in air was based on the use of a mixture of 4-(4′-nitrobenzyl)pyridine and *N*-benzylphenylamine in diethyl 1,2-benzenedicarboxylate solution, which produces a brilliant red color on exposure to phosgene. The absorbance of the sample solution is usually determined spectrophotometrically at a wavelength of 475 nm, with a concentration as low as 5 ppb being detectable.

Infrared spectroscopic methods are particularly suitable for the determination of **phosgene** at concentrations below the currently established threshold limit value. Measurements of low concentrations (25–500 ppb) [14] have been reported. Phosgene has strong absorption bands at 849 and 1827 cm^{-1}, but the intensity of the combination band at 1011 cm^{-1} is less than one-thirtieth of that at 1827 cm^{-1}.

8.3
Monitoring Chlorinated Equivalents of Phosgene (Triphosgene)

All solid **triphosgene** has triphosgene vapor associated with it. Phosgene color badges become colored during the initial opening of any bottle, can, or bag. Precautions should be taken when handling the solid in order to avoid the uncontrolled exposure of the operator. The safety measures should be identical to those applied for phosgene.

The occupational hygiene effect of triphosgene has not yet been fully determined. A *Consent Order* was issued because the substance may present an unreasonable risk of injury to health and a two-year, two-species bioassay test was recommended [15–18].

In the following, some recommendations are given based on the authors' experience. No responsibility is taken for any unforeseen result occurring as a consequence of applying the information contained herein. Professional advice should be sought before adopting any of the procedures described.

When solid crystalline **triphosgene** is immersed in water at ambient temperature, no significant change of pH (HCl release) occurs, and hence no decomposition into phosgene is observed. This is due to the very low solubility of triphosgene in water and the slow reaction rate. The situation is different when solvents such

as tetrahydrofuran or dioxane are used. Water miscibility with such (basic) solvents is significant, and therefore the reaction between **triphosgene** and nucleophilic water can proceed in a homogeneous liquid–liquid system. In this case, temperature and basic catalysts play important roles in accelerating decomposition.

It is strongly recommended that a Karl-Fischer water analysis is performed on a solvent before it is used in a **triphosgene** reaction as solvents can be a source of nucleophilic water (for example, at 25 °C, the solubility of water in EtOAc is around 3.3% *w*/*w*!). Much of the ''released process phosgene'' originates from residual water. Both phosgene and triphosgene are hydrolyzed to HCl and carbon dioxide. The difference lies in the magnitudes of the reaction rate constants, **phosgene** hydrolysis being a thousand times faster (for phosgene dissolved in a liquid phase) than **triphosgene** hydrolysis. Hydrolysis of triphosgene generates phosgene. The latter reaction is considerably accelerated by the presence of bases and by an increase in temperature. Under such conditions, the phosgene produced can be released in the off-gases.

It is for this reason that in the process handling of triphosgene the reaction mixture must be stringently protected from accidental contact with water or alkali metal hydroxide solutions (warning on scrubber).

When **triphosgene** hydrolysis is occurring, one has to consider the effect of moisture on the reactivity. The bimolecular nature of the process should also be kept in mind. One has to estimate the amount of water present (i.e. water dissolved in the reaction solvent containing triphosgene) during those process stages in which triphosgene can generate phosgene. Theoretically, 18 g of water can destroy 297 g of **triphosgene**. The generated **phosgene** would then react very rapidly with excess water to give carbon dioxide and hydrochloric acid [18].

As regards the preparation of **triphosgene** solutions, i.e. dissolution of crystalline triphosgene in a solvent, and the storage of such solutions prior to reaction, any data concerning the so-called ''hold points'' and acceptable ''holding times'' of such solutions should be useful. Reaction progress is then monitored with particular emphasis on the off-gases and checking of the scrubber (indeed, the scrubber effectively becomes a second ''phosgenation reactor''). Lastly, when it comes to work-up and final hydrolysis, the product should only be separated when no trace of phosgene remains.

The standard operating procedures must always include a nitrogen atmosphere with moderate flushing (with control of the water content in the nitrogen flow).

When an experiment is performed in the laboratory (homogeneous phase or a biphasic system), **phosgene** is usually detected in the off-gassing, and in all the layers (organic, aqueous, reactor cleaning solvent, etc.) after the reaction. The organic phase can show up to 100 ppm phosgene.

In all cases, aqueous ammonia (as described above for phosgene) should be used to ''neutralize'' the **phosgene**-containing off-gases. Aqueous NaOH is much more reactive and, at higher temperatures, can decompose triphosgene violently, releasing phosgene. Higher pH does not necessarily guarantee the destruction of phosgene in the off-gases; the design of the ''destruction reactor'' is a more important question, and its downstream effluent should show 0 ppm phosgene.

No *chromogenic method* is available to qualitatively distinguish between **phosgene**, **diphosgene**, and **triphosgene** in the liquid phase, at the interface between the liquid and gas phases, or in the gas phase.

The color reaction of **triphosgene** with Harrison's reagent (a mixture of 4-(*N*,*N*-dimethylamino)benzaldehyde and diphenylamine in a non-aqueous solvent) yields a yellow to deep-orange hue, according to the concentration [19].

In the laboratory or in other small-scale operations, specific *Draeger* tubes are used to detect **phosgene**. Information on suppliers of such equipment can be found on the Internet. The *Data Sheet* for *phosgene badges* lists the following positive interferences: dust, chloroformates, cyanuric chloride, carbonyl bromide; some phosgene derivatives such as carbonates are also detected. On the other hand, acetyl chloride, oxalyl chloride, chlorine, and very high concentrations of hydrogen chloride will suppress the response to phosgene.

For the use of the *React-IR* technique to distinguish between chlorinated equivalents and to monitor **triphosgene** decomposition, see [20].

For the quantitative determination of **triphosgene**, the recommended methods are the same as those for **phosgene**:

- *Colorimetric method*: after reaction of 4-(4′-nitrobenzyl)pyridine and *N*-benzylphenylamine in diethyl 1,2-benzenedicarboxylate, exposure to **triphosgene** produces a brilliant red color.
- *Titration*: **phosgene** and **triphosgene** liberate iodine from sodium iodide in acetone.
- *Argentometric titration*: titration of the liberated chloride ions after hydrolysis.

For a quantitative determination in large-scale chemical processing, automatic gas level sensors, such as the OLDHAM-GZ-ARRAS (France) M/42, having a four-channel programmable alarm system, are used [19]. Electrochemical phosgene detectors (0.1–3.0 ppm) and handy pumps with phosgene tubes (AUER GAS-TESTER II) (from 0.1 ppm) are also employed.

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9
Outlook

Where will the chemistry of phosgenation reactions go?

Contradictions about phosgene chemistry will endure, albeit in another sense and manner as outlined in Chapter 1. As we see it, there will probably be four, partially contradictory, pathways.

Methods and processes for the supply of **phosgene** *on demand of the consumers* will be developed further. In this way, the present gap of providing consumers with 1–100 kg amounts of phosgene per day will be closed. This will be the field of safety phosgenation (see Sections 2.2.2.1 and 7.1.2).

The development of phosgene equivalents and substitutes is still not at an end. Phosgene equivalents with lower vapor pressures and higher TLVs remain a desirable aim, and a furtherance in the use of **triphosgene** for the same applications as phosgene is likely.

Specifically designed sustainable phosgene substitutes for specific applications will be increasingly used (like the already used **BOP**, **BDDC**, **CDC**, and **Burgess reagent**; see Chapter 4) to perform selective reactions that comply with the intrinsic (*yield, reactivity, handling, work-up*) and extrinsic (*safety, toxicity, environmental impact*) criteria set out in Chapter 6.

Fulfilment of the requirements of "*green chemistry*", such as atom-efficiency, the avoidance of waste, toxic and dangerous chemicals, better performing compounds, their biodegradability, eco-compatible solvents (H_2O, supercritical CO_2), energy reduction, and renewable materials, will be the fourth path for the future of phosgene chemistry.

Phosgene chemistry may then be renamed, or it might keep its traditional name in remembrance of a very small molecule of four atoms, with all its enormous synthetic potential and economic importance that has endured since the very beginnings of organic and industrial chemistry.

Only the future will tell what pathway(s) will be followed up.

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Appendix

Risk and Safety (R + S)-Phrases (according to European regulations, revised lastly 3/9/2002)

Risk (R)-phrases

R10	Flammable
R11	Highly flammable
R14	Reacts violently with water
R20	Harmful by inhalation
R21	Harmful in contact with skin
R22	Harmful if swallowed
R23	Toxic by inhalation
R23/24/25	Toxic by inhalation, in contact with skin and if swallowed
R24	Toxic in contact with skin
R25	Toxic if swallowed
R26	Very toxic by inhalation
R28	Very toxic if swallowed
R29	Contact with water liberates toxic gas
R34	Causes burns
R35	Causes severe burns
R36	Irritating to eyes
R36/37/38	Irritating to eyes, respiratory system and skin
R37	Irritating to respiratory system
R38	Irritating to skin
R40	Limited evidence of a carcinogenic effect
R41	Risk of serious damage to eyes
R42	May cause sensitisation by inhalation
R43	May cause sensitisation by skin contact
R44	Risk of explosion if heated under confinement
R48	Danger of serious damage to health by prolonged exposure
R50	Very toxic to aquatic organisms
R53	May cause long-term adverse effects in the aquatic environment
R61	May cause harm to the unborn child

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Safety (S)-phrases

S3	Keep in a cool place
S7	Keep container tightly closed
S8	Keep container dry
S9	Keep container in a well-ventilated place
S15	Keep away from heat
S16	Keep away from sources of ignition – No smoking
S22	Do not breathe dust
S23	Do not breathe gas/fumes/vapour/spray (to be specified by the manufacturer)
S24	Avoid contact with skin
S26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
S27	Take off immediately all contaminated clothing
S28	After contact with skin, wash immediately with plenty of … (to be specified by the manufacturer)
S36	Wear suitable protective clothing
S36/37/39	Wear suitable protective clothing, gloves and eye/face protection
S37	Wear suitable gloves
S38	In case of insufficient ventilation wear suitable respiratory equipment
S39	Wear eye/face protection
S43	In case of fire use … (indicate the precise type of fire-fighting equipment)
S45	In case of accident or if you feel unwell seek medical advice immediately (show the label)
S60	This material and its container must be disposed of as hazardous waste
S61	Avoid release to the environment. Refer to special instructions/safety data sheet

Subject Index

Note on index entries:
– Boldface page numbers refer to main section(s) of interest;
– *(P)* refers to typical procedures for compound preparation.

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