Studies in Organic Chemistry 34

PREPARATIVE ACETYLENIC CHEMISTRY

SECOND EDITION

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Preface

"Preparative Acetylenic Chemistry", the first book of a series of laboratory manuals containing experimental procedures that are based upon the author's personal bench experience, appeared in 1971. The book has been frequently used by students during practical courses and their research period in our laboratory. Several procedures have been carried out one or more times by persons with a relatively limited bench experience. Discussions with them about their results were highly useful and have in many cases resulted in modified procedures or descriptions. These have been included in the present edition which is considerably different from the first one, *e.g.*:

1. A number of procedures have been omitted or replaced by others.
2. The subdivision and titling of the chapters and experiments have been changed.
3. Some new and attractive methods, for example eliminations under phase-transfer conditions and couplings under the influence of zero-valent palladium compounds, have been included.
4. In a number of cases additional experiments have been described in order to give a more complete picture of the scope of the concerned methods.
5. The indexes of the first edition have been replaced by a type-compound-method index.

The author is indebted to Mrs. Y.A. Heus-Kloos and Mr. D.M. Grove for helpful suggestions during the preparation of this edition.

Financial support and gifts of chemicals by AKZO-Chemie (Deventer), Andeno (Venlo), Chemetall GmbH (Frankfurt am Main, F.R.G.), Diosynth (Oss), DSM (Geleen), Quest International (Naarden) and Shell (Amsterdam) are gratefully acknowledged.

L. Brandsma, January, 1988

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Chapter I
General Practical Information

1. Introduction

With many chemists the word acetylenes evokes associations with vigorous explosions: they remember the stories with which their high-school chemistry teacher illustrated his lessons on the difference in stability of acetylenes and alkanes or alkenes. Indeed, accidents have occurred during welding with acetylene from inadequately equipped cylinders. Furthermore, attempts in the laboratory to prepare mono- and dichloroacetylene in an undiluted state are extremely risky and the structure of highly unsaturated, unsubstituted compounds such as HC≡CC≡CC≡CH, is in itself a sufficiently strong warning to be cautious during preparation. It is not justified, however, to consider acetylenic chemistry as the playground of reckless dare-devils*.

An important aim of this book, which complements a large number of books and reviews [3-32], is to make organic chemists familiar with the experimental methods (some being unconventional) that give access to a versatile and interesting class of compounds.

2. Laboratory Equipment and Techniques for the Procedures in this Book

2.1 General

By far the most of the syntheses described in this book are carried out in the **standard apparatus (fig. 1)**, a round-bottomed three-necked flask, equipped with a combination of a gas inlet and a dropping funnel, a mechanical stirrer and a thermometer-gas outlet combination. A flask with **slanting necks (fig.-1)**** is **extremely impractical** for the following reasons. First it is very difficult to place the thermometer (or a gas inlet tube) in such a position that contact with the stirrer during its motion is avoided. Secondly, in some reactions it is essential that the reagent added from the dropping funnel is distributed immediately over the liquid in the reaction flask and does not flow along the glass wall before it comes into contact with the bulk of the solution (*e.g.* Chap. IV, exps. 5 and 8).

In most procedures described in this book, stirring is carried out mechanically, using a **glass rod** (diameter not less than 5 mm) ending in or connected to a **paddle** (*e.g.* a piece of

*Many teachers in chemistry seem to know better what one should not do than what one has to do in order to carry out a synthesis in a successful way.

**Compare also H.J.E. Loewenthal, "A Guide to the Perplexed Organic Experimentalist", Heyden, 1978.

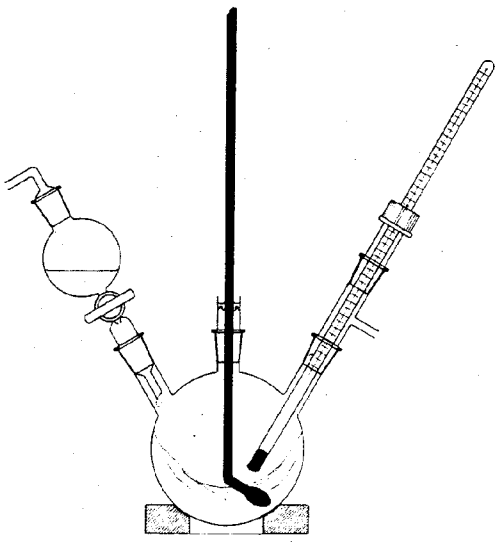


fig. -1 A negative start

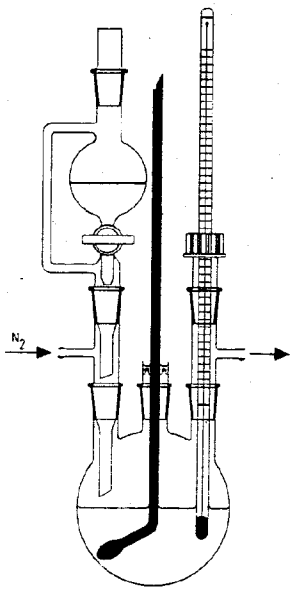


fig. 1

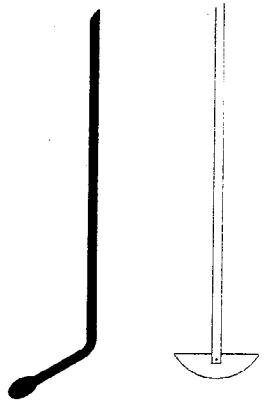


fig. 2

fig. 3

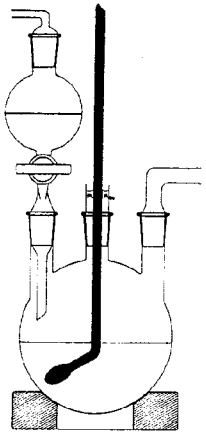
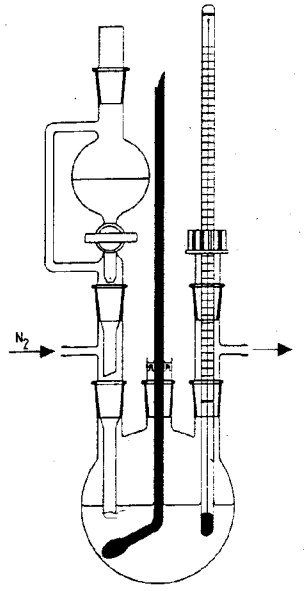


fig. 4



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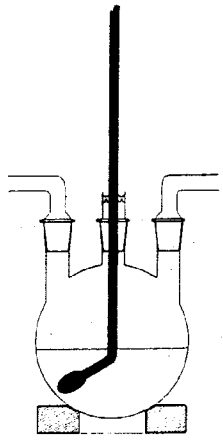

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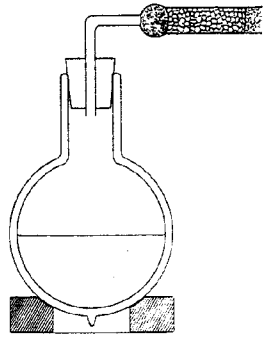


fig. 7

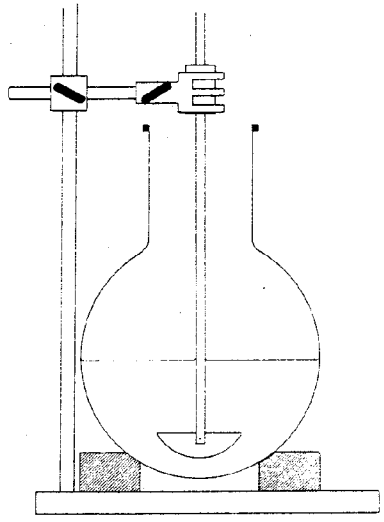


fig. 8

fig. 10

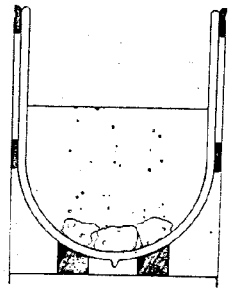


fig. 9

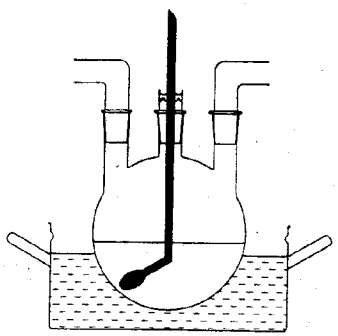


fig. 12

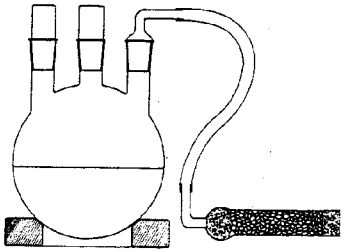


fig. 11

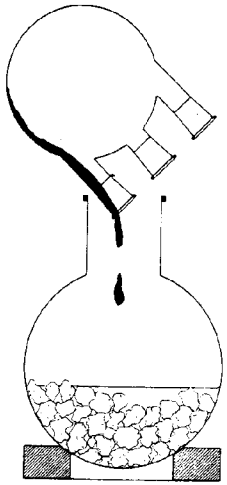


fig. 13

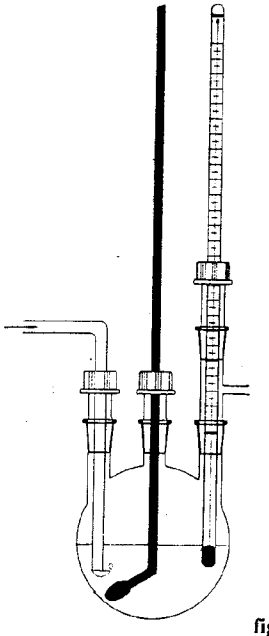


fig. 16

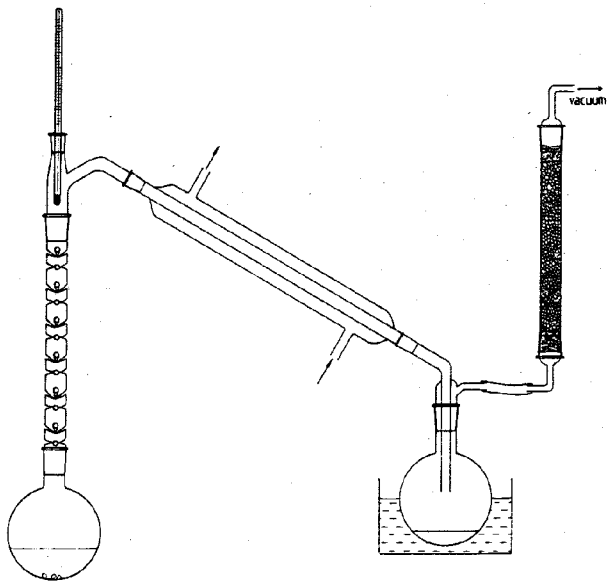


fig. 14

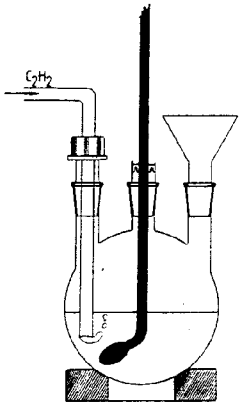


fig. 15

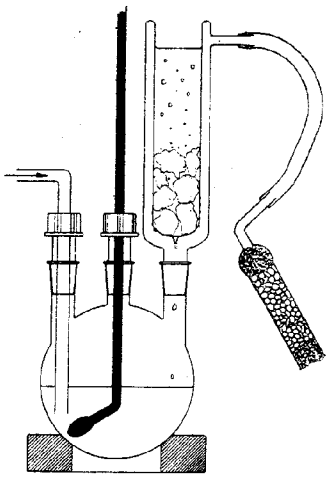


fig. 17

the rod that is flattened, surface ~1 cm^2) with the upper side of the rod being connected to the stirring motor. The stirring rod passes through a ground glass-joint with a gas-tight O-ring seal (**fig. 2**). This hockey-stick like stirrer does not suffice when the reaction mixture has a high "viscosity" (*e.g.* thick suspension) or when the volume to be stirred is larger than 3 l. In such cases a **metal rod** equipped with a **chromium-plated paddle** may be used (**fig. 3**).

The various types of reaction flasks and auxiliary equipment are shown in the **figs. -1 to 17** and/or described in the experiments.

2.2 Reactions in Liquid Ammonia

A large number of acetylenic compounds can be prepared with excellent results using **anhydrous liquid ammonia** as the solvent. The conversions can be performed under normal pressure at the boiling point (-33°C) of ammonia or, if necessary, at a lower temperature. The usual apparatus is a **three-necked round-bottomed flask,** equipped with a **mechanical stirrer (see fig. 4).** The liquid ammonia is obtained directly from the cylinder which, if it is equipped with a dip tube, can remain in an upright position during tapping or otherwise is placed on a stand at an angle of about 30° to the floor with the tap pointing down (see A.I. Vogel, A textbook of Practical Organic Chemistry, 4th ed. (Longmans), p. 98).On opening the tap, liquid ammonia flows through the plastic tube connected to the cylinder. Since this tube may contain some moisture, a volume of 100 to 150 ml should first be allowed to flow into the hood before the end of the tube is placed into one of the open necks of the reaction flask. Several liters of liquid ammonia can be obtained within a few minutes. The losses due to evaporation during tapping are relatively small (20% or less). After the required volume of ammonia has been obtained, the tap is closed and the necessary equipment is **immediately** placed on the flask (or plugs of cotton wool are temporarily placed on the necks). In view of the possibility of splashing or frothing while carrying out the synthesis, the flask should **never** be filled more than 50% (preferably only ~35%). It is completely unnecessary to fill the flask by condensing ammonia into it, unless extremely careful working conditions with small amounts of NH_3 are required or the water content of the ammonia is greater than 0.2%. The **water content** of the liquid ammonia is readily checked. This can be done semi- quantitatively by gently stirring in small pieces of alkali metal (~0.1 g of Na or 0.02 g of Li) preferably under a nitrogen atmosphere. The next piece of metal is added after the blue colour has disappeared completely. The weight of the metal required to obtain a persisting blue colour, gives a fairly good impression of the water content. Too large an amount of water in the ammonia may give rise to frothing during the preparation of Li- or NaC≡CH from the alkali metals and acetylene: the solutions of the alkali acetylides in these cases are turbid due to the presence of alkali hydroxide.

Introduction of **alkali metal** into the flask containing liquid ammonia is most easily done with a **powder funnel,** which temporarily replaces a part of the equipment. The cleaned lumps of metal are held above the funnel and cut into pieces (for handling alkali metals see our previous book "Preparative Polar Organometallic Chemistry", Springer-Verlag, 1987.)

Thanks to the relatively high heat of evaporation of ammonia, many reactions can be carried out at its **boiling point, -33°C.** The use of a dry ice-acetone reflux condenser is absolutely unnecessary. Losses due to evaporation are easily compensated by adding ammonia from the cylinder. The rate of evaporation can be limited by insulating the flask with cotton wool; the ice which forms on the outside of the flask as a result of condensation can, to some extent, have a similar function.

If a **volatile compound** is to be prepared in liquid ammonia, it is desirable to cool the flask to a temperature **below the b.p.** (-33°C) of ammonia. To prevent introduction of air and moisture during cooling, nitrogen is led through the apparatus (see **fig. 1**).

In the case of **slow reactions** it is inconvenient trying to maintain a sufficiently low temperature throughout the conversion in a normal flask, even with the use of a dry ice-acetone condenser. It is much easier to allow the reaction to proceed in a **round- bottomed Dewar flask (fig. 7,** a flask with an evacuated space between the two walls). The rate of evaporation is reduced to a minimum (10 g/h or less) if the inner wall is covered with a silver mirror (covering the flask with aluminum foil is a good alternative). An example of a reaction in a Dewar flask is the conversion of LiC≡CH with oxirane to $HC{\equiv}CCH_2CH_2OLi$ (Chap. III, exp. 23). The ammoniacal solution of LiC≡CH is first prepared in the usual apparatus and then transferred (by pouring) into the Dewar flask. The oxirane is subsequently added over a short period and a stopper with a drying tube is placed on the flask. After 24 h the solution is poured into a normal round-bottomed flask and the ammonia is removed by evaporation.

This book contains a few procedures that are preferably carried out in a big (5-10 l) **round-bottomed flask with one, wide neck (fig. 8).** The stirring rod is then placed centrally and the reagent is added portion-wise through the neck.

If, during the addition of a reagent **contact with ammonia vapour has to be avoided,** the reagent is added through a tube ending a few cm above the surface of the liquid ammonia, while a vigorous stream of **nitrogen** is passed through the tube **(fig. 5).** Relatively small amounts may also be introduced by means of a syringe, being careful to keep the injection needle a few cm above the surface of the liquid.

2.3 Reactions in Other Solvents

Several acetylenic derivatives are prepared by dehydrohalogenation of vicinal dibromo compounds, which are obtained by adding bromine to olefinic compounds.

Addition reactions of halogens to double bonds are usually carried out in carbon tetrachloride. Textbook knowledge about radical substitutions makes some chemists hesitant in using **chloroform** ($CHCl_3$) or **dichloromethane** (CH_2Cl_2), which in fact are easily removable substances. Halogenation of $CHCl_3$ and CH_2Cl_2 only occurs under forcing conditions, so that addition reactions with Br_2 and even Cl_2 can be carried out in CH_2Cl_2 (with Cl_2 below 0°C) if they are sufficiently fast. The use of **diethyl ether** in additions of Br_2 to olefins may be advantageous, because in many cases removal of the ether before carrying out the subsequent reaction is not necessary.

In many reactions with organolithium- or Grignard intermediates **tetrahydrofuran** has distinct advantages over diethyl ether, as the solubility in THF of these intermediates is generally much better (see Table I, p. 37).

For the alkylation of metallated acetylenes, diethyl ether and tetrahydrofuran are unsuitable solvents, unless a certain amount of dimethylsulfoxide **(DMSO)** or hexamethylphosphoric triamide **(HMPT)** is added. Alkylations in liquid ammonia with higher alkyl bromides are also slow, though addition of DMSO or HMPT followed by evaporation of (part of) the ammonia in most cases gives rise to a smooth conversion. For methods of **purifying solvents,** one should consult our previous book [1, Chapter I].

2.4 Cooling and Heating Baths for Reactions

The choice of the heating or cooling bath is determined by the temperature range in which the reaction is to be carried out, the sensitivity of the reaction to deviations from this range, and the desired addition rate of the reagent. A **bath with ice water** seems the likely choice in the case of reactions that are to be carried out in the region of 0°C (e.g. conversions of alcohols into tosylates by addition of powdered KOH to a mixture of ROH and tosyl chloride in Et_2O). However, if an ice bath is used, the addition of KOH can be carried out only slowly, since otherwise the temperature of the mixture may become considerably higher than 0°C; this could result in either hydrolysis of the tosylate by hydroxide, or elimination of water. A **bath with dry ice and acetone** provides a greater flexibility in controlling the temperature. For a fast reaction, carried out at about -70°C, cooling in a **bath with liquid N_2** (-190°C) has the advantage that the addition of the reagent can be carried out in a very short time.

For **heating reaction mixtures** up to temperatures of 70°C, an electrically heated **water bath** seems most practical. For heating at higher temperatures, an **oil bath** (heated electrically or with a flame) is recommended. It should be pointed out, however, that any system whereby the reaction mixture is heated indirectly is not foolproof: in the case of a threatening emergency situation (*e.g.* a sudden rise in temperature of the reaction mixture) the bath has to be removed, which may take several seconds. Although one may not be easily convinced, we can assure the reader that in many cases it is much better to heat the reaction flask with an **open flame** (cautiously moving the flame under the flask*). A water bath should always be at hand to neutralize a sudden rise in temperature.

A practical container for holding coolants is the cylindrical **Dewar vessel (fig. 9,** diameter ~15 cm, height ~20 cm). For reactions in flasks with a volume greater than 1 l, the cooling liquid may be **placed in a pan** which is insulated by straw or cotton wool contained in a **larger pan (fig. 10).**

*For chemists in some industrial laboratories this proposal is irrelevant, since there is no gas for heating.

2.5 Frothing During Reactions in Liquid Ammonia

During some conversions in this solvent **frothing** may occur, especially in the case of thick suspensions of alkali acetylides and also when alkali hydroxide is present (if the ammonia contains much water). This can result in the loss of part of the reaction mixture! The reaction flask should therefore never be more than **half-filled. Frothing** can be **suppressed** by adding small amounts of **diethyl ether** (a flask containing 50-100 ml should be at hand). If, in connection with the volatility of the product being prepared, this addition is not allowed, frothing can be suppressed effectively by **lifting the stirring motor,** so that the paddle of the stirrer rotates just below the surface of the reaction mixture. Another method is to spray some liquid ammonia onto the frothing reaction mixture.

2.6 The Work-up and Isolation

The choice of methods for working up and isolation is the result of careful consideration, taking into account *inter alia* the thermal stability and the volatility of the product. In many procedures water (or ice) is added after the conversion is terminated. Salts and water-soluble (co-)solvents such as DMSO and HMPT are separated in this manner from the product or organic solution of the product.

If the product of a reaction in liquid ammonia is **not volatile** (b.p. > 120°C/760 mmHg), the ammonia may be **allowed to evaporate** overnight or during a weekend. For this the flask is equipped with **rubber** stoppers and one outlet connected with a plastic tube to a drying tube filled with KOH pellets placed on a level with the bottom of the flask (**fig. 11**). A protective atmosphere of ammonia remains in the flask after evaporation. A **fast evaporation** is effected by placing the flask in a **water bath** at **30 to 50°C (fig. 12,** not applicable in the case of frothing!). In the case of volatile products (b.p. < 100°C) evaporation of the ammonia results in considerable losses. The problem of isolation is effectively solved by adding an extraction solvent to the reaction flask and subsequently **pouring** the mixture (cautiously) onto **crushed ice** in a large, wide-necked, round-bottomed or conical flask **(fig. 13).** For examples see Chap. III, exps. 1 and 3.

In a number of elimination reactions carried out in liquid ammonia, an **alkali alkynylide** is formed. In these cases the ammonia has to be removed completely or partly by **evaporation** before the acetylene is liberated by hydrolysing the reaction mixture. The heat produced in the remaining solid mass by this hydrolysis must be "neutralized" efficiently and this is realized by adding a **large amount of finely crushed ice over a very short period.** For this reason, the reaction must be carried out in a **wide-necked** round-bottomed flask **(fig. 8).** Examples are the preparation of $HC{\equiv}COR$ and $HC{\equiv}CCH(OR)_2$ (Chap. IX, exps. 10 and 11).

If the b.p. of the product is **higher than 110°C/760 mmHg,** a **volatile extraction solvent** (diethyl ether or pentane) is generally used. Compounds with a b.p. > 130°C/760 mmHg can be isolated by removing this solvent in a water-pump vacuum and subsequently distilling the remaining liquid. Compounds with b.p. up to ~160°C/760 mmHg can be partly swept along

during the removal of the extraction solvent on a rotary evaporator if the evaporation is carried out too fast (bath temperature > 30°C). If the thermal stability of the product allows it, the greater part of the ether or pentane can first be distilled off at normal pressure through a Vigreux column. The remaining liquid is then distilled in a "partial" vacuum (50-100 mmHg).

Particularly in the cases of hydroxyacetylenes, the question "How many extractions with Et_2O have to be carried out?" may arise. The following practical tip may be useful. Take a small (2 ml) sample from the extract with a Pasteur pipet and allow the solution to flow along a glass stopper. Further extraction is superfluous when, after the ether has evaporated, no residue is visible on the ground glass.

Compounds with **b.p.'s between 20 and 110°C/760 mmHg** may be extracted with a **high-boiling solvent** (e.g. a fraction of petroleum ether with b.p. > 170°C/760 mmHg). To isolate the product, the extract is gradually heated in a distillation apparatus **(fig. 14)** evacuated at 10-20 mmHg. The volatile compound is collected in a strongly (< -60°C for volatile compounds) cooled **single** receiver. Evacuation and heating are terminated when some of the solvent begins to reflux in the head of the column. If the product is sufficiently stable, the contents of the receiver are redistilled under atmospheric pressure. In the case of unstable products, the above procedure is repeated, otherwise redistillation in a partial (100-200 mmHg) vacuum may carried out.

In some procedures with **THF as a solvent** it is desirable or even necessary to **remove** this solvent as completely as possible, in order to facilitate the isolation of the product in a pure state. A good example is the preparation of $Me_3SiC{\equiv}CH$ from $HC{\equiv}CMgBr$ and Me_3SiCl in THF (Chap. VI, exp. 1). The b.p. of the silylacetylene is only 10° lower than that of THF. Since a satisfactory distillative separation would take many hours using an extremely efficient column, it is much more effective to remove the greater part of the THF by repeated washing with a cold aqueous solution of ammonium chloride. Subsequent distillation can then be carried out in a few hours, giving pure $Me_3SiC{\equiv}CH$.

2.7 Recovery of Compounds After Long Periods of Storage

Acetylenic compounds may undergo deterioration during storage. Decomposition of the residue which remains after redistillation can then sometimes lead to an explosion. A method to minimize the danger of vigorous decomposition is to add an amount of paraffin oil prior to distillation. The residue then remains as an emulsion or dispersion in the oil after the compound has been distilled off. It is further advisable to carry out the distillation *in vacuo* even when the compound itself has a reasonable thermal stability. The apparatus depicted in **fig. 14** can be used for this purpose.

2.8 Foaming During Distillation

Formation of foam during distillation (especially in the case of amines and compounds with a long carbon chain) can be prevented to some extent by adding a drop of anti-foaming liquid before distillation. In some cases foaming can be suppressed by completely immersing the distillation flask in the liquid of the heating bath, or by heating the upper part of the distillation flask with an open flame. If attempts to suppress foaming are unsuccessful, the liquid should be distilled from a considerably larger flask.

3. Abbreviations and Some General Remarks

The following abbreviations are used in this book for some solvents and reagents:

Dimethylsulfoxide	DMSO
Hexamethylphosphoric triamide, $(Me_2N)_3P{=}O$	HMPT
Diethyl ether	Et_2O
Tetrahydrofuran	THF
Tetramethylethanediamine, $Me_2NCH_2CH_2NMe_2$	TMEDA
n-Butyllithium	BuLi
Potassium *tert*-butoxide	*t*-BuOK (refers to the commercially available base, not complexed with *t*-BuOH)
Lithium diisopropylamide	LDA

Purities of the end products in the procedures are generally > 95%. The boiling points given refer to small intermediate fractions.

"Vigorous stirring" means: vigorous agitation of the reaction mixture.

Detailed information about the use, handling and disposal of strongly basic reagents and alkali metals is given in Chapter I of Preparative Polar Organometallic Chemistry, Vol. I [1].

Various **organolithium compounds** are available today in technical amounts; information about **handling** the material is supplied by **Chemetall GmbH,** Reuterweg 14, D-6000 Frankfurt am Main 1, F.R.G.

Chapter II
Metallation of Acetylenes

1. Monometallation of Acetylenes with a Terminal Triple Bond

The preparation of many acetylenic derivatives proceeds *via* metallated acetylenes, RC≡CM (M = Li, Na, K, MgX). These are generated by abstracting the ethynyl proton in RC≡CH with a strongly basic reagent or a Grignard reagent, usually C_2H_5MgBr. The most frequently applied bases are alkali amides in liquid ammonia or alkyllithium in Et_2O or THF. Although lithium dialkylamides can be applied instead of alkyllithium, their use has no special advantage in most cases. An exception is the generation of the carbenoid $LiC{\equiv}CCH_2Br$ from propargyl bromide and lithium diisopropylamide (LDA). Butyllithium and methyllithium are unsuitable as a reagent for the deprotonation, as Br/Li exchange is the predominant reaction [2].

$$RC{\equiv}CH + MNH_2 \longrightarrow RC{\equiv}CM + NH_3 \ (M = Li, Na, K)$$
$$RC{\equiv}CH + R'Li \longrightarrow RC{\equiv}CLi + R'H$$
$$RC{\equiv}CH + C_2H_5MgBr \longrightarrow RC{\equiv}CMgBr + C_2H_6$$
$$HC{\equiv}CCH_2Cl + R'Li \longrightarrow LiC{\equiv}CCH_2Cl + R'H$$
$$HC{\equiv}CCH_2Br + LDA \longrightarrow LiC{\equiv}CCH_2Br + HDA$$

Since the bases used for the metallation of the acetylenes are much stronger (in a thermodynamic sense) than the acetylides, the deprotonations are essentially complete, a condition that has to be met for most functionalization reactions. Some ethynylations form an exception. Ethynylcyclohexanol, for example, can be obtained in yields greater than 90% by adding cyclohexanone to a suspension of potassium acetylide (or even KOH) in THF while introducing acetylene [2]. The formation of potassium acetylide is likely to be an equilibrium:

$$HC{\equiv}CH + t\text{-BuOK} \rightleftharpoons HC{\equiv}CK + t\text{-BuOH}$$

$$HC{\equiv}CK + >C{=}O \rightleftharpoons HC{\equiv}C\text{-}\underset{|}{\overset{|}{C}}\text{-}OK$$

The metallation of acetylenes with alkyllithium is generally an extremely fast reaction, even at temperatures in the region of -80°C and in Et_2O, a solvent of low polarity. The same holds true for the reaction between acetylenes and alkali amides in liquid ammonia. However, in contrast, the formation of acetylenic Grignard derivatives from RC≡CH and C_2H_5MgBr in Et_2O or THF does not proceed instantaneously. Completion of the reaction between $C_4H_9C{\equiv}CH$ and C_2H_5MgBr in Et_2O at 35°C, for example, takes at least 1 hour, and in THF, at the same temperature, at least 15 min (at "preparative" concentrations of the order of

0.5 to 1 mol/l). The deprotonation by the Grignard reagent nicely reveals the differences in kinetic acidity of the various types of acetylenes. 1,3-Diynes, RC≡CC≡CH, and the hetero-substituted acetylenes ROC≡CH, RSC≡CH and $Me_3SiC{\equiv}CH$ are all metallated within 15 minutes at temperatures between 0 and 10°C with C_2H_5MgBr in THF [2]. Inductive effects (1,3-diynes or $C_2H_5OC{\equiv}CH$) or other effects ($C_2H_5SC{\equiv}CH$, $Me_3SiC{\equiv}CH$) may explain the increased acidity.

Mono-metallation of acetylene in organic solvents is only possible under special conditions. If acetylene is introduced into a solution of BuLi in Et_2O or THF at 0°C or higher temperatures, a fine suspension of LiC≡CLi is formed immediately and irreversibly. Ammonia or other amines ($H_2NCH_2CH_2NH_2$ [33], TMEDA [2]) and, to a lesser extent lithium bromide [47] and THF [34], stabilize the monolithium compound. Thus, the reaction of acetylene with BuLi.TMEDA in a THF-hexane mixture at low temperature gives a clear solution of LiC≡CH (presumably complexed to TMEDA), which gives excellent yields of carbinols HC≡CCH(OH)R in the reaction with aldehydes RCH=O [2]. Experimentally, this method of preparing LiC≡CH is simpler than that of Midland, whereby a BuLi solution is slowly added to a strongly cooled solution of acetylene in THF [34].

The Organic Syntheses procedure [35] for the preparation of HC≡CMgBr in THF requires careful experimentation: a solution of C_2H_5MgBr in THF is slowly added to a solution of acetylene in THF which is kept saturated with acetylene by continuously introducing this gas. To prevent disproportionation of HC≡CMgBr into BrMgC≡CMgBr, the temperature should be carefully kept below 30°C. We found [2] that direct introduction of acetylene into a concentrated solution (>1 mol/l) of C_2H_5MgBr is not a reliable method for preparing HC≡CMgBr. The formation of BrMgC≡CMgBr, which sometimes starts suddenly, seems to be an auto-catalytic process. However, it is possible to apply the normal order of addition with more diluted Grignard solutions, keeping the temperature below 20°C.

Preparation of BrMgC≡CMgBr and LiC≡CLi is carried out by simply introducing acetylene into a solution of C_2H_5MgBr in THF (above 40°C) and BuLi in Et_2O (above 0°C) respectively (compare [36]).

Solutions of LiC≡CH and NaC≡CH in liquid NH_3 are mostly prepared by the so-called titration method, which involves controlled addition of pieces of metal to boiling ammonia while introducing acetylene. The blue colour of the dissolved metal serves as an indicator. This method is also applicable in the case of homologues, but is less attractive for economical reasons (one third of the acetylene is reduced to ethene). Derivatization of solutions of HC≡CM obtained from MNH_2 or M and acetylene, in most cases gives only minor amounts of disubstituted acetylenes RC≡CR, so it is inferred that di-metallated acetylene $^-C{\equiv}C^-$ occurs at best in only very small concentrations in liquid ammonia.

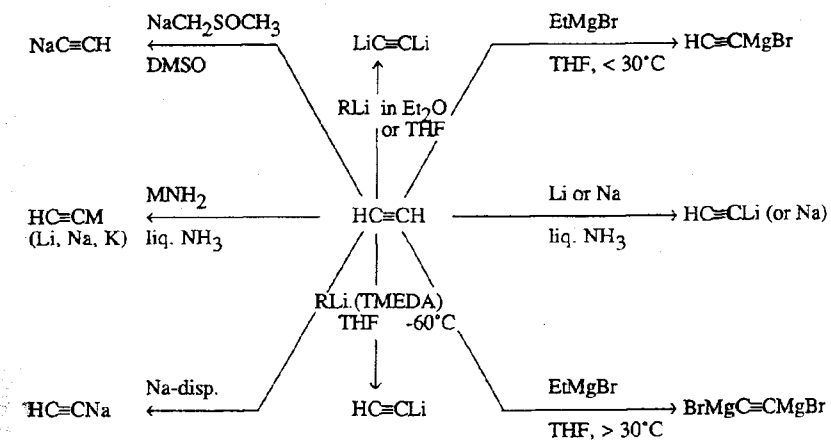
A solution of NaC≡CH in DMSO may be prepared by reacting acetylene with dimsyl sodium (prepared from NaH and DMSO) in DMSO [39], other acetylenes can in principle be metallated in a similar way. The kinetic stability of $NaC{\equiv}CCH_2R$ in DMSO is limited, however. At somewhat elevated temperatures a slow isomerization to $CH_3C{\equiv}CR$ occurs, whereby DMSO acts as the proton source [37].

$$RCH_2C{\equiv}\bar{C} + CH_3SOCH_3 \rightleftharpoons RCH_2C{\equiv}CH + \bar{C}H_2SOCH_3 \rightleftharpoons R\bar{C}HC{\equiv}CH \longleftrightarrow$$

$$RCH{=}C{=}\bar{C}H \longrightarrow RCH{=}C{=}CH_2 \longrightarrow R\bar{C}{=}C{=}CH_2 \longleftrightarrow RC{\equiv}C\bar{C}H_2 \longrightarrow RC{\equiv}CCH_3$$

Sodium acetylide has also been prepared from acetylene and a sodium dispersion in an inert solvent at elevated temperatures [38]. This method seems more suitable for industrial application, since preparation of a sufficiently fine dispersion is not easily realized with the usual laboratory means.

Summarizing, the following methods are available for the preparation of monometallated and dimetallated acetylene:



For solubilities of metallated acetylenic compounds see Table 1 on page 37.

2. Side- and Subsequent Reactions

Mono-metallation of most simple acetylenic compounds in organic solvents can be accomplished without complications. The same holds for reactions of RC≡CH with alkali amides in liquid ammonia. However, $HC{\equiv}CSiR_3$ and $HC{\equiv}CSnR_3$ cannot be metallated in this way, because the bonds between C and Si and between C and Sn are cleaved. HC≡CSeR and $HC{\equiv}CPR_2$ disproportionate into HC≡CH and RSeC≡CSeR or $R_2PC{\equiv}CPR_2$, respectively, under the influence of alkali amides [40,102].

The metallation of 3,1-enynes and 1,3-diynes with butyllithium requires careful experimentation, because dilithiation (and in the case of the enynes subsequent dimerization) occurs when the base is present in excess [2,41]:

$$RCH_2CH{=}CHC{\equiv}CH \longrightarrow RCH_2CH{=}CHC{\equiv}CLi \xrightarrow{(1)} RCH(Li)CH{=}CHC{\equiv}CLi \xrightarrow{(1)} \text{dimer.}$$

$$RCH_2C{\equiv}CC{\equiv}CH \longrightarrow RCH_2C{\equiv}CC{\equiv}CLi \longrightarrow RCH(Li)C{\equiv}CC{\equiv}CLi$$

In liquid ammonia with alkali amides, or in Et_2O or THF with lithium dialkylamides, these complications do not occur, because these bases are considerably weaker than BuLi.

Vinylacetylene, $H_2C{=}CHC{\equiv}CH$, undergoes a fast oligomerization if it is treated with a slight excess of BuLi [1].

$$H_2C{=}CHC{\equiv}CH \longrightarrow \underset{(1)}{H_2C{=}CHC{\equiv}CLi} \xrightarrow{BuLi} BuCH_2CH(Li)C{\equiv}CLi \xrightarrow{(1)}$$

$$BuCH_2\underset{|}{C}HC{\equiv}CLi \quad \underset{CH_2CH(Li)C{\equiv}CLi}{} \quad \rightarrow \cdots\cdots \rightarrow \cdots\cdots \rightarrow \text{oligomers}$$

This process can be avoided if the solution of BuLi is cautiously added to a small excess of vinylacetylene. Alkali amides or lithium dialkylamides do not cause such an oligomerization.

Treatment of "skipped" enynes $HC{\equiv}CCH_2CH{=}CHR$ with alkali amides presumably will lead to extensive isomerization into $^-C{\equiv}CCH{=}CHCH_2R$. With alkyllithium bases inverse addition has to be applied to avoid dimetallation. This isomerization reaction is likely to be even more serious in the case of the diynes $HC{\equiv}CCH_2C{\equiv}CR$, since the CH_2-protons have kinetic acidities comparable with that of the ethynyl proton.

3. Dimetallated Acetylenes

Lithiated 1-alkynes can be metallated relatively smoothly in the 3-position, using an extra equivalent of butyllithium. The efficiency of the dimetallation may be at least 90%, as can be concluded from the excellent results of the quenching reaction with Me_3SiCl [2]:

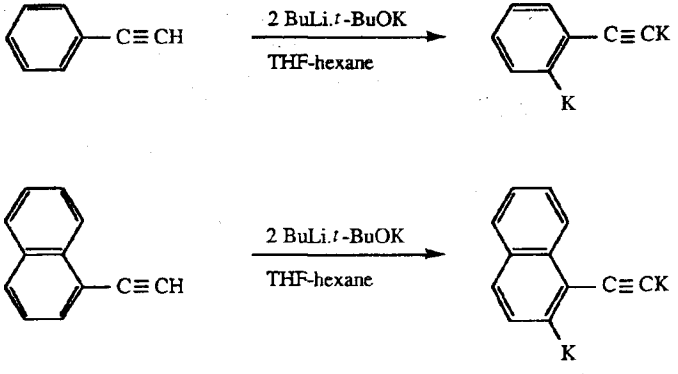
$$RCH_2C{\equiv}CH \longrightarrow RCH_2C{\equiv}CLi \longrightarrow RCH(Li)C{\equiv}CLi \xrightarrow{Me_3SiCl} RCH(SiMe_3)C{\equiv}CSiMe_3$$

R = H, alkyl, phenyl, S-alkyl, vinyl

The dilithiation can be carried out with BuLi in Et_2O or THF at temperatures varying from about -20°C for R = R'S, Ph, vinyl, to +30°C in the case of aliphatic hydrocarbons [42]. Dimetallation of the latter compounds also proceeds excellently with BuLi.TMEDA in refluxing hexane [43].

Further metallation of lithiated propargylic ethers $LiC{\equiv}CCH_2OR$, has to be carried out with the super-basic reagent BuLi.*t*-BuOK in THF; the introduction of the second metal atom using this base proceeds at a sufficient rate at temperatures in the region of -50°C. This low temperature is necessary in view of the limited stability of $MC{\equiv}CCH(M)OR$.

Abstraction of a proton at a position remote from the ethynyl group is possible if this proton is sufficiently activated. Synthetically useful examples are the dimetallations of phenylacetylene [44], 1-naphthylacetylene [2] and isopropenylacetylene [45,46].



$$HC{\equiv}CC(CH_3){=}CH_2 \xrightarrow[\text{THF-hexane}]{\text{2 BuLi.}t\text{-BuOK}} KC{\equiv}CC(CH_2K){=}CH_2$$

4. Experiments

All temperatures are internal, unless indicated otherwise

4.1 Lithium Acetylide in Liquid Ammonia (from Lithium and Acetylene)

$$2\,Li + 3\,HC{\equiv}CH \xrightarrow[-33°C]{NH_3} 2\,LiC{\equiv}CH + H_2C{=}CH_2\uparrow$$

Scale: 1.0 molar (Li).

Apparatus: 3-l round-bottomed, three-necked flask, equipped with a gas inlet tube, a mechanical stirrer and a powder funnel (fig. 15), the powder funnel is replaced by a vent as soon as the introduction of the metal is completed.

Introduction

A convenient way to prepare a solution of $LiC{\equiv}CH$ in liquid ammonia consists of adding lithium to boiling NH_3 through which acetylene is being bubbled. In this reaction ethene is also formed, but this does not react with alkali metal in liquid ammonia. The reaction with

acetylene is extremely fast and can be followed visibly, since the blue colour of the dissolved metal disappears as the reaction proceeds to completion. It seems, however, that the disappearance of the blue colour takes longer when high concentrations of metal are used. Therefore, the addition of the metal pieces should proceed at such a rate that no uniformly blue solution is formed. The dissolution of metal (and hence conversion into the acetylide) is also sluggish when concentrations of LiC≡CH are higher than 2 mol/l. This method of preparing alkali metal acetylides is called the titration method, because the blue colour indicates the progress of the conversion. Formation of MC≡CM does not occur at all in liquid ammonia.

For some syntheses the presence of an excess of dissolved acetylene in the ammonia is undesirable: in these cases, the addition of metal and introduction of acetylene in the last stage of the preparation, are carried out in a very controlled way. The best guarantee for the absence of free acetylene is a (faint) uniformly blue solution at the end. Solutions of alkali acetylide prepared from alkali *amide* and acetylene may contain appreciable amounts of acetylene.

Procedure

Liquid ammonia (1.2-1.5 l) is placed in the flask. Acetylene (note 1) is passed through the liquid with efficient stirring. The gas flow (measured with a flow meter or estimated by bubbling the gas through a washing bottle filled with paraffin oil) may vary between 0.5 and 1.5 l/min. Lithium (6.9 g, 1.0 mol) is introduced through the funnel in pieces of ~ 0.1-0.3 g at such a rate that the solution does not become uniformly blue. The metal is cut from one or more flattened pieces, which are held above the funnel (note 2). The addition of the metal is carried out over 20-30 min. When about 80% of the metal has been added, the rate of acetylene introduction is considerably diminished or stopped (provided that the solution is colourless) (note 3). The remaining metal is introduced in smaller pieces and the flow adjusted to 200-400 ml/min, and even slower when the blue colour has nearly disappeared. The gas inlet tube is immediately removed after the flow has been stopped (since there is a danger that the solution will be sucked back). The end volume of the solution is between 0.7 and 1 l. If the starting volume of the NH_3 is considerably less than 1 l, the concentration of the acetylide will become so high that the last 10 to 20% of metal will dissolve very sluggishly. Very concentrated solutions of LiC≡CH can be obtained by allowing part of the NH_3 to evaporate, or by introducing acetylene into a concentrated (thick) suspension of $LiNH_2$.

If completely anhydrous ammonia is used, the solutions of LiC≡CH and NaC≡CH are almost clear, even in the case of concentrations of 2 to 2.5 mol/l. The presence of water, for example by using poor quality ammonia, may lead to gelatinous (alkali hydroxide suspension) solutions.

Notes

1. The gas is freed from acetone, the usual solvent in the cylinders, by passing it through a number of traps cooled at -78°C (CO_2-acetone). One or two traps are sufficient if the pressure in the cylinder is high, but if it has dropped to 5 atm. or less, more traps should be used.

2. The use of pre-cut metal is dissuaded since the coating of oxide and nitride on the cutting surface makes dissolution difficult.
3. In many syntheses the presence of an excess of dissolved acetylene is favourable: the rapid flow of gas can then be maintained throughout the preparation of LiC≡CH. Stirring is not absolutely necessary in these cases.

4.2 Sodium Acetylide in Liquid Ammonia (from Sodium and Acetylene)

$$2\,Na + 3\,HC{\equiv}CH \xrightarrow[-33^\circ C]{} 2\,NaC{\equiv}CH + H_2C{=}CH_2\uparrow$$

Scale: 1.0 molar (Na).

Apparatus: see exp. 1.

Introduction and performance: see exp. 1. For handling alkali metals see ref. 1.

4.3 Sodium Acetylide in Liquid Ammonia (from $NaNH_2$ and Acetylene)

$$Na + NH_3 \xrightarrow[NH_3,\,-33^\circ C]{Fe^0} NaNH_2\downarrow + 1/2\,H_2\uparrow$$

$$NaNH_2\downarrow + HC{\equiv}CH \longrightarrow NaC{\equiv}CH + NH_3$$

Scale: 1.0 molar.

Apparatus: $NaNH_2$: fig. 6, 2 l; NaC≡CH: fig. 16; for the purification of acetylene see exp. 1, note 1.

Introduction

It is possible to prepare concentrated suspensions of sodamide in liquid ammonia of up to 3 mol/liter, and subsequent introduction of acetylene gives a very concentrated solution of NaC≡CH, which cannot be obtained by the procedure of exp. 2. The metallation of acetylene (pK ~ 25) by the strong base $NaNH_2$ (pK NH_3 ~ 34) is extremely fast. This reaction can be carried out in the presence of a small amount of triphenylmethane. As long as sodamide is still present, the red colour of Ph_3CNa is visible and the conversion is considered to be complete when this colour has definitely disappeared. Using this method, wastage of acetylene can be avoided.

Lithium acetylide can be prepared in a similar way, though stirring of concentrated suspensions of $LiNH_2$ is difficult.

Procedure

Liquid ammonia (700-800 ml) is placed in the 2-l flask. Stirring is started and ~ 400 mg (note 1) of iron(III)nitrate (hydrate) is added, followed after an interval of 10 s by 2 to 4 g of sodium. As soon as the blue colour has disappeared, the remainder of the 1.0 mol of sodium is cut in to the grey to black solution (colloidal zerovalent Fe). The conversion into $NaNH_2$ (compare ref.1) takes, as a rule, 25 to 30 min. The volume of the greyish, coarse suspension which has formed, is about 500 ml. Triphenylmethane (0.5 g) is added whereupon a reddish colour is developed. Acetylene (1 to 1.5 l/min) is introduced with efficient stirring. The suspension gradually disappears (note 2). The introduction of acetylene is stopped (removal of the inlet tube) when the red colour has disappeared. Sometimes the colour may reappear, in that case the introduction of acetylene is recontinued for a short time.

Notes:

1. If considerably more is added, it will be difficult to observe the red indicator colour of Ph_3CNa, since the solution will become very dark by the colloidal iron. In the case of smaller amounts of catalyst the conversion into sodamide takes too long.
2. Frothing can be effectively suppressed by cooling the suspension of alkali amide to a temperature just below the b.p. (-33°C) of ammonia (dry ice/acetone bath).

4.4 Conversion of Ethynyl Compounds into Solutions or Suspensions of the Alkali Acetylides in Liquid Ammonia

$$RC{\equiv}CH + MNH_2 \xrightarrow[-33°C]{NH_3} RC{\equiv}CM + NH_3 \qquad M = Li \text{ or } Na$$

Scale: 0.3 to 0.6 molar.

Apparatus: MNH_2: fig. 6, 1 l;
RC≡CM: fig. 1, 1 l (no dropping funnel is used) and fig. 4, 1 l.

Introduction

All acetylenes with a terminal triple bond are instantaneously converted into the alkali acetylides by alkali amides in liquid ammonia. For many alkylations with primary alkyl halides liquid ammonia is the solvent of choice and the functionalization with oxirane can also be carried out in it with good results. Reactions of RC≡CM with sulfenylating agents (R'SSR', R'SC≡N, $R'SSO_2R'$) or elemental sulfur, selenium or tellurium are mostly very successful in ammonia, the same holds for the preparation of RC≡CI from RC≡CM and iodine. The results of couplings with carbonyl compounds are very variable.

For the deprotonation of $R_3SiC{\equiv}CH$, $R_3SnC{\equiv}CH$, $R_2PC{\equiv}CH$, and $RSeC{\equiv}CH$, the alkali amide-ammonia combination is unsuitable because of the easy cleavage of the heteroatom-C bond, which in the last two cases leads to the formation of $R_2PC{\equiv}CPR_2$ and $RSeC{\equiv}CSeR$, respectively.

Interaction between "skipped" enynes or diynes ($RCH{=}CHCH_2C{\equiv}CH$ or $RC{\equiv}C{-}CH_2C{\equiv}CH$) and alkali amides will lead to partial or complete isomerization (into $RCH_2CH{=}CHC{\equiv}CM$ or $RCH{=}C{=}CHC{\equiv}CM$). Alkali amides in ammonia are unsuitable reagents if the compounds $RSCH_2C{\equiv}CH$ and $PhCH_2C{\equiv}CH$ are to be terminally metallated (isomerization to $RSCH{=}C{=}CH_2$ and $PhCH{=}C{=}CH_2$).

Procedure

a. Volatile acetylenes (b.p. < 40°C/760 mmHg). Addition to the alkali amides in boiling ammonia may result in considerable losses due to the acetylene being swept out with the ammonia vapour. For this reason the following procedure should be applied. The flask is equipped with a gas inlet for the introduction of nitrogen and a thermometer-gas outlet combination. The suspension of lithium or sodium amide (0.3 to 0.6 mol in 250 to 400 ml of ammonia, for the preparation of the amides, see ref.1), is cooled to -50 to -70°C (cooling in a bath with dry ice and acetone, or occasional cooling in a bath with liquid nitrogen, respectively) while introducing nitrogen. When the required temperature has been reached, the gas inlet is removed and 5-10% excess of the acetylene (undiluted if the b.p. is between ~10 and ~40°C or diluted with 20-40 ml of Et_2O or THF, if the b.p. is lower than 10°C/760 mmHg) is poured into the flask over a few seconds, while stirring vigorously. One minute after this addition the cooling bath is removed.

b. Less volatile acetylenes (b.p. > 40°C/760 mmHg). The acetylene (5 to 10% excess) is added from the dropping funnel to the stirred suspension of the alkali amide in 400 ml of boiling ammonia. The addition is carried out over about 10 min. Some acetylides are thick suspensions (e.g. *t*-BuC≡CLi, higher-alkyl-C≡CNa, $LiC{\equiv}CCH_2NEt_2$). A few ml of dry Et_2O may help to suppress frothing in these cases.

c. If *acetylenic alcohols*, e.g. $HC{\equiv}CCH_2OH$, are to be (di)metallated, 0.15 to 0.30 mol is added over ~15 min to the suspension of alkali amide (0.3 to 0.6 mol, respectively) in 300 to 500 ml of NH_3. $LiC{\equiv}CCH_2OLi$ is obtained as an almost clear solution.

4.5 Replacement of Ammonia in Solutions or Suspensions of Alkali Alkynylides by THF or DMSO

Scale: 0.5 molar.

Apparatus: fig. 6, 2 l; in the last stage of the evaporation of the NH_3 one of the stoppers is replaced by a gas inlet for the introduction of N_2, the other stopper by a thermometer-gas outlet combination (compare fig. 1).

Introduction

Some coupling reactions of alkali alkynylides proceed sluggishly in liquid ammonia, either

because the temperature (-33°C) is too low (for reactions with epoxides) or because the solubility of the reagent is insufficient (in the case of higher alkyl bromides). Higher temperatures and better solubility of alkyl halides can be attained by adding a sufficient amount of THF, DMSO or HMPT and subsequently evaporating part (or all) of the ammonia.

It should be pointed out that even in the case of complete evaporation of the ammonia solvent the alkynylide still contains ammonia, which is rather tightly bound. It is probably this NH_3 that stabilizes LiC≡CH in the same manner as do $H_2NCH_2CH_2NH_2$ and TMEDA (compare exp. 6).

Procedure

Dry THF (200 ml) or DMSO (200 ml) is cautiously added (pouring through the open neck) to the solution or suspension of 0.5 mol of RC≡CM (see exps. 1 and 2) in liquid ammonia (~300 ml, note 1). The flask is then placed in a water bath, which is gradually heated from room temperature to 50°C. When the stream of NH_3 becomes faint, introduction of N_2 is started. During the evaporation of the NH_3 the mixture is stirred at a moderate rate, while an additional volume of 250 ml of THF or 100 ml of DMSO is gradually added. Heating is stopped when the thermometer indicates 20 to 25°C (note 2). In THF, many alkynylides are obtained as suspensions, in DMSO their solubility is better.

Notes

1. If the original volume of the suspension or solution of RC≡CM was more than 300 ml, part of the ammonia is first removed by placing the flask in a water bath at 30 to 40°C. In the case of frothing during this operation, heating should be interrupted and/or a few ml of Et_2O may be occasionally added.
2. Especially in the case of *sodium* acetylides, $RCH_2C{\equiv}CNa$, there is some risk of formation of $RC{\equiv}CCH_3$, if the DMSO solution is heated at temperatures higher than 25°C.

General note

This replacement-of-solvent operation should not be carried out with Li- or $NaC{\equiv}COC_2H_5$ and Li- or NaC≡CCl (danger of vigorous decomposition or even explosion!) or acetylides with the structure $MC{\equiv}CC{\equiv}CCH_2R$ or $MC{\equiv}CCH{=}CHCH_2R$ (increased risk of isomerization processes).

4.6 Monolithium Acetylide.TMEDA

$$HC{\equiv}CH + BuLi.TMEDA \xrightarrow[-60°C]{THF\text{-}hexane} HC{\equiv}CLi.TMEDA + C_4H_{10}$$

Scale: 0.10 molar.

Apparatus: fig. 16, 1 l.

Introduction

When acetylene is introduced at ambient temperatures into a solution of alkyllithium in Et_2O or THF, a precipitate of dilithium acetylide is formed. The monolithium compound is unstable under these conditions. Midland [34] published a procedure for the preparation of monolithium acetylide in THF, involving controlled addition of butyllithium to a strongly cooled saturated solution of acetylene in THF. Subsequent reaction with carbonyl compounds gave the expected carbinols in good yields. Apparently THF stabilizes LiC≡CH to some extent. Other stabilizing reagents are (anhydrous) LiBr [47] and 1,2-diaminoethane [33]. The $LiC{\equiv}CH.NH_2CH_2CH_2NH_2$ complex is commercially available. The procedure in exp. 3.6 describes a convenient method to prepare a solution of the LiC≡CH.TMEDA complex. This solution remains clear over a wide temperature range and can be used for the preparation of ethynyl carbinols (Chap. IV, exp. 2).

Procedure

BuLi (0.10 mol) in 70 ml of hexane is placed into the 1-l flask and TMEDA (0.12 mol, dried by distillation from $LiAlH_4$ in partial vacuum) is added over a few min at room temperature. THF (80 ml) is added with cooling below -60°C. Acetylene is then bubbled through the solution with vigorous stirring, while keeping the temperature between -60 and -70°C (cooling in a bath with liquid N_2 is most effective). About 4 l of acetylene is introduced: inexperienced persons should use a flow meter (rate ~0.5 l/min), or the flow may be estimated using a washing bottle filled with paraffin oil. The presence of an excess of dissolved acetylene is not detrimental in most subsequent reactions.

4.7 Dilithium Acetylide in THF or Et_2O

$$HC{\equiv}CH + 2\ BuLi \xrightarrow{Et_2O \text{ or THF}} LiC{\equiv}CLi\downarrow + 2\ C_4H_{10}\uparrow$$

Scale: 0.20 molar (BuLi).

Apparatus: fig. 16, 1 l; at a later stage the thermometer-gas-outlet combination is replaced by a reflux condenser.

Introduction: see exp.6.

Procedure

A solution of 0.20 mol of BuLi in 140 ml of hexane is placed into the 1-l flask and Et_2O (140 ml) or THF (140 ml, or, if desired, less) is added (in the case of THF with cooling below 0°C). Acetylene (see exp. 1, note 1) is introduced with vigorous stirring. The rate of introduction is about 200 ml/min (to be measured with a flow meter or estimated with the aid

of a washing bottle filled with paraffin oil). Since the reaction is virtually instantaneous and the heating effect strong, a cooling bath with dry ice and acetone is required. In the case of THF, the temperature should be kept between 5 and 15°C (note 1), while the temperature during the lithiation in Et_2O should be maintained between 15 and 20°C. When no significant further rise of the temperature is observed, the thermometer is replaced by a reflux condenser and the introduction of acetylene is stopped. Nitrogen (~0.5 l/min) is now introduced while the Et_2O and THF are heated to reflux (note 2). After 15 min the fine suspension is cooled to room temperature.

Notes

1. At higher temperatures THF is cleaved by BuLi to give ethene and $H_2C{=}CHOLi$ [51]
2. Traces of acetylene are removed in this way.

4.8 Solutions or Suspensions of LiC≡CR in THF or Et_2O

$$RC{\equiv}CH + Alk.Li \xrightarrow{THF\ or\ Et_2O} RC{\equiv}CLi + Alk.H$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

Compared to deprotonations of many other organic compounds, the metallations of terminal acetylenes are very fast reactions. The lithiation of acetylenes RC≡CH by BuLi proceeds instantaneously, even at temperatues as low as -80°C in Et_2O. The best way to prepare lithium alkynylides in Et_2O or THF consists of the dropwise addition of alkyllithium in Et_2O (prepared from alkyl halide and lithium, [1]) or in hexane (commercially available) to a solution of a slight (~5%) excess of the acetylene in Et_2O or THF, cooled below -10°C or –if unstable alkynylides are to be prepared– at -80°C. For simple acetylenes, such as $CH_3C{\equiv}CH$, inverse addition (*i.e.* acetylene is added to lithium reagent) may be applied as well, but other acetylenes may give undesirable subsequent reactions under the influence of the excess of basic reagent. Examples of compounds that are readily dilithiated are $PhCH_2C{\equiv}CH$, $RCH_2C{\equiv}CC{\equiv}CH$, $RC{\equiv}CCH_2C{\equiv}CH$ and $RCH{=}CHCH_2C{\equiv}CH$. Vinylacetylene, $HC{\equiv}C{-}{-}CH{=}CH_2$, undergoes "anionic" polymerization, starting with the addition of BuLi across the double bond in $LiC{\equiv}CCH{=}CH_2$. The lithiation of these acetylenic compounds therefore has to be carried out as described below.

Procedure (compare [36])

A solution of 0.10 mol of BuLi in 70 ml of hexane (note 1) is added dropwise to a mixture of 0.11 mol of the acetylene in 80 ml of Et_2O or THF cooled below -50°C. The resulting solution or suspension can be used immediately for further reactions.

Notes

1. If a volatile product is to be prepared in a subsequent reaction, the presence of hexane or THF may be undesirable. In such cases the lithiation can be carried out with a solution of EtLi.LiBr in Et_2O (prepared as described in ref. 1).

4.9 Lithiation of Propargyl Chloride

$$HC{\equiv}CCH_2Cl + BuLi \xrightarrow[-70°C]{Et_2O\text{-hexane}} LiC{\equiv}CCH_2Cl + C_4H_{10}$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

Although the halogen in propargyl halides is very readily displacable in reactions with nucleophiles, interaction at low temperatures between BuLi and propargyl chloride leads to specific metallation at the acetylenic carbon atom. It is preferable to use Et_2O as a solvent since the chance of a competitive nucleophilic displacement of chlorine seems less likely than in the more polar THF. For similar reasons inversed-order addition is applied. The "carbenoid" $LiC{\equiv}CCH_2Cl$ [48] is reasonably stable in Et_2O, permitting successful reactions with a number of reactive electrophiles, such as trimethylchlorosilane and carbonyl compounds. If alkyl substituents are present on the propargylic carbon atom, the stability is poor. Thus, the "carbenoid" $LiC{\equiv}CC(CH_3)_2Cl$ eliminates LiCl at low temperatures [237]. We were unable to prepare $CH_3SC{\equiv}CCH(CH_3)Cl$ by treating $HC{\equiv}CCH(CH_3)Cl$ with BuLi and subsequently adding $CH_3SC{\equiv}N$ [2].

Procedure

Freshly distilled propargyl chloride (0.10 mol) and Et_2O (100 ml) are placed in the 1-l flask. A solution of 0.10 mol of BuLi in 70 ml of hexane or 0.10 mol of EtLi.LiBr in ~90 ml of Et_2O [1] is added dropwise, while keeping the temperature of the solution around -70°C. If cooling in a bath with liquid N_2 is applied, the addition can be carried out over a few min. The resulting clear solution should be used without too much delay.

4.10 Lithiation of Propargyl Bromide

$$HC{\equiv}CCH_2Br + LDA \xrightarrow[-75°C]{Et_2O\text{-hexane}} LiC{\equiv}CCH_2Br + HDA$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

In contrast to propargyl chloride (exp. 9), the bromide cannot be metallated at the acetylenic carbon with alkyllithium [2]. The main reaction is possibly a bromine-lithium exchange with formation of $HC{\equiv}CCH_2Li$ (and possibly also $LiC{\equiv}CCH_2Li$). Such a reaction is unikely to occur with lithium diisopropylamide because the "driving force" for this reaction is weak (low energy of the N-Br bond, compare [49]). As judged from the result of the subsequent functionalization with Me_3SiCl (Chap. VI, exp. 9), the lithiation with LDA is very successful. The preference for Et_2O over THF as as solvent is explained in exp. 4.9.

Procedure

Diisopropylamine (0.12 mol, dried by shaking with machine-powdered KOH and subsequent distillation of the decanted liquid) is added over a few min to a solution of 0.12 mol of BuLi in 84 ml of hexane and 90 ml of Et_2O (a solution of EtLi.LiBr prepared as described in ref. 1 may be suitable as well) with cooling below 0°C. The obtained solution is cooled to below -80°C and freshly distilled propargyl bromide (0.10 mol, see Chap. XII, exp. 1.1) is added dropwise over 5 min while keeping the temperature between -75 and -80°C (a cooling bath with liquid N_2 is indispensable). After an additional 5 min (at -80°C) the clear solution is ready for further reactions.

4.11 Lithiation of 1-Bromo-5-hexyne

$$HC{\equiv}C(CH_2)_4Br + BuLi \xrightarrow[-80°C]{\text{THF-hexane}} LiC{\equiv}C(CH_2)_4Br + C_4H_{10}$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

Exps. 9 and 10 are convincing illustrations of the high kinetic acidity of the ethynyl proton. In principle, there are four reaction pathways if 1-bromo-5-hexyne and a strongly basic reagent are allowed to interact: abstraction of the acetylenic proton, Br-metal exchange, displacement of Br by the "nucleophilic" part of the base, and elimination of HBr with formation of $HC{\equiv}C(CH_2)_2CH{=}CH_2$. Only the first process takes place under the conditions of this experiment. The kinetic stability of the intermediate $LiC{\equiv}C(CH_2)_4Br$ is sufficient to allow for successful functionalizations with a number of reagents. For *alkylations* with most of the alkyl halides, the polarity of the medium will usually be insufficient.

Even with lithium- or sodium amide in liquid ammonia, specific deprotonation at the ethynyl group is expected, but in this polar solvent subsequent nucleophilic substitution of Br^- might be a serious subsequent reaction ($Br(CH_2)_4C{\equiv}C^- + Br(CH_2)_4C{\equiv}C^- \longrightarrow Br(CH_2)_4\text{-}C{\equiv}C\text{-}(CH_2)_4C{\equiv}C^-$ *etc.*).

Procedure

A mixture of 0.10 mol of 1-bromo-5-hexyne (Chap. XII, exp. 1.5) and 70 ml of THF is cooled to between -60 and -80°C. A solution of 0.105 mol (slight excess) of BuLi in hexane is added dropwise over ~15 min, while maintaining the temperature range indicated. Two minutes after this addition, derivatization reactions can be carried out with the clear solution.

4.12 Dilithium Diacetylide

$$HC{\equiv}CC{\equiv}CH + 2\,BuLi \xrightarrow[< -20°C]{\text{THF or } Et_2O} LiC{\equiv}CC{\equiv}CLi + 2\,C_4H_{10}$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Procedure

A solution of 0.10 mol of freshly prepared diacetylene (Chap. IX, exp. 14) in 140 ml of Et_2O or THF is cooled to below -20°C and a solution of 0.20 mol of BuLi in 140 ml of hexane is added dropwise, while maintaining this temperature. $LiC{\equiv}CC{\equiv}CLi$ is formed as a white suspension.

4.13 Ethynylmagnesium Bromide in THF

$$HC{\equiv}CH + C_2H_5MgBr \xrightarrow{\text{THF}} HC{\equiv}CMgBr + C_2H_6\uparrow$$

Scale: variable.

Introduction

In the procedure described in Organic Syntheses [35] a solution of C_2H_5MgBr in THF is added dropwise to a saturated solution of acetylene in THF through which acetylene is being bubbled. The temperature is kept between 25 and 30°C. We have carried out this procedure several times on a 2 to 3 molar scale with excellent results in derivatization reactions, e.g. the conversion with Me_3SiCl. For syntheses on a relatively small ($\leq$ 0.3 molar) scale, the following procedure gives satisfactory results.

Procedure

A solution of C_2H_5MgBr (0.3 mol) in THF (~350 ml) is placed in a 1-l round-bottomed, three-necked flask (see fig. 16). A vigorous stream of acetylene (1.5 to 2 l/min) is passed

through the vigorously stirred solution while efficient cooling is applied to keep the temperature, which initially is 5°C, between 15 and 20°C. When the exothermic reaction has subsided *i.e.* when there is no, or only a slight temperature rise without external cooling, the flow of acetylene is diminished to 0.5 l/min and introduction of gas is continued for an additional 10 min at 18 to 20°C. The greyish to black solution (a suspension is formed upon cooling) is then used for further conversions.

If acetylene is introduced at 20-25°C into a more concentrated solution of C_2H_5MgBr, the characteristic gelatinous suspension of BrMgC≡CMgBr may appear. Further introduction of acetylene does not lead to conversion into HC≡CMgBr.

4.14 Acetylene Dimagnesium Bromide

$$HC{\equiv}CH + 2\,C_2H_5MgBr \xrightarrow{THF} BrMgC{\equiv}CMgBr\downarrow + 2\,C_2H_6\uparrow$$

Scale: 1 molar (C_2H_5MgBr).

Apparatus: fig. 16, 3 l; stirrer: fig. 3.

Introduction

When acetylene is passed through a 0.5 to 1 molar solution of C_2H_5MgBr, kept just below 30°C (compare exp. 13) the solution initially remains clear, but there is a fair chance that the characteristic precipitate of BrMgC≡CMgBr appears (clearly different from the coarser suspension which is sometimes formed when solutions of HC≡CMgBr are cooled). If acetylene is introduced at 50°C into a solution of C_2H_5MgBr, the suspension of the di-Grignard derivative is formed immediately.

Procedure

A solution of ~1 mol of ethylmagnesium bromide (prepared from 1.10 mol of C_2H_5Br and Mg as described in ref. 4) in ~1000 ml of THF (note 1) is heated to 50°C. Acetylene (note 2) is then introduced at a rate of 300-400 ml/min (flow meter) with vigorous stirring, while keeping the temperature between 50 and 55°C (note 3). The introduction of gas is stopped when the temperature has dropped to between 40 and 45°C (without external cooling). The jelly-like suspension is then heated for an additional 30 min at 50°C with introduction of N_2 (300-500 ml/min, note 4).

Notes

1. An additional 100-200 ml of THF may be added if the suspension of BrMgC≡CMgBr becomes too thick.
2. Freed from acetone by passing through two or more cold traps (-75°C).
3. The heating effect due to the metallation is strongly reduced by the ethane which escapes from the reaction mixture.
4. Most of the dissolved acetylene is removed.

4.15 Alkynylmagnesium Bromides in Et_2O

$$RC{\equiv}CH + C_2H_5MgBr \xrightarrow{Et_2O} RC{\equiv}CMgBr + C_2H_6\uparrow$$

Scale: 0.5 molar.

Apparatus: for $CH_3C{\equiv}CH$, $C_2H_5C{\equiv}CH$ and $H_2C{=}CHC{\equiv}CH$: a 1-l three-necked, round-bottomed flask, equipped with a gas inlet tube, a mechanical stirrer and a "cold finger" reflux condenser (-75°C, fig. 17), cooled with dry ice and acetone; the top of the condenser is connected to a cold trap;
for the other acetylenes: 1-l round-bottomed, three-necked flask with a gas inlet, a dropping funnel and an efficient reflux condenser, connected to a cold trap. N_2 is introduced in all cases (100-150 ml/min); the stirrer and all connections should be gas-tight in the cases of the Grignardation of propyne, butyne or vinylacetylene.

Introduction

In Et_2O the formation of acetylenic Grignard derivatives from acetylenes and C_2H_5MgBr is slower than in THF (compare exp. 16) and refluxing for 1-3 hours (depending upon the acidity of the acetylene) is necessary to complete the conversion. In the case of volatile acetylenes this may give rise to some experimental problems, since part of the acetylene is swept along with the liberated ethane. The best solution is to use a reflux condenser of the "cold-finger" type. The gas evolved from the reaction mixture passes the condenser and is subsequently led through a cold trap. The small amount of unconverted acetylene which condenses in this trap is led through the reaction mixture again.

Procedure

The trap containing 0.6 mol of liquified $CH_3C{\equiv}CH$, $C_2H_5C{\equiv}CH$ or $H_2C{=}CHC{\equiv}CH$ is placed in a water bath at 0°, 25° and 20°C, respectively, and the gas led through a vigorously stirred solution of ~0.5 mol of C_2H_5MgBr in 400 ml of Et_2O (prepared from 0.57 mol of C_2H_5Br), which is heated to ~32°C. After 1.5 h the traps before and after the apparatus are interchanged and warming at 30-35°C is continued for another 2 h.

The other acetylenes (0.55 mol) are added dropwise over 45 min to a gently refluxing and vigorously stirred solution of ~0.5 mol of C_2H_5MgBr in 400 ml of Et_2O. In the case of acidic acetylenes, ($HC{\equiv}CC{\equiv}CR$, $HC{\equiv}CSiMe_3$, $HC{\equiv}COR$, $HC{\equiv}CSR$) refluxing is continued for another half hour, in the other cases for 2 h.

4.16 Alkynylmagnesium Bromides in THF

$$RC{\equiv}CH + C_2H_5MgBr \xrightarrow{THF} RC{\equiv}CMgBr + C_2H_6\uparrow$$

Scale: 0.5 molar.

Apparatus: 1-l three-necked, round-bottomed flask, equipped with a dropping funnel-gas inlet combination, a mechanical stirrer and an efficient reflux condenser; in the case of volatile acetylenes with b.p. < 60°C/760 mmHg, the top of the condenser is connected to a trap cooled at -75°C; in the case of more acidic acetylenes (HC≡CC≡CR, HC≡COR, HC≡CSR, $HC{\equiv}CSiMe_3$, HC≡CAryl), a thermometer-outlet combination is used instead of a reflux condenser; all connections should be made gas-tight, especially in the case of gaseous acetylenes. N_2 (~ 200 ml/min) is led through the apparatus.

Introduction

In contrast to the metallation with alkyllithium or alkali amides, Grignardation of HC≡CR with alkylmagnesium halide is not an instantaneous reaction. The more acidic 1,3-diynes and hetero-substituted acetylenes react most readily. In the other cases heating for several minutes to 1 h is necessary to complete the conversion.

Procedure

a. Acidic Acetylenes (HC≡CC≡CR, HC≡COR, HC≡CSR, and $HC{\equiv}CSiMe_3$, 0.5 mol) are added dropwise over 20 min to a solution of ~0.5 mol of C_2H_5MgBr in 350 ml of THF (prepared from 0.57 mol of C_2H_5Br) while maintaining the temperature between 0 and 5°C. After this addition the cooling bath is removed and the temperature allowed to rise to 20°C. The suspended material dissolves. After an additional 15 min the solution can be used for derivatization reactions.

b. Gaseous Acetylenes (propyne, butyne, vinylacetylene, 0.6 mol) are introduced with vigorous stirring and warming at 45°C. The gas is obtained by placing a trap containing the liquified acetylene in a water bath (see exp. 15). After the introduction of the acetylene (taking ~30 min), the traps before and after the apparatus are interchanged. This operation is repeated twice.

c. Volatile Acetylenes (*e.g.* *t*-BuC≡CH, 0.6 mol) are added dropwise over 30 min, while heating the Grignard solution in a water bath at 50°C. Fifteen min after completion of the addition, the contents of the trap are diluted with 30 ml of THF and this mixture is added over 5 min. After an additional period of 30 min (at 50°C) this operation is repeated and the reaction mixture is heated for a further 15 min.

c. Other acetylenes (b.p. > 60°C/760 mmHg, 0.5 mol) are added over 30 min, while heating the reaction mixture in a water bath at 50°C. After an additional 1 h the solution is ready for further conversions.

4.17 1,3-Dilithiation of 1-Alkynes with BuLi in THF

$$RCH_2C{\equiv}CH + 2\,BuLi \xrightarrow{THF\text{-}hexane} RCH(Li)C{\equiv}CLi + 2\,C_4H_{10}$$

R = H, CH_3, C_4H_9, Ph.

Scale: 0.10 and 0.20 molar (1-alkyne).

Apparatus: fig. 1, 1 l.

Introduction

1-Alkynes are converted instantaneously into the lithium compounds with alkyllithium reagents in Et_2O or THF. In the presence of an excess of basic reagents, a relatively slow further metallation at the propargylic position takes place. Propyne has been tetrametallated, using a large excess of BuLi.TMEDA in hexane [50]. In the presence of THF, the chance of trimetallation of aliphatic alkynes is small, the reaction will stop at the stage of 1,3-dimetallated compound and any excess of alkyllithium will react with THF to form H_2C=CHOLi and ethene [51], products which are not likely to interfere seriously during further reactions with the dimetallated acetylenes.

Procedure

A solution of 0.22 or 0.25 mol (for propyne and butyne, respectively, note 1) of butyllithium in *ca.* 175 or 155 ml (respectively) of hexane is placed into the flask. After cooling to below -10°C, THF (130 ml) is added. Subsequently, a cold (-30°C) mixture of 0.10 mol of propyne or 1-butyne (Chap. IX, exp 1) and 30 ml of THF is added over 10 min in a number of portions, while keeping the temperature of the reaction mixture below -20°C. The cooling bath is then removed and the temperature allowed to rise. A white or yellow suspension is gradually formed in the case of propyne and 1-butyne, respectively. The dimetallations are completed by warming the suspensions for an additional 1 or 1.5 h, respectively, at 35-40°C.

After the addition of *1-hexyne* at ~ -10°C (0.10 mol in 30 ml of THF to 0.25 mol of BuLi in 175 ml of hexane and 130 ml of THF), the resulting brown solution is warmed for 2.5 h at 40°C. *Benzylacetylene* (0.10 mol in 30 ml of THF, [4]) is added over 10 min with cooling at ~ -40°C to a solution of 0.21 mol of BuLi in 77 ml of hexane and 70 ml of THF, then the cooling bath is removed and the temperature allowed to rise to 10 °C. A dark brown solution, and, at a later stage, a suspension is formed.

Notes

1. The excess is used to effect a complete dimetallation and to compensate for losses due to the presence of traces of oxygen and moisture in THF. Any remaining excess of BuLi is destroyed during warming by reaction with THF.

4.18 Dilithiation of Benzylacetylene and Methyl Propargyl Sulfide in Et_2O

$$RCH_2C{\equiv}CH + 2\,EtLi \xrightarrow{Et_2O} RCH(Li)C{\equiv}CLi + 2\,C_2H_6{\uparrow} \qquad R = Ph \text{ or } CH_3S$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

The propargylic protons in benzylacetylene and methyl propargyl sulfide are more acidic than those in aliphatic 1-alkynes $RCH_2C{\equiv}CH$. Using ethyllithium in Et_2O, benzylacetylene can be completely dilithiated in 2 h (or less) at 10 to 15°C, while the sulfide reacts at a convenient rate at -15°C. Dilithiation of 1-hexyne with EtLi.LiBr in Et_2O requires heating under reflux for several hours.

Procedure

Benzylacetylene (0.10 mol, see ref. 4) or methyl propargyl sulfide (0.10 mol, see Chap. XII, exp.2.10) is added dropwise over 10 min to a solution of 0.22 mol of EtLi.LiBr in Et_2O [1] cooled to ~ -30°C. Stirring at 10 to 15°C, or -15°C, respectively, is continued for another 1.5 h. The dilithio derivatives form brown solutions.

In the case of aliphatic 1-alkynes, the mixture is heated for 6 h under reflux, using a 20% excess of EtLi.LiBr. Yellow suspensions or brown solutions are formed.

4.19 Dilithiation of 1-Heptyne with BuLi.TMEDA in Hexane

$$C_4H_9CH_2C{\equiv}CH + 2\,BuLi \xrightarrow[\text{reflux}]{\text{hexane, TMEDA}} C_4H_9CH(Li)C{\equiv}CLi + 2\,C_4H_{10}{\uparrow}$$

$$\xrightarrow[\downarrow\ Me_3SiCl]{THF} C_4H_9CH(SiMe_3)C{\equiv}CSiMe_3$$

Scale: 0.10 molar (1-heptyne).

Apparatus: A 500-ml round-bottomed, three-necked flask, equipped with a gas inlet, a dropping funnel and a reflux condenser. The top of the condenser is connected to a washing bottle containing hexane. The inlet tube should not dip more than 0.5 cm in the hexane. The solution is stirred magnetically. All connections should be made gas-tight.

Introduction

Addition of TMEDA to a solution of BuLi in hexane gives a solution of the 1:1 complex BuLi.TMEDA, which is a highly efficient deprotonating reagent. It is capable of deprotonating alkynyllithium at the propargylic carbon atom in a relatively short time. In the procedure of exp. 19, a 15% excess of BuLi.TMEDA is used to compensate for losses due to

decomposition of the TMEDA under the influence of the base, and to effect a complete dimetallation.

Procedure

Dry TMEDA (0.23 mol) is added dropwise over 10 min to a solution of 0.23 mol of BuLi in 160 ml of hexane without external cooling. Subsequently 0.10 mol of 1-heptyne (Chap. IX, exp. 10) is added dropwise, while keeping the temperature between 20 and 30°C (ice-water bath). Introduction of N_2 is then stopped and the light-yellow solution is heated under gentle reflux for 3 h. The evolution of butane has then stopped (occasional sucking back of the hexane in the washing bottle). The brown solution is cooled to -40°C and 50 ml of THF is added. Subsequently 0.25 mol of trimethylchlorosilane is added over a few min with vigorous stirring. The cooling bath is removed and the temperature allowed to rise to 15-20°C. A white suspension in a yellow to orange solution is formed. After 30 min, 200 ml of ice water is added. After separation of the layers, three extractions with pentane are carried out. The combined organic solutions are washed three times with water and subsequently dried over $MgSO_4$. The solvent is removed under reduced pressure. Careful distillation of the remaining liquid gives the disilyl product, b.p. 95°C/15 mmHg, $n_D(20°C)$ 1.448, in ~ 90% yield, indicating that the dimetallation was very successful.

4.20 Dimetallation of Methyl Propargyl Ether with BuLi.*t*-BuOK

$$HC{\equiv}CCH_2OCH_3 + 2\,BuLi.t\text{-}BuOK \xrightarrow[-45°C]{\text{THF-hexane}} KC{\equiv}CCH(K)OCH_3 + 2\,t\text{-}BuOLi + 2\,C_4H_{10}$$

Scale: 0.10 molar ($HC{\equiv}CCH_2OCH_3$).

Apparatus: fig. 1, 1 l.

Introduction

Attempts to isolate 1,3-dilithiated propargylic ethers with two equivalents of BuLi at temperatures above -20° give unsatisfactory results, because the dilithio compounds are unstable. In the case of $HC{\equiv}CCH_2O$*t*-Bu, $HC{\equiv}CCH(t\text{-}Bu)OH$ is found after aqueous hydrolysis, possibly as a result of a Wittig-rearrangement [2]. At temperatures below -20°C the dilithiation is too sluggish to be of practical interest. With the super-basic reagent BuLi.*t*-BuOK in a THF-hexane mixture dipotassiation can be effected in a relatively short time at low temperatures.

Procedure

A solution of 0.22 mol of BuLi in 155 ml of hexane is cooled to between -90 and -100°C. THF (70 ml) is added and subsequently, over 15 min, a solution of 0.22 mol of *t*-BuOK in 90

ml of THF, while keeping the temperature between -90 and -100°C (occasional cooling in a bath with liquid N_2). Freshly distilled and dry methyl propargyl ether (Chap. XII, exp. 2.1), 0.10 mol) is added over 10 min with cooling at ~ -80°C. The temperature is then allowed to rise to -45°C and the mixture is stirred for another 2.5 h at this temperature (note 1). The brown solution is used for further conversions as soon as possible.

Notes

1. Stirring should be carried out at a low rate in order to prevent splashing of the mixture into the upper part of the flask. The best way of maintaining this temperature is to dip the reaction flask as far possible into the cooling vessel, with the bottom just above the liquid N_2.

4.21 Dimetallation of Isopropenylacetylene

$$HC{\equiv}CC(CH_3){=}CH_2 + 2\ BuLi.t\text{-}BuOK \xrightarrow[-70°C]{THF\text{-}hexane} KC{\equiv}CC(CH_2K){=}CH_2{\downarrow} + 2\ C_4H_{10} + 2\ t\text{-}BuOLi$$

$$KC{\equiv}CC(CH_2K){=}CH_2{\downarrow} + 2\ LiBr \longrightarrow LiC{\equiv}CC(CH_2Li){=}CH_2{\downarrow} + 2\ KBr{\downarrow}$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

Treatment of isopropenylacetylene with an excess of BuLi or BuLi.TMEDA does not give rise to double deprotonation, but to a slow addition with formation of an adduct. With the super basic reagent BuLi.*t*-BuOK [45,46,52,53] in a mixture of THF and hexane, dimetallation can be accomplished in a short time at low temperatures. The high efficiency of the dimetallation appears from the excellent yield (≥ 90%) of $Me_3SiC{\equiv}CC(CH_2SiMe_3){=}CH_2$ obtained by quenching with Me_3SiCl. Addition of anhydrous lithium bromide converts the dipotassium compound into the dilithio derivative, which can be used for regiospecific functionalizations.

Procedure

A solution of 0.10 mol of freshly distilled isopropenylacetylene (Chap. IX, exp. 37) in 60 ml of THF is cooled to -80°C (occasional cooling in a bath with liquid N_2) and solutions of 0.22 mol of BuLi in 155 ml of hexane and 0.22 mol of *t*-BuOK in 60 ml of THF, are succesively added over 20 min with cooling between -75 and -85°C. A yellow suspension is formed. After stirring for an additional 30 min at -70°C, the cooling bath is removed and the temperature allowed to rise to +5°C. After an additional 10 min at 5°C (note 1), a solution of 0.22 mol of anhydrous LiBr (note 2) in 60 ml of THF is added at -20°C with vigorous stirring. The colour of the suspension changes into light-yellow.

Notes

1. The excess of BuLi.*t*-BuOK (0.02 mol) is destroyed by reaction with THF to give ethene and $H_2C{=}CHOK$.
2. The commercial anhydrous salt (~20 g) is heated for 20 min (occasional swirling by hand) at 150°C in a 1-l round-bottomed flask, evacuated at 5 mmHg or lower pressure.

4.22 Allenylmagnesium bromide

$$HC{\equiv}CCH_2Br + Mg \xrightarrow[0\text{-}5°C]{Et_2O} H_2C{=}C{=}CHMgBr$$

Scale: 1 molar.

Apparatus: fig. 1, 1 l.

Introduction

Attempts to prepare the Grignard reagent from propargyl bromide under the usual conditions give rise to undesired reactions (compare [54]):

$$HC{\equiv}CCH_2\,Br + H_2C{=}C{=}CHMgBr \longrightarrow BrMgC{\equiv}CCH_2Br + \text{allene or propyne}$$
$$\downarrow$$
$$H_2C{=}C{=}CHCH{=}C{=}CH_2 + HC{\equiv}CCH_2CH{=}C{=}CH_2$$

These reactions can be largely avoided by strongly activating the Mg with a small amount of mercury(II)chloride, which allows the Grignard reagent to be formed at a convenient rate at temperatures in the region of 0°C. This reagent is usually prepared in Et_2O; THF seems less suitable because in this solvent the ethynyl H-atom is removed more easily than in Et_2O.

Procedure

Magnesium turnings (1.5 mol, excess) and dry Et_2O (600 ml, dried over machine-powdered KOH and subsequently distilled from $LiAlH_4$) are placed into the flask. Mercury(II)chloride (1.5 g) is added and the mixture is stirred for 30 min at 20°C, then the flask is placed in a bath with ice and ice water (note 1). When the temperature in the flask has dropped to 0°C, 8 ml of the total amount of 1.2 mol of $HC{\equiv}CCH_2Br$ is added in one portion (for the preparation of the bromide see Chap. XII, exp. 1.1). The reaction, which usually starts within 20 min, is evidenced by a distinct rise of the temperature to 3°C or higher. If necessary, a bath with dry ice and acetone (note 1) is used to keep the temperature below +10°C. When the exothermic reaction has subsided, the remaining $HC{\equiv}CCH_2Br$ is added dropwise over 1 h. After an additional 45 min, the grey solution is decanted from the excess of Mg under a blanket of inert

gas (note 2). The solution contains approximately 1 mol of Grignard reagent as indicated by the results of coupling reactions.

Notes

1. A bath with dry ice and acetone (-78°C) should be held in readiness.
2. The solution can subsequently be stored for several days at -20°C.

4.23 Alkynylzinc Chloride

$$RC{\equiv}CLi + ZnCl_2 \xrightarrow{\text{THF-hexane}} RC{\equiv}CZnCl + LiCl$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

Alkynylzinc chlorides are useful intermediates in Pd^0-catalysed couplings with vinyl, heteroaryl [56] and acyl halides [89] (see Chaps. V and X). The conversion of lithium alkynylides into alkynylzinc halides with anhydrous zinc chloride in THF proceeds smoothly and quantitatively under mild conditions.

Procedure

A solution of 0.10 mol of anhydrous zinc chloride (note 1) in 40 ml of THF is added over a few sec to a solution or suspension of 0.10 mol of alkynyllithium in 60 ml of THF and 70 ml of hexane (compare exp. 8) cooled to -30°C. Temperature control is generally not essential: the temperature is usually allowed to rise to 0-10°C during the addition. Depending upon the temperature and the ratio of THF to hexane, a homogeneous solution or a two-layer system is formed.

Notes

1. Making anhydrous $ZnCl_2$ from gaseous HCl and zinc in Et_2O is a time-consuming operation, which will be considered as boring by a dynamic synthetic organic chemist. He/she should rather rely on the indication "trocken" or "dry" on a bottle, provided with an extra plastic seal, which is reserved for his/her personal use only. Zinc chloride that is suspected of containing water, may be dried by refluxing it for a few hours with a mixture of $SOCl_2$ and an inert organic solvent (e.g. CCl_4) and subsequently thoroughly removing the volatile compounds by evacuation (water pump, then oil pump).

Table I.

Solubility of metallated acetylenic compounds.*

Acetylide	Counter ion	Chelating agent	Solvent	Susp.	Soln.
$HC{\equiv}C^-$	Li	TMEDA	THF		+
	Li	NH_3	THF	+	
	Li		DMSO		+
	Li		liq. NH_3		+
$HC{\equiv}C^-$	Na		liq. NH_3		+
	Na		THF	+	
$HC{\equiv}C^-$	MgBr		THF		+
$^-C{\equiv}C^-$	MgBr		THF	+	
	Li		Et_2O	+	
	Li		THF	+	
$CH_3C{\equiv}C^-$	Li		Et_2O	+	
	MgBr		Et_2O	"oil"	
	Li		THF	+	
	Li	LiBr	THF		+
	Li		liq. NH_3		+
	Li	NH_3	THF	+	
	Na		THF	+	
	Na		liq. NH_3	+	
	MgBr		THF		+
$C_4H_9C{\equiv}C^-$	Li		liq. NH_3	+	
	Li		Et_2O		+
	Li		THF		+
	Na		liq. NH_3	+	
	MgBr		Et_2O		+
	MgBr		THF		+
	Li	TMEDA	hexane		+
t-$BuC{\equiv}C^-$	Li or Na		liq. NH_3	+	
	Li		Et_2O	+	
	Li		THF		+
c-$C_6H_{11}C{\equiv}C^-$	Li or Na		liq. NH_3	+	
$Et_2NCH_2C{\equiv}C^-$	Li		liq. NH_3	+	
$Me_2NC{\equiv}C^-$	Li		THF	+	
$(EtO)_2CHC{\equiv}C^-$	Li		liq. NH_3	+	
$EtOC{\equiv}C^-$	Li		liq. NH_3		+
	Li		THF		+

Acetylide	Counter ion	Chelating agent	Solvent	Susp.	Soln.
$EtSC{\equiv}C^-$	Li		liq. NH_3		+
	Li		THF		+
$CH_3OCH_2C{\equiv}C^-$	Li		liq. NH_3		+
	Li		THF		+
	Li		Et_2O	+	
	MgBr		Et_2O	oil	
$CH_3SCH_2C{\equiv}C^-$	Li		Et_2O		+
$ClCH_2C{\equiv}C^-$	Li		Et_2O		+
$BrCH_2C{\equiv}C^-$	Li		Et_2O		+
$LiOCH_2C{\equiv}C^-$	Li		NH_3		+
$PhC{\equiv}C^-$	Li		Et_2O		+
	Li		THF		+
	Li		liq. NH_3		+
	Na		liq. NH_3		+

* The denotation "suspension" or "solution" refers to *synthetic* concentration (0.5-1 mol/l).

Trends

1. The solubility of RC≡CM in liq. NH_3 decreases with increasing length of the carbon chain in R.
2. The solubility of RC≡CMgBr or RC≡CLi in THF or Et_2O increases with increasing length of the carbon chain.
3. Addition of chelating agents (TMEDA, LiBr) to RC≡CLi in THF, Et_2O or hexane, causes dissolution of the suspension or an increase of the solubility.
4. Acetylides RC≡CM having a double or triple bond in conjugation with the terminal triple bond are more soluble in NH_3 or organic solvents than acetylides, in which this conjugation is absent.
5. The solubility of RC≡CM decreases with increasing size of the counter ion. Most potassium acetylides are insoluble in liq. NH_3 and in organic solvents.

Chapter III
Reaction of Metallated Acetylenes with Alkyl Halides, α-Halo-ethers, Epoxides and Alkyl Orthoformates

1. Alkylation with Alkyl Halides. Scope and Limitations

1.1 General

Compared to many other types of synthetic intermediates, acetylides, RC≡CM (M = Li, Na, K), show a moderate reactivity towards alkyl halides in the usual organic solvents Et_2O and THF and in liquid ammonia [2]. In this respect acetylides resemble enolates >C=COM. In the absence of dipolar aprotic co-solvents (DMSO or HMPT), lithium alkynylides, RC≡CLi, react sluggishly in Et_2O or THF with most alkyl halides [2]. In liquid ammonia the alkylation of alkali acetylides with the lower (up to C-5) alkyl bromides or iodides proceeds at a satisfactory rate [5]. A certain amount of DMSO added to the reaction mixture increases the solubility of halides with a longer carbon chain. A second effect of the addition of this co-solvent is that the temperature of the reaction mixture can gradually rise as more ammonia evaporates. In this way, the reaction can proceed gradually over the range from -33°C (b.p. NH_3) to room temperature. Specific alkylation on the acetylenic carbon takes place if an equivalent amount of an alkyl halide is added to dilithiated propargyl alcohol in liquid ammonia:

$$LiC{\equiv}CCH_2OLi + RBr\ (or\ I) \longrightarrow RC{\equiv}CCH_2OLi$$

This reaction may be extended to other types of acetylenic alcohols such as $HC{\equiv}C(CH_2)_4OH$ and $HC{\equiv}CCH{=}CHCH_2OH$. Di-sodio compounds, which have a poor solubility in ammonia, give disappointing results.

1.2 Scope

With metallated acetylenes the scope of successful alkylation reactions is confined to CH_3Br, CH_3I and alkylating agents with the general structure XCH_2CH_2R, in which X = Br or I and R = H, alkyl, alkylO, NH_2, or NR'_2 [5,8,10,20,21].

1.3 Limitations

Sec-alkyl halides: very sluggish reaction; under forcing conditions dehydrohalogenation occurs.

RCH_2CH_2Br (Cl or I) in which R is R'S, Ph, R'C=C, R'C≡C, COOH, *etc.*: dehydro-

halogenation.

$Br(CH_2)_3Br$: decreased yields of $RC{\equiv}C(CH_2)_3C{\equiv}CR$.

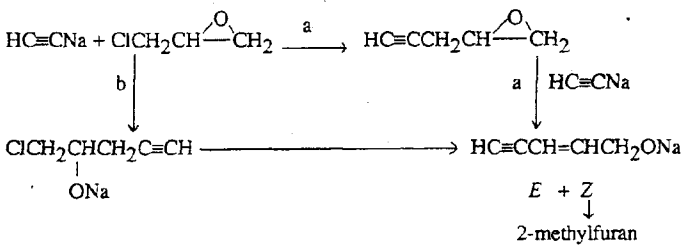
$(CH_3)_2CHCH_2Br$ and *i*-$BuCH_2Br$ (or I): no or sluggish reaction in liquid NH_3.

$BrCH_2CH(OC_2H_5)_2$: no reaction in liquid NH_3.

Allylic halides, propargylic halides and benzylic halides: complicated mixtures of products resulting from isomerization of the initial coupling products; in the case of $ArCH_2Br$ formation of $ArCH_2CH_2Ar$ is also possible [58,59].

1.4 Reaction with epichlorohydrine

E-Pentenynol $HC{\equiv}CCH{=}CHCH_2OH$ [60] can be obtained in reasonable yields from sodium acetylide and epichlorohydrine in liquid ammonia. The formation of the alcohol may take place along one or both of the following routes (a and b):



The moderate yield (between 40 and 55% in the various experiments) can in part be explained by the fast cyclization of *Z*-$HC{\equiv}CCH{=}CH_2ONa$ to 2-methylfuran. With *lithium* acetylide, a mixture of the *E*- and *Z*-isomer is obtained. Apparently cyclization of the *Z-lithium*-alcoholate proceeds less easily [61].

2. Reaction of Metallated Acetylenes with Epoxides and Alkyl Orthoformates

Alkali acetylides in liquid ammonia react rather slowly with oxirane and homologues to give "homopropargylic" alcohols [5,55,57]:

Excellent yields can be obtained when the mixture of $RC{\equiv}CLi$ and the epoxide in ammonia is allowed to stand for 12 to 24 hours [2]. With *sodium* acetylides, there is some risk of subsequent attack of the acetylenic alcoholate on the epoxide, especially when the latter compound is used in excess. The reaction of acetylenic magnesium halides, $RC{\equiv}CMgX$, with epoxides also leads to "homopropargylic" alcohols, but this is generally not recommended as a satisfactory method, as impure products are often obtained [62]. Coordination of the epoxide-oxygen atom with the Lewis acid may give rise to a S_N1-like attack of $RC{\equiv}C^-$ on

both ring carbon atoms. Furthermore, Lewis acids can effect ring opening of the epoxide with formation of aldehydes and ketones which, in their turn, can couple with $RC{\equiv}CMgX$. Finally, nucleophilic attack of X^- on the epoxide ring may occur, resulting in halohydrines $XCH_2CH(R')OH$.

In the presence of (a sufficient amount of) DMSO or HMPT, alkali acetylides react smoothly and cleanly with epoxides to give the desired alcohols [2].

Alkynyl Grignard compounds and alkyl orthoformates give acetylenic acetals in good yields. The reaction is usually carried out in Et_2O [65]:

$$RC{\equiv}CMgX + HC(OC_2H_5)_3 \xrightarrow{Et_2O} RC{\equiv}CCH(OC_2H_5)_2 + C_2H_5OMgX$$

3. Choice of the Counter-Ion for Alkylation Reactions in Liquid Ammonia

For many alkylation reactions of alkynylides in liquid ammonia Li^+ is preferred to both Na^+ and K^+ as counter-ion, since lithium alkynylides generally have a better solubility. Furthermore, the principal side-reaction, dehydrohalogenation of the alkyl halide, occurs to a lesser extent with lithium compounds.

4. Reaction of Metallated Acetylenes with α-Haloethers

Reactions of polar organometallic and Grignard reagents with α-haloethers generally proceed much more easily than the familiar S_N2 displacements with alkyl halides. This may be explained by the large extent of S_N1 character due to the ionization:

$$CH(X)\text{-}OR \rightarrow [\ CH\text{-}OR \leftrightarrow CH{=}\underline{O}\ ]^+ X^-$$

The reactions of α-haloethers are not very demanding with regard to the polarity of the solvent and the nature of the counter-ion: alkali acetylides as well as acetylenic Grignard compounds react smoothly, even in Et_2O [63]. Ammonia and dipolar aprotic solvents do not seem favourable media since ammonolysis or dehydrohalogenation may become serious side-reactions. If α,β-dihaloethers, *e.g.* $BrCH_2CH(Br)OC_2H_5$, are reacted with a Grignard compound, the α-halogen atom is specifically displaced [64]. The reaction of *lithium* alkynylides with aliphatic and cycloaliphatic α,β-dibromoethers, gave poor results (tar) [2].

$$RC{\equiv}CMgBr + BrCH_2CH(Br)OC_2H_5 \xrightarrow{THF} BrCH_2CH(OC_2H_5)C{\equiv}CR$$

$$RC{\equiv}CM + R'CH(Cl)OC_2H_5 \xrightarrow{Et_2O \text{ or } THF} R'CH(OC_2H_5)C{\equiv}CR$$

M = Li, Na, K, MgX

5. Experiments

All temperatures are internal, unless indicated otherwise

5.1 Methylation of *t*-Butylacetylene

$$t\text{-BuC}\equiv\text{CH} + \text{LiNH}_2\downarrow \xrightarrow[< -33^\circ\text{C}]{\text{liq. NH}_3} t\text{-BuC}\equiv\text{CLi}\downarrow + \text{NH}_3$$

$$t\text{-BuC}\equiv\text{CLi}\downarrow + \text{CH}_3\text{I} \xrightarrow[< -33^\circ\text{C}]{+\text{HMPT}} t\text{-BuC}\equiv\text{CCH}_3 + \text{LiI}$$

Scale: 1.0 molar.

Apparatus: *t*-BuC≡CLi: fig. 1, 2 l; stirrer: fig. 3.
t-BuC≡CCH$_3$: fig.5.

Introduction

This introduction includes discussion of several experimental problems which are frequently encountered during working with liquid ammonia. First of all, the volatile *t*-butylacetylene (b.p. 38°C) has to be converted quantitatively into its lithium compound by reaction with lithium amide. This reaction proceeds instantaneously and consequently the amount of "heat" produced per time unit is large. If carried out at the boiling point of ammonia (-33°C), this conversion would certainly give rise to losses of the acetylene, as it will be swept along with the ammonia vapour. Since the lithium derivative formed is insoluble, frothing may occur, and this can lead to loss of part of the reaction mixture. For these reasons, the suspension of lithium amide is cooled to below -33°C. During the addition of *t*-BuC≡CH the reaction mixture becomes very thick and stirring becomes increasingly difficult. Addition of HMPT (or DMSO) appears to remedy this problem: it effectuates homogeneous distribution of the acetylene through the suspension and then complete conversion into the lithium alkynylide can be achieved. In view of the volatility of the product *t*-BuC≡CCH$_3$ and the chance of frothing, the methylation with CH$_3$I is also carried out with external cooling. An additional reason for using a cooling bath is that methyl iodide is readily attacked by ammonia vapour to give $CH_3NH_3^+I^-$, which will inactivate part of the lithium alkynylide by protolysis. The special manner in which the CH$_3$I is introduced, is an additional measure to prevent prior contact of this alkylating agent with ammonia vapour. For syntheses on a smaller scale (up to ~0.5 molar) it may be (more) convenient to introduce CH$_3$I from a syringe, holding the end of the needle just above the surface of ammonia. Even when the CH$_3$I is added in this way, part of it may react with the (liquid) ammonia. To compensate for inactivation of *t*-BuC≡CLi due to its protolysis by $CH_3NH_3^+I^-$, an excess of LiNH$_2$ is used: any free *t*-BuC≡CH formed by this protolysis is remetallated by the excess of LiNH$_2$.

Procedure

A suspension of 1.2 mol of lithium amide in 1 l of liquid ammonia (see ref. 1 and fig. 6) is cooled to below -40°C, while N$_2$ (0.5 l/min) is introduced. Dry HMPT (75 ml, DMSO may also be suitable, for drying these solvents see ref. 1) is poured into the flask over a few minutes (while temporarily increasing the stirring rate). Pre-cooled (0°C) *t*-butylacetylene (1.0 mol, p. 166-167) is added over 20 min with efficient stirring, while keeping the temperature around -40°C. After a 10-min interval, the flow of N$_2$ is increased to 1.5 l/min and methyl iodide (1.25 mol) is added over 20 min with vigorous stirring and cooling to between -35 and -45°C. The suspension clears completely. Ten min after this addition, 250 ml of high-boiling petroleum ether (b.p. > 170°C) is added over a few min with vigorous stirring, after which the solution is cautiously poured into a 5-l wide-necked, round-bottomed flask (fig. 13) containing 2 kg of finely crushed ice. After separation of the layers, the aqueous layer is extracted four times with small (~50 ml) portions of petroleum ether. The combined organic solutions are washed with water and then dried over MgSO$_4$. For further work-up and isolation, see Chap I-2.6. Redistillation of the contents of the receiver gives the methyl derivative, b.p. 82°C/760 mmHg, $n_D(20^\circ)$ 1.4075, in greater than 90% yield.

5.2 Methylation of Cyclohexylacetylene

$$c\text{-}C_6H_{11}\text{C}\equiv\text{CH} + \text{LiNH}_2\downarrow \xrightarrow[-40^\circ\text{C}]{\text{liq. NH}_3} c\text{-}C_6H_{11}\text{C}\equiv\text{CLi}\downarrow + \text{NH}_3$$

$$c\text{-}C_6H_{11}\text{C}\equiv\text{CLi}\downarrow + \text{CH}_3\text{I} \xrightarrow[-40^\circ\text{C}]{} c\text{-}C_6H_{11}\text{C}\equiv\text{CCH}_3 + \text{LiI}$$

Scale: 0.30 molar.

Apparatus: see exp. 1; size of the flask 1 l; stirrer: fig. 3.

Procedure (for Introduction see exp. 1)

Dry HMPT or DMSO (60 ml, for drying these solvents see ref. 1) is cautiously added over a few min to an efficiently stirred suspension of 0.40 mol (excess) of LiNH$_2$ in 300 ml of liquid ammonia, cooled to below -40°C. Subsequently cyclohexylacetylene (0.30 mol, see p. 166, 169) is added dropwise over 10 min with cooling below -33°C. After a 10-min interval, methyl iodide (0.40 mol) is added in small portions over 10 min using a syringe (the dropping funnel is removed and the end of the needle is held a few cm above the stirred suspension while introducing N$_2$ (1.5 l/min)). Efficient cooling is applied to keep the temperature below -40°C and a completely clear solution is obtained. The ammonia is then allowed to evaporate (fig. 11) (or the solution is cautiously poured onto 1 kg of finely crushed ice in a 5-l wide-necked round-bottomed flask, fig.13). The remaining mass is treated with 500 ml of water. After dissolution of the salts, at least three extractions with Et$_2$O or pentane are carried

out. The combined organic solutions are washed with saturated aqueous NH_4Cl and subsequently dried over $MgSO_4$. The liquid remaining after removal of the solvent *in vacuo* is carefully distilled through a 40-cm Widmer column to give *c*-$C_6H_{11}C{\equiv}CCH_3$, b.p. 51°C/12 mmHg, $n_D(20°)$ 1.4712, in > 90% yield.

A similar procedure can be followed to prepare $CH_3C{\equiv}CCH_2NEt_2$, b.p. 40°C/12 mmHg, $n_D(20°)$ 1.4438, from $HC{\equiv}CCH_2NEt_2$ (p. 273); $CH_3C{\equiv}CCH(OEt)_2$, b.p. 62°C/12 mmHg, $n_D(20°)$ 1.4264, from $HC{\equiv}CCH(OEt)_2$ (p. 176) and $CH_3C{\equiv}C$-1-cyclohexenyl, b.p. 66°C/9 mmHg, $n_D(20°)$ 1.5180, from 1-ethynylcyclohexene (see p. 203). In the last case, the co-solvent can be omitted since the lithiated acetylene has a reasonable solublity in liquid ammonia.

5.3 1,3-Pentadiyne

$$ClCH_2C{\equiv}CCH_2Cl + 3\,NaNH_2 \xrightarrow[<-33°C]{\text{liq. } NH_3} NaC{\equiv}CC{\equiv}CH + 2\,NaCl\downarrow$$

$$NaC{\equiv}CC{\equiv}CH + CH_3I \xrightarrow[-45°C]{} CH_3C{\equiv}CC{\equiv}CH + NaI$$

Scale: 1.0 molar.

Apparatus: $NaC{\equiv}CC{\equiv}CH$: fig. 1, 3 l; stirrer fig. 3.
$CH_3C{\equiv}CC{\equiv}CH$: fig. 5; cooling bath: fig. 10.

Introduction

For reasons discussed below, a successful performance of this procedure requires a considerable experimental skill at the various stages.

The formation of $NaC{\equiv}CC{\equiv}CH$ from 1,4-dichloro-2-butyne and three equivalents of sodamide in liquid ammonia is an extremely vigorous reaction. Efficient cooling, using a bath with dry ice and acetone (-78°C) should therefore be applied. Since methyl iodide is readily attacked by ammonia, previous contact of this reagent with ammonia vapour has to be avoided during its addition. These conditions can be met provided that CH_3I is added *via* a tube through which a vigorous stream of N_2 is led, and the reaction mixture is cooled to below -33°C, the b.p. of ammonia. Undoubtedly, there will be some competition from the reaction with (liquid) ammonia, resulting in CH_3NH_3I which converts the acetylide into free butadiyne. The use of an excess of alkali amide (as applied in exp. 1) to reconvert this butadiyne into the acetylide is not allowed, since this would also give rise to a subsequent metallation of $CH_3C{\equiv}CC{\equiv}CH$ which in its turn would be methylated to give $CH_3C{\equiv}C$-$C{\equiv}CCH_3$.

The isolation procedure is analogous to the one in exp. 1. During the extraction, problems may be encountered with the separation of the organic and aqueous layer. This is

mainly caused by the formation of amorphous by-products (possibly resulting from nucleophilic displacement of Cl^- by NH_2^- and further reaction of the amino-compound). It is advisable to limit the amount of ferric nitrate used in the initial conversion of the sodium to $NaNH_2$, because the $Fe(OH)_3$ gel may cause extra difficulties during the separation. Several extractions with high-boiling petroleum ether are necessary to obtain optimal yields of pentadiyne. It seems that this compound has a better solubility in the ammonia-water mixture than expected for a hydrocarbon; this might be explained by some H-bridging: $CH_3C{\equiv}C$-$C{\equiv}CH$----OH_2, which is favoured by the increased acidity of the ethynyl-H.

Possible side- and subsequent reactions

It is a reasonable assumption that with the nucleophiles $^-NH_2$ and NH_3 some displacement on methylene carbon occurs with formation of $ClCH_2C{\equiv}CCH_2NH_2$ or $NH_2CH_2C{\equiv}C$-CH_2NH_2, compounds which have good water-solubility.

In the last stage of the distillative separation of the products from the solvent, some 2,4-hexadiyne solidifies in the condenser. This may be the result of one (or both) of the following reactions:

$$2\,HC{\equiv}CC{\equiv}CNa \longrightarrow HC{\equiv}CC{\equiv}CH + NaC{\equiv}CC{\equiv}CNa \xrightarrow{2\,CH_3I} CH_3C{\equiv}CC{\equiv}CCH_3$$

$$CH_3C{\equiv}CC{\equiv}CH + NaC{\equiv}CC{\equiv}CH \longrightarrow CH_3C{\equiv}CC{\equiv}CNa \xrightarrow{CH_3I} CH_3C{\equiv}CC{\equiv}CCH_3$$

The contents of the receiver need to be redistilled in order to separate the desired 1,3-pentadiyne from small amounts of $HC{\equiv}CC{\equiv}CH$, $CH_3C{\equiv}CC{\equiv}CCH_3$ and petroleum ether. A distillation at normal pressure would be effective, but unfortunately, such an operation is risky because of the low thermostability of pentadiyne. Distillation in a partial vacuum with moderate heating is therefore carried out. In practice it is difficult to attain a constant pressure (using a manostat) because of the presence of the volatile $HC{\equiv}CC{\equiv}CH$ (b.p. between 10 and 20°C at 760 mmHg). Moreover, the difference in volatility of $CH_3C{\equiv}CC{\equiv}CH$ and $CH_3C{\equiv}CC{\equiv}CCH_3$ is not large. It will be clear from this discussion that it is difficult to obtain very pure 1,3-pentadiyne in a good yield by using a safe isolation procedure.

Procedure (compare [66])

A suspension of 3.1 mol of sodamide in 1.5 l of liquid ammonia is cooled to between -40 and -50°C, and dichlorobutyne (1.0 mol, p. 254) is added dropwise over ~45 min, while keeping the temperature between -40 and -50°C. After an additional 15 min methyl iodide (1.1 mol) is added over 30 min, while maintaining the temperature around -40°C. Fifteen minutes later, 500 ml of high-boiling petroleum ether (b.p. >170°C) is added and the equipment is removed. The dark-brown suspension is cautiously poured onto 2.5 kg of finely crushed ice contained in a 5-l wide-necked, round-bottomed flask (fig.13). The remaining salt is rinsed out of the

flask with a limited amount of ice water. After the ice has melted (some heating may be applied) the layers are separated as completely as possible. The aqueous layer is extracted at least six times with small portions of petroleum ether. The combined organic solutions (together with some $Fe(OH)_3$ gel) are treated with cold dilute hydrochloric acid (to remove the gel) and subsequently washed with water. After drying over $MgSO_4$, the extract is transferred into a distillation flask and the pentadiyne is isolated *via* an evacuation procedure (see exp. 1, Chap.I-2.6, and fig. 14). Careful redistillation of the contents of the receiver at ~200 mmHg gives reasonably pure (> 93%) 1,3-pentadiyne, b.p. ~50°C, $n_D(20°)$ 1.4762, in yields between 45 and 64%. Although the compound quickly turns brown at room temperature, it can be stored for several months under N_2 at -20°C without significant deterioration. Distillation under N_2 of a small sample (< 10 g) at normal pressure through a 30-cm column may be carried out to obtain a purer sample (b.p. ~73°C).

5.4 2,4-Hexadiyne

$$ClCH_2C{\equiv}CCH_2Cl + 4\,NaNH_2 \xrightarrow[< -33°C]{\text{liq. } NH_3} NaC{\equiv}CC{\equiv}CNa + 2\,NaCl{\downarrow}$$

$$NaC{\equiv}CC{\equiv}CNa + 2\,CH_3I \xrightarrow[< -33°C]{} CH_3C{\equiv}CC{\equiv}CCH_3 + 2\,NaI$$

Scale: 0.50 molar (dichlorobutyne).

Apparatus: $NaC{\equiv}CC{\equiv}CNa$: fig. 1, 2 l.
$CH_3C{\equiv}CC{\equiv}CCH_3$: fig. 5.

Introduction

The isolation of reasonable (>50%) yields of 1,3-pentadiyne from the reaction of dichlorobutyne, 3 equiv. of $NaNH_2$ and CH_3I, suggests that the predominant intermediate in the ammoniacal solution is the *mono*-sodium diacetylide. Although there is no definite proof, it is assumed that interaction between dichlorobutyne and *four* equivalents of sodamide affords *di*-sodium diacetylide, which in the procedure below is methylated to give 2,4-hexadiyne. The good yield of this compound does not preclude, however, a contribution of the following sequence of reactions:

$$ClCH_2C{\equiv}CCH_2Cl \xrightarrow{^-NH_2} HC{\equiv}CC{\equiv}C^- \xrightarrow{CH_3I} HC{\equiv}CC{\equiv}CCH_3 \xrightarrow{^-NH_2} {}^-C{\equiv}CC{\equiv}CCH_3$$

$$\xrightarrow{CH_3I} CH_3C{\equiv}CC{\equiv}CCH_3$$

The procedure of working up is less laborious than in the case of 1,3-pentadiyne. Using pentane as extraction solvent, an easy separation of the aqueous and organic layer can be

effected. The advantage of pentane (over Et_2O) is that the brown amorphous products do not dissolve, so that the product remaining after distillative removal of the solvent is reasonably pure 2,4-hexadiyne.

Procedure

A suspension of 2.0 mol of sodamide (ref. 1) in 1.2 l of liquid ammonia is cooled to between -40 and -50°C. Dichlorobutyne (0.50 mol, p. 254) is added dropwise over 30 min with efficient stirring (fig. 3) and cooling between -35 and -45°C. After an interval of ~10 min, methyl iodide (0.55 mol) is introduced over 30 min (for the procedure see fig. 5), while keeping the temperature around -40°C. Fifteen min after the addition, 250 ml of pentane is added (with stirring). The equipment is removed and the solution and salt mass are cautiously poured onto 1.5 kg of crushed ice contained in a 5-l wide-necked, round-bottomed flask (fig. 13). The remaining salt is rinsed out of the reaction flask with ice water. After melting of the ice and separation of the layers, three extractions with small amounts of pentane are carried out. The organic solutions are washed with dilute HCl and subsequently dried over $MgSO_4$. The greater part (70%) of the solvent is distilled off under N_2 through a 40-cm Vigreux column, keeping the bath temperature below 80°C. Strong cooling of the remaining liquid gives light-brown crystals, which are isolated on a sintered-glass funnel (suction filtration). From the mother liquor a second crop of crystals may be obtained, bringing the yield to ~75%. Very pure crystals (m.p. 67°C) may be obtained by sublimation.

5.5 Methylation of Ethoxyethyne

$$BrCH{=}CHOC_2H_5 + 2\,LiNH_2 \xrightarrow[-40°C]{\text{liq. } NH_3} LiC{\equiv}COC_2H_5 + LiBr{\downarrow} + NH_3$$

$$LiC{\equiv}COC_2H_5 + CH_3I \longrightarrow CH_3C{\equiv}COC_2H_5 + LiI$$

Scale: 0.50 molar.

Apparatus: dehydrohalogenation: fig. 1, 2 l.
methylation: fig. 5.

Introduction

Homologues of ethoxyacetylene can be obtained by reaction of the metallated ethynyl ether in liquid ammonia with primary alkyl bromides and iodides [67]. Because of their better solubility, the *lithium* compounds are preferred over their sodium and potassium analogues. Lithium ethoxyacetylide is generated from the readily accessible 2-bromovinyl ethyl ether and two equivalents of lithium amide. This starting compound is obtained as a mixture of the *E*- and *Z*-isomer. When this mixture is heated with powdered KOH, only the *Z*-isomer is converted into ethoxyethyne. Alkali amides are able to convert both isomers into ethoxyethyne and its alkali compounds. A possible explanation for this violation of the "rule of

anti-elimination" is the transient formation of the "carbanion" $^-C(Br)=CHOC_2H_5$ from the *E*-isomer and a subsequent "Fritsch-Wiechell-Buttenberg" rearrangement to $HC\equiv COC_2H_5$.

The best extraction solvent for the volatile methylation product (b.p. ~90°C at atmospheric pressure) is high-boiling petroleum ether (b.p. > 170°C).

Procedure

A suspension of 1.2 mol of lithium amide in ~0.8 l of liquid ammonia is prepared (see ref. 1 and fig. 6). 2-Bromovinyl ethyl ether (0.50 mol, see p. 196) is then added dropwise over 30 min with cooling between -35 and -45°C. The initial thick suspension is gradually replaced by a more coarse suspension of lithium bromide (complexed with NH_3). After an additional period of 30 min (note 1) methyl iodide (0.65 mol) is added over 20 min. During this addition N_2 (~1 l/min) is introduced, while the mixture is kept at ~-40°C. Fifteen minutes later, 200 ml of high-boiling petroleum ether (b.p. >170°C) is added, and the product is isolated as described in exp. 3 (five extractions are carried out, the extract should not be washed with hydrochloric acid since acetylenic ethers are very easily converted into esters by acid hydrolysis!). $CH_3C\equiv COC_2H_5$, b.p. ~50°C/120 mmHg, $n_D(20°)$ 1.4120, is obtained in 80-85% yield.

$CH_3C\equiv CCH_2OCH_3$ b.p. ~50°C/100 mmHg, $n_D(20°)$ 1.4212, can be obtained in ~80% yield by a similar procedure from 0.50 mol of $HC\equiv CCH_2OCH_3$ (p. 259), 0.60 mol of $LiNH_2$ and 0.65 mol of CH_3I.

Notes

1. The *Z*-isomer reacts instantaneously, the conversion of the *E*-isomer is somewhat slower.

5.6 C-Methylation of Propargyl Alcohol

$$HC\equiv CCH_2OH + 2\,LiNH_2 \xrightarrow[-33°C]{\text{liq. } NH_3} LiC\equiv CCH_2OLi + 2\,NH_3$$

$$LiC\equiv CCH_2OLi + CH_3I \xrightarrow[-40°C]{} CH_3C\equiv CCH_2OLi + LiI \xrightarrow{H_2O} CH_3C\equiv CCH_2OH$$

Scale: 1.0 molar.

Apparatus: $LiC\equiv CCH_2OLi$: fig 4; stirrer: fig. 3.
$CH_3C\equiv CCH_2OH$: fig. 5.
see further below.

Introduction

Propargyl alcohol can be specifically alkylated at the triple bond by adding one equivalent of a

(primary) alkyl bromide or iodide to a solution of the dilithiated alcohol in liquid ammonia. Especially in the case of the ammonia-sensitive methyl iodide careful experimentation is required. Reaction of the iodide with ammonia results in the formation of $CH_3NH_3^+I^-$, which protonates $LiC\equiv CCH_2OLi$ to $HC\equiv CCH_2OLi$. Separation of $CH_3C\equiv CCH_2OH$ from the propargyl alcohol which is reformed will presumably be very difficult. It will be clear that during the addition of methyl iodide prior contact with ammonia vapour has to be avoided! In connection with the good solubility of the product in water, a continuous-extraction procedure has to be applied.

Procedure

A suspension of 2.1 mol of lithium amide in 1.3 l of liquid ammonia is prepared as described in ref. 1 (see also fig. 6). Propargyl alcohol (1.0 mol, distilled in a partial water pump vacuum) is added dropwise over 20 min to this suspension with vigorous stirring. A grey to black solution is formed. Methyl iodide (1.1 mol) is then added over 30 min with cooling between -35 and -40°C (for the cooling vessel see fig. 10) and introducing nitrogen (1.5 l/min). Ten min after the addition, stirring and introducing N_2 are stopped and the ammonia is allowed to evaporate (see fig. 11). The solid is hydrolysed by stirring with a solution of 120 g of ammonium chloride in 500 ml of water. The resulting solution is subjected to continuous extraction with Et_2O (12-40 h, depending on the efficiency of the perculation). The extract is dried by stirring it with 50 g of $MgSO_4$ for 1 h. After filtration (sintered-glass funnel) and rinsing the $MgSO_4$ with Et_2O, the greater part of the Et_2O is distilled off through a 30-cm Vigreux column. Careful distillation through a 40-cm Widmer column gives, after a small water-containing first fraction, the product, b.p. 48°C/15 mmHg, $n_D(20°)$ 1.4535, in 75% yield.

E-$CH_3C\equiv CCH=CHCH_2OH$, b.p. 90°C/15 mmHg, $n_D(20°)$ 1.5105, can be obtained in a similar way from *E*-$HC\equiv CCH=CHCH_2OH$ (see exp. 22) in greater than 90% yield. Homologues, *e.g.* $HC\equiv CCH=CH(CH_2)_4OH$, can be methylated successfully at the acetylenic function.

5.7 C-Ethylation of Propargyl Alcohol

$$HC\equiv CCH_2OH + 2\,LiNH_2 \xrightarrow[-33°C]{\text{liq. } NH_3} LiC\equiv CCH_2OLi + 2\,NH_3$$

$$LiC\equiv CCH_2OLi + C_2H_5Br \xrightarrow[-33°C]{} C_2H_5C\equiv CCH_2OLi + LiBr \xrightarrow{H_2O} C_2H_5C\equiv CCH_2OH$$

Scale: 1.0 molar ($HC\equiv CCH_2OH$).

Apparatus: $C_2H_5C\equiv CCH_2OH$: fig. 1, 2 l.

Introduction (compare exp. 3)

Ethyl bromide is much less sensitive towards ammonia than methyl iodide and therefore it is not necessary to avoid previous contact with ammonia vapour during its addition to dilithiated propargyl alcohol. If the ethylation is carried out at -33°C (the b.p. of NH_3), however, part of the ethyl bromide may be swept along with the escaping ammonia vapour. In this way, the ethylation would be incomplete and one would be confronted with the problem of separating the product from propargyl alcohol (both compounds dissolve in Et_2O during continous extraction). Addition of an excess of C_2H_5Br is not advisable since this would result in partial formation of $C_2H_5C{\equiv}CCH_2OC_2H_5$ which has a b.p. that is only ~20°C lower than that of $C_2H_5C{\equiv}CCH_2OH$. The best solution is to carry out the ethylation at a temperature that is only a few °C below -33°C.

Procedure

A suspension of lithium amide (2.1 mol in 1.3 l of liquid NH_3) is prepared as described in ref. 1 (see also fig. 6). Propargyl alcohol (1.0 mol) is added over 20 min. The flask is then equipped as shown in fig. 1 and ethyl bromide (1.1 mol) is added dropwise over 45 min, while keeping the temperature of the suspension between -35 and -38°C. During these additions N_2 is introduced at a rate of ~200 ml/min. Stirring is continued for an additional 1 h at the b.p. of ammonia. The ammonia is then allowed to evaporate (see fig. 11). The work-up and the isolation of the product is carried out in a way similar to that in exp. 6. $C_2H_5C{\equiv}CCH_2OH$, b.p. 56°C/12 mmHg, $n_D(20°)$ 1.4525, is obtained in greater than 80% yield.

5.8 Ethylation of Ethoxyethyne

$$BrCH{=}CHOC_2H_5 + 2\,LiNH_2 \xrightarrow[-40°C]{\text{liq. } NH_3} LiC{\equiv}COC_2H_5 + LiBr{\downarrow} + NH_3$$

$$LiC{\equiv}COC_2H_5 + C_2H_5Br \xrightarrow[-33°C]{} C_2H_5C{\equiv}COC_2H_5 + LiBr{\downarrow}$$

Scale: 0.50 molar.

Apparatus: $LiC{\equiv}COC_2H_5$: fig. 1, 2 l; cooling vessel: fig. 10.
$C_2H_5C{\equiv}COC_2H_5$: fig. 4.

Procedure (for Introduction see exp. 5)

A suspension of 1.1 mol of $LiNH_2$ in 1.3 l of liquid ammonia is prepared as described in ref. 1 (see also fig. 6). 2-Bromovinyl ethyl ether (0.50 mol, see p. 196) is added dropwise over 20 min with efficient stirring and cooling between -35 and -40°C. After an additional 20 min the cooling bath is removed and 0.7 mol of ethyl bromide is added dropwise over 45 min with vigorous stirring. After an additional period of 30 min, stirring is stopped, 200 ml of Et_2O is added and the ammonia is allowed to evaporate overnight (see fig. 11). Ice water (500 ml) is added to the remaining mass and the salts are dissolved. The product is extracted four times with small portions of Et_2O. The combined extracts are dried over K_2CO_3. The greater part of the Et_2O is distilled off at 760 mmHg through a 40-cm Widmer column, keeping the bath temperature below 80°C (note 1). After cooling to room temperature, the remaining liquid is distilled using a partial water-pump vacuum. $C_2H_5C{\equiv}COC_2H_5$, b.p. ~50°C/90 mmHg, $n_D(20°)$ 1.4153, is obtained in yields between 75 and 80%.

Notes

1. Ethyl and higher-alkyl alkynyl ethers eliminate ethene at elevated temperatures [68].

5.9 1,3-Hexadiyne

$$ClCH_2C{\equiv}CCH_2Cl + 3\,NaNH_2 \xrightarrow[-40°C]{\text{liq. } NH_3} NaC{\equiv}CC{\equiv}CH + 2\,NaCl{\downarrow} + 2\,NH_3$$

$$NaC{\equiv}CC{\equiv}CH + C_2H_5Br \xrightarrow[-35 \text{ to } -40°C]{} C_2H_5C{\equiv}CC{\equiv}CH + NaBr{\downarrow}$$

Scale: 0.50 molar.

Apparatus: fig. 1, 2 l; cooling vessel: fig. 10.

Introduction

The product is rather volatile, with an estimated b.p. between 100 and 110°C at 760 mmHg. If the ethylation was carried out at the b.p. of ammonia and this solvent allowed to evaporate, 5-10% of the product would be lost. For this reason and also in view of the limited thermal stability of 1,3-hexadiyne (danger of explosive decomposition at elevated temperatures) we propose a work-up procedure similar to that used in exp. 3.

Procedure

A suspension of 1.6 mol of sodamide in 1.3 l of liquid NH_3 is prepared as described in ref.1 (see also fig. 6). Dichlorobutyne (0.50 mol, see p. 254) is added dropwise over 30 min with efficient stirring (for the stirrer see fig. 3) and cooling between -35 and -40°C. After an additional 10 min, 0.65 mol of ethyl bromide is added over 45 min, at the same temperature. One hour later, 300 ml of high-boiling petroleum ether (b.p. >170°C) is added and the suspension is cautiously poured onto 1.5 kg of finely crushed ice contained in a 5-l wide-necked round-bottomed flask (fig. 13) or conical flask. The reaction flask is rinsed with ice water, which is added to the bulk. After the ice has melted, the layers are separated and the aqueous layer is extracted 5 times with small portions of high-boiling petroleum ether (note 1). The combined extracts are washed with 2N hydrochloric acid and subsequently dried over $MgSO_4$. 1,3-Hexadiyne, b.p. ~50°C/120 mmHg, $n_D(20°)$ 1.4735, is isolated in 55-60%

yield as described in exps. 1 and 3, and in Chap. I-2.6.

$C_2H_5C{\equiv}CCH{=}CH_2$, b.p. ~50°C/140 mmHg or 89°C/760 mmHg, $n_D(20°)$ 1.4595, can be prepared by a similar procedure from *E*-1,4-dichloro-2-butene (commercially available), 3 equiv. of $NaNH_2$ and C_2H_5Br. The yield is *ca.* 70%. Starting from *Z*-dichlorobutene the enyne is obtained in a considerably lower yield. The aqueous work-up in the latter case is very difficult because of the presence of large amounts of amorphous by-products. Peculiarly, *lithium* amide and *Z*-dichlorobutene react much more cleanly.

Notes

1. The separation of the layers may be difficult due to formation of amorphous products.

5.10 1-Pentyne and 1-Hexyne

$$NaC{\equiv}CH + RBr \xrightarrow[-38°C]{\text{liq. } NH_3} RC{\equiv}CH + NaBr\downarrow$$

Scale: 2.0 molar.

Apparatus: NaC≡CH: fig. 15, 3 l.
RC≡CH: fig. 1.
cooling bath: fig. 10.

Introduction

For the rationalization of the procedure of work-up and isolation see exps. 1, 3 and Chap. I-2.6.

Since the differences in boiling points of the alkyl bromides and the alkynes is only some 25°C, distillative separation will be rather difficult. In order to attain a complete conversion of the alkyl bromides, the reactions are carried out with a 25% excess of sodium acetylide.

Procedure

A solution of 2.5 mol of sodium acetylide in liquid NH_3 (p. 17-19) is cooled to ~-40°C and a vigorous stream of acetylene is introduced for 2 min (3 l/min). The alkyl bromide (2.0 mol) is then added dropwise over 1 h while maintaining the temperature as close as possible to -38°C. Stirring at this temperature is continued for another 1.5 h (for the type of stirrer see fig 3), then 300 ml of high-boiling petroleum ether (b.p. >170°C) is added. The mixture is cautiously poured onto 2 kg of finely crushed ice in a 5-l wide-necked round-bottomed (fig. 13) or conical flask. The reaction flask is rinsed with a small amount of ice water which is added to the bulk. After separation of the layers, three extractions with small amounts of petroleum ether are carried out. The extracts are washed with dilute hydrochloric acid and subsequently dried over $MgSO_4$. Isolation is carried out as described in exps. 1 and 3, and in Chap. I-2.6. The product is carefully redistilled through a 40-cm Widmer column. 1-Pentyne, b.p.

41°C/760 mmHg, $n_D(20°)$ 1.3860, and 1-hexyne, b.p. 71°C/760 mmHg, $n_D(20°)$ 1.3990, are obtained in yields between 75 and 83%.

1-Heptyne, b.p. 100°C/760 mmHg, $n_D(20°)$ 1.4093, can be obtained in yields between 75 and 85% by carrying out the reaction with $C_5H_{11}Br$ in the presence of 200 ml of DMSO.

5.11 Propylation and Butylation of Vinylacetylene and Diacetylene

$$NaC{\equiv}CCH{=}CH_2 + RBr \xrightarrow[-33°C]{\text{liq. } NH_3} RC{\equiv}CCH{=}CH_2 + NaBr\downarrow$$

$R = C_3H_7, C_4H_9$

$$NaC{\equiv}CC{\equiv}CH + RBr \xrightarrow[-33°C]{\text{liq. } NH_3} RC{\equiv}CC{\equiv}CH + NaBr\downarrow$$

Scale: 0.5 molar.

Apparatus: fig. 4, 2 l; stirrer: fig. 3.

Introduction

In the preparation of 1-pentyne and 1-hexyne (exp. 10) complete conversion of the alkyl bromides is effected by using an excess of sodium acetylide. A reasoning based on economics prompts the use of an excess of the alkyl halide if alkali vinylacetylide or alkali diacetylide (generated from alkali amide and dichlorobutene or dichlorobutyne, respectively) are to be alkylated. If slightly more than the stoichiometrical amount of alkyl bromide is used, no serious separation problems will be encountered during the final distillation. A relatively small amount of DMSO is added to enhance the solubility of the alkyl bromides, thereby facilitating the alkylation reaction.

Procedure

A solution of 0.5 mol of sodium vinylacetylide or sodium diacetylide in 1.3 l of liquid ammonia is prepared as described in exps. 3 and 9. The reaction flask is then equipped as shown in fig. 4. The alkyl bromide (0.6 mol) is added dropwise over 45 min with efficient stirring and without external cooling. When the addition is completed, 100 ml of dry DMSO is added and stirring is continued for an additional 1.5 h. The flask is then equipped as shown in fig. 11 and the ammonia is allowed to evaporate. The remaining mass is treated with 1 l of water and the product is extracted with pentane (note 1). The presence of some amorphous material may cause difficulties in the separation of the layers. Suction filtration through sintered glass followed by rinsing of the material on the filter with pentane may help. The extracts are washed with dilute HCl and subsequently dried over $MgSO_4$. In the case of the propyl compounds, the greater part of the pentane is first distilled off through a 40-cm Vigreux column, keeping the bath temperature below 80°C. The remaining liquid is carefully distilled through a 40-cm Widmer column using a partial water-pump vacuum. The butyl

derivatives are isolated by evaporating the pentane using a rotary evaporator and carefully distilling the remaining liquids through a 40-cm Widmer column. The folowing compounds $RC{\equiv}CCH{=}CH_2$ are obtained in ~70% yield; the yields of $RC{\equiv}CC{\equiv}CH$ are between 58 and 62%:

$C_3H_7C{\equiv}CCH{=}CH_2$, b.p. 50°C/60 mmHg, $n_D(20°)$ 1.4532;
$C_3H_7C{\equiv}CC{\equiv}CH$, b.p. 40°C/40 mmHg, $n_D(20°)$ 1.4748;
$C_4H_9C{\equiv}CCH{=}CH_2$, b.p. 65°C/70 mmHg, $n_D(20°)$ 1.4564;
$C_4H_9C{\equiv}CC{\equiv}CH$, b.p. 40°C/15 mmHg, $n_D(20°)$ 1.4757.

Notes

1. The undesired resinous products do not dissolve in pentane.

5.12 Propylation and Butylation of Ethoxyethyne

$$BrCH{=}CHOC_2H_5 + 2\,LiNH_2 \xrightarrow[-40°C]{\text{liq. } NH_3} LiC{\equiv}COC_2H_5 + LiBr{\downarrow} + NH_3$$

$$LiC{\equiv}COC_2H_5 + RBr \xrightarrow[-33°C]{} RC{\equiv}COC_2H_5 + LiBr{\downarrow} \qquad (R = C_3H_7, C_4H_9)$$

Scale: 0.50 molar.

Apparatus: fig. 4, 2 l; stirrer: fig. 3.

Procedure (for Introduction see exps. 3, 5 and 11)
Propyl bromide (0.65 mol) or butyl bromide (0.60 mol) is added dropwise over 45 min to a solution of 0.50 mol of lithium ethoxyacetylide in 1.3 l of liquid ammonia at -33°C (see exp. 5). In the case of the reaction with butyl bromide, 100 ml of dry DMSO is added after this period. Stirring is continued for an additional 1.5 h, then 200 ml of Et_2O is added and the ammonia is allowed to evaporate (fig. 11) (it is also possible to pour the mixture onto 1.5 kg of crushed ice in a 5-l wide-necked, round-bottomed or conical flask and to rinse the remaining salt mass out of the reaction flask with ice water). After the salt mass has dissolved in the water, the product is extracted with Et_2O. The combined organic solutions are washed with water and then dried over $MgSO_4$. After the greater part of the solvent has been distilled off at normal pressure through a 40-cm Vigreux column (bath temperature < 80°C), the remaining liquid is carefully distilled through the same column at reduced pressure. $C_3H_7C{\equiv}COC_2H_5$, b.p. ~45°C/40 mmHg, $n_D(20°)$ 1.4218, and $C_4H_9C{\equiv}COC_2H_5$, b.p. 45°C/12 mmHg, $n_D(20°)$ 1.4273, are obtained in > 80% yield.

5.13 4,6-Decadiyne and 3,5-Octadiyne

$$NaC{\equiv}CC{\equiv}CNa + 2\,C_3H_7Br \xrightarrow[-33°C]{\text{liq. } NH_3} C_3H_7C{\equiv}CC{\equiv}CC_3H_7 + 2\,NaBr{\downarrow}$$

Scale: 0.5 molar.

Apparatus: $NaC{\equiv}CC{\equiv}CNa$: fig. 1, 2 l; stirrer: fig. 3.
alkylation: fig. 4.

Procedure (for Introduction see exp. 4)
Propyl bromide (1.3 mol) is added dropwise over 1 h to an efficiently stirred solution of 0.5 mol of $NaC{\equiv}CC{\equiv}CNa$ in about 1.2 l of liquid ammonia (exp. 4). After an additional 2 h stirring is stopped and the ammonia is allowed to evaporate (fig. 11) overnight. Water (~500 ml) is then added and the product is extracted with pentane (see note of exp. 11). The brown extract is washed with dilute HCl and subsequently dried over $MgSO_4$. The liquid remaining after concentration of the solution under reduced pressure, is distilled through a 40-cm Vigreux column to give the diyne, b.p. 80°C/15 mmHg, $n_D(18°)$ 1.4897, in 65% yield.

$C_2H_5C{\equiv}CC{\equiv}CC_2H_5$, b.p. 47°C/15 mmHg, $n_D(20°)$ 1.4931, is obtained in 70% yield by a similar procedure, with the difference that the extract is concentrated by distilling off the greater part of the solvent at 760 mmHg.

5.14 5-Decyne

$$HC{\equiv}CLi + LiNH_2 + 2\,C_4H_9Br \xrightarrow[-33°C]{\text{liq. } NH_3} C_4H_9C{\equiv}CC_4H_9 + 2\,LiBr{\downarrow} + NH_3$$

Scale: 0.5 molar ($HC{\equiv}CLi$ and $LiNH_2$).

Apparatus: $HC{\equiv}CLi$: fig. 15, 3 l.
$LiNH_2$: fig. 6, 1 l.
$C_4H_9C{\equiv}CC_4H_9$: fig. 4, 3 l; stirrer: fig. 3.

Introduction
Dropwise addition of alkyl bromides to an equimolar mixture of lithium amide and lithium acetylide in liquid ammonia gives dialkylacetylenes in good yields. Apparently, there is no serious competition from the reaction of $LiNH_2$ with alkyl bromide, *i.e.* no formation of alkylamine or dehydrohalogenation of the alkyl bromide. The result might lead to the assumption that $LiNH_2$ and $LiC{\equiv}CH$ react with each other to give $LiC{\equiv}CLi$, which is subsequently dialkylated. However, it is doubtful whether $LiC{\equiv}CLi$ is formed in a significant

concentration. A reasonable alternative explanation for the formation of the disubstituted acetylene is the following reaction sequence in which RBr reacts preferentially with the soluble HC≡CLi and RC≡CLi:

$$\underset{\text{soluble}}{HC{\equiv}CLi} \xrightarrow{RBr} HC{\equiv}CR \xrightarrow{LiNH_2} \underset{\text{soluble}}{LiC{\equiv}CR} \xrightarrow{RBr} RC{\equiv}CR$$

Procedure

A suspension of 0.6 mol (note 1) of lithium amide in ~700 ml of liquid ammonia (see ref. 1), is cautiously poured (note 2) into a flask containing a solution of 0.5 mol of lithium acetylide (pag. 18 and note 3) in 600 ml of liquid ammonia. Butyl bromide (1.1 mol) is then added dropwise over 1.5 h with efficient stirring. After an additional 1.5 h stirring is stopped and the ammonia is allowed to evaporate overnight (fig. 11). The product is isolated as described in exp. 13. Distillation through a 40-cm Widmer column gives $C_4H_9C{\equiv}CC_4H_9$, b.p. 58°C/10 mmHg, $n_D(20°)$ 1.4329, in ~70% yield.

Notes

1. The excess is to compensate for small amounts remaining in the flask after transferring the suspension into the other flask.
2. During this operation the outer necks of the flasks are open. A small amount of Et_2O may be added to suppress frothing (see Chap. I-2.5).
3. No excess of HC≡CH should be introduced during the preparation of LiC≡CH (see exp. 1).

5.15 Butylation of Chloroacetylene

$$ClCH{=}CHCl + 2\,LiNH_2 \xrightarrow[-40°C]{\text{liq. } NH_3} LiC{\equiv}CCl + LiCl{\downarrow} + NH_3$$

$$LiC{\equiv}CCl + C_4H_9Br \longrightarrow C_4H_9C{\equiv}CCl + LiBr{\downarrow}$$

Scale: 0.50 molar.

Apparatus: LiC≡CCl: fig. 1, 2 l; cooling vessel: fig. 10; stirrer: fig. 3.
$C_4H_9C{\equiv}CCl$: fig. 1.

Introduction

Although this alkylation of alkali chloroacetylide is completely analogous to the alkylations described in the previous experiments, the procedure for the preparation of 1-chloro-1-hexyne warrants a brief explanation.

Since the boiling point of chlorohexyne differs only some 15°C from that of butyl bromide, it is not advisable to use an excess of butyl bromide. Butyl iodide is unsuitable for

the same reason. A consequence of the use of an excess of the *chloroacetylide* would be the liberation of extremely dangerous monochloroacetylene during the aqueous work-up. This risk is avoided by adding an amount of CH_3I corresponding to the excess of LiC≡CCl. Methyl chloroacetylene is very volatile. DMSO is added to facilitate the reaction with butyl bromide by an increase of the solubility of this compound.

Procedure

A mixture of *E*- and *Z*-dichloroethene (0.60 mol) is added dropwise over 30 min to a suspension of 1.2 mol of lithium amide (ref. 1 and fig. 6) in 900 ml of liquid ammonia. During this addition the temperature of the suspension is kept at *ca.* -40°C, while N_2 (0.5 l/min) is passed through the apparatus. To minimize splashing of the suspension into the upper regions, stirring is carried out at a moderate rate but nevertheless efficiently. After an interval of 10 min, 100 ml of dry DMSO (for drying DMSO see ref. 1) is cautiously added (over 1 min) from the dropping funnel. Butyl bromide (0.50 mol, short measure) is then added dropwise over 1 h, while continuing the introduction of N_2 and keeping the temperature between -35 and -40°C. After an additional 2 h, 0.2 mol of methyl iodide is added over a few min. Pentane (200 ml) is then added with stirring, and the auxiliary equipment is removed with the exception of the N_2-inlet. Acetone is sprayed along the inner walls of the flask (note 1), while N_2 is introduced at a rate of 2 l/min. The mixture is then cautiously poured onto 1.5 kg of finely crushed ice in a 5-l wide-necked, round-bottomed flask (fig. 13). The remaining salt is rinsed out of the flask with ice water. After the remaining ice has melted (some warming may be necessary), three extractions with small amounts of pentane are carried out. The combined pentane solutions are washed with water and then dried over $MgSO_4$. The greater part of the solvent is distilled off through a 40 to 50-cm Widmer column. Careful distillation of the remaining liquid through the same column gives $C_4H_9C{\equiv}CCl$, b.p. ~60°C/100 mmHg, $n_D(20°)$ 1.4358, in 70% yield (based on C_4H_9Br).

Notes

1. Traces of LiC≡CCl, which may be present on the upper part of the glass wall, are converted into $(CH_3)_2C(OH)C{\equiv}CCl$.

5.16 C-Butylation of Propargyl Alcohol

$$LiC{\equiv}CCH_2OLi + C_4H_9Br \xrightarrow[-33°C]{\text{liq. } NH_3} C_4H_9C{\equiv}CCH_2OLi + LiBr{\downarrow} \xrightarrow{H_2O} C_4H_9C{\equiv}CCH_2OH$$

Scale: 0.50 molar.

Apparatus: $LiC{\equiv}CCH_2OLi$: fig. 4, 2 l; stirrer: fig. 3.
$C_4H_9C{\equiv}CCH_2OH$: fig. 4.

Procedure (for Introduction see exp. 6)

Butyl bromide (0.50 mol) is added dropwise over 1 h to an efficiently stirred solution of 0.50 mol of $LiC{\equiv}CCH_2OLi$ in 1.2 l of liquid ammonia (see exp. 6). Stirring is continued for an additional 1.5 to 2 h, then the ammonia is allowed to evaporate (fig. 11). Water (500 ml) is added to the remaining solid mass. The acetylenic alcohol is isolated by extracting six times with Et_2O, drying the (unwashed) extracts over $MgSO_4$, removing the solvent *in vacuo* and distilling the remaining liquid through a 40-cm Vigreux column. $C_4H_9C{\equiv}CCH_2OH$, b.p. 83°C/12 mmHg, $n_D(20°)$ 1.4550, is obtained in ~75% yield.

The homologues $C_3H_7C{\equiv}CCH_2OH$ and $C_5H_{11}C{\equiv}CCH_2OH$ may be prepared by a similar procedure. In the case of the propyl derivative, more extractions with Et_2O should be carried out.

5.17 C-Alkylation of Propargyl Alcohol with a Higher Alkyl Bromide

$$LiC{\equiv}CCH_2OLi + C_8H_{17}Br \xrightarrow[-33 \rightarrow +15°C]{\text{liq. } NH_3 \rightarrow \text{ DMSO}} C_8H_{17}C{\equiv}CCH_2OH + LiBr\downarrow$$

(after hydrolysis)

Scale: 0.40 molar.

Apparatus: $LiC{\equiv}CCH_2OLi$: fig. 4, 2 l.
$C_8H_{17}C{\equiv}CCH_2OH$: fig. 1.

Introduction

As a consequence of the poor solubility of higher alkyl bromides in ammonia and of the moderate C-nucleophilicity of acetylides, the alkylations proceed sluggishly at the boiling point of ammonia. In the procedure for undecynol, a considerable amount of DMSO is used as co-solvent. The effect of this addition is that the temperature of the reaction mixture can rise gradually as more ammonia is lost by evaporation. Furthermore, the solubility of the higher alkyl bromide is increased. Et_2O and THF may have similar favourable effects. However, these solvents cause a decrease of the solubility of the alkali acetylide when a considerable part of the ammonia has evaporated. We do not believe that the characteristic properties of DMSO as a dipolar aprotic solvent will appear to full advantage before practically all the ammonia has evaporated.

Procedure

Propargyl alcohol (0.50 mol) is added dropwise over 15 min to a suspension of 1.10 mol of lithium amide in ~700 ml of liquid ammonia. Subsequently, 0.40 mol of octyl bromide (short measure) is added over 30 min, directly followed by 350 ml of DMSO (for drying DMSO see ref. 1). The temperature of the reaction mixture rises gradually while salt begins to separate (this may redissolve at a later stage). The ice crust on the outside of the flask is occasionally removed by spraying with acetone. Stirring at 10 to 15°C is continued for an additional hour,

then 1.5 l of ice water is cautiously added and the mixture is extracted 7 times with Et_2O. The combined organic solutions are washed with a saturated solution of NaCl (2x) and then dried over $MgSO_4$. After removal of the solvent, the remaining liquid is distilled through a 20-cm Vigreux column to give $C_8H_{17}C{\equiv}CCH_2OH$, b.p. ~90°C/0.5 mmHg, $n_D(18°)$ 1.4597, in ~85% yield.

All alcohols $RC{\equiv}CCH_2OH$ with R longer than C_6H_{13} can be prepared in this way.

5.18 1-Octyne, 1-Nonyne and 1-Decyne

$$HC{\equiv}CLi + RBr \xrightarrow{\text{liq. } NH_3 \rightarrow \text{ DMSO}} HC{\equiv}CR + LiBr\downarrow$$

Scale: 0.5 molar.

Apparatus: $LiC{\equiv}CH$: fig. 15, 2 l; stirrer: fig. 3.
$HC{\equiv}CR$: fig. 1.

Procedure (for Introduction see exp. 6)

DMSO (200 ml) is cautiously added over a few min to a solution of 0.8 mol (note 1) of lithium acetylide (note 2) in ~0.5 l of liquid ammonia (p. 17-19). The alkyl bromide (0.5 mol) is added dropwise over 15 min with efficient stirring. The ice crust on the outside of the flask is occasionally removed by spraying with acetone. After 2-3 h the temperature has reached *ca.* -10°C. The heating effect then may become easily observable and the temperature may rise over a few min to 10°C or higher: occasional cooling in an ice-bath may be necessary to keep the temperature between 10 and 15 °C. After an additional period of 30 min at 10 to 15°C, a solution of 25 g of NH_4Cl in 800 ml of water is cautiously added with stirring. The mixture is then extracted with small portions of pentane. The combined organic solutions are washed twice with dilute HCl and subsequently dried over $MgSO_4$. The pentane is distilled off at normal pressure. In the case of 1-octyne the distillation is continued through a 30-cm Vigreux column: b.p. 128°C, $n_D(20°)$ 1.4160, yield ~80%. In the other cases the products are distilled through a 40-cm Vigreux column: 1-nonyne, b.p 42°C/12 mmHg, $n_D(20°)$ 1.4212, and 1-decyne, b.p. 58°C/12 mmHg, $n_D(20°)$ 1.4263, are obtained in greater than 80% yields. Small amounts of solid residue of the disubstituted acetylene, $RC{\equiv}CR$, remain in the distillation flask.

Notes

1. The relatively large excess of lithium acetylide serves in part to neutralize small amounts of water in the DMSO.
2. Sodium acetylide may also be used. However, the lithium derivative is preferred because with it the risk of an isomerization to $CH_3C{\equiv}CR'$ at temperatures above 0°C under the influence of excess acetylide is less.

5.19 Octa-1,7-diyne, Nona-1,8-diyne, and Deca-1,9-diyne

$$2\ NaC{\equiv}CH + Br(CH_2)_nBr \xrightarrow{\text{liq. } NH_3} HC{\equiv}C(CH_2)_nC{\equiv}CH + 2\ NaBr$$

(n = 4,5,6)

Scale: 0.50 molar $Br(CH_2)_nBr$.

Apparatus: NaC≡CH: fig. 15, 3 l; stirrer: fig. 3.
alkylation: fig. 4.

Procedure

The dibromide (0.50 mol) is added dropwise over 45 min to a solution of 1.3 mol of sodium acetylide (exps. 1 and 2) in 1.6 l of liquid ammonia at -33°C. After 4 h, finely crushed ice and ice water (500 g) are cautiously added with vigorous stirring (a few ml of Et_2O may be added in the case of frothing). The diyne is isolated by extraction with small portions of pentane. The organic solution is dried over $MgSO_4$. Evaporation of the solvent, followed by distillation *in vacuo* gives octa-1,7-diyne, b.p. 37°C/10 mmHg (single receiver, cooled at 0°C), $n_D(20°)$ 1.4474, nona-1,8-diyne b.p. 52°C/10 mmHg, $n_D(20°)$ 1.4495, and deca--1,8-diyne, b.p. 70°C/10 mmHg, $n_D(20°)$ 1.4515, in yields of ~70% (octadiyne) and 80%.

5.20 1,3-Decadiyne

$$HC{\equiv}CC{\equiv}CNa + C_6H_{13}Br \xrightarrow[-33 \rightarrow 20°C]{\text{liq. } NH_3 \rightarrow \text{DMSO}} HC{\equiv}CC{\equiv}CC_6H_{13} + NaBr\downarrow$$

Scale: 0.50 molar.

Apparatus: NaC≡CC≡CH: fig. 1, 2 l; stirrer: fig. 3.
alkylation: fig. 4.
evaporation of NH_3: fig. 11.

Introduction

1,3-Diynes are more acidic than HC≡CH (pK probably at least 3 units lower [69]). Thus NaC≡CC≡CH is a weaker base than NaC≡CH and consequently a weaker nucleophile. As in exp. 17, the use of DMSO as a co-solvent is necessary to attain a satisfactory rate of conversion in the reaction of NaC≡CH with $C_6H_{13}Br$. The assistance of DMSO will therefore also be required in the reaction of alkali diacetylides with higher alkyl bromides.

Procedure

Dry DMSO (300 ml, for drying DMSO see ref. 1) is cautiously added over a few min to a

solution of 0.6 mol of sodium diacetylide (p. 44) in 800 ml of liquid ammonia. Subsequently, 0.50 mol of hexyl bromide is added over 5 min, and the mixture is stirred for 5 h. The remaining ammonia is then allowed to evaporate overnight. After adding 250 ml of pentane and 500 ml of water, the mixture is stirred until the salts have dissolved (5 to 10 min). The separation of the layers may be hindered by the presence of dark amorphous material: acidification with dilute HCl may give improvement. After separation of the layers, two extractions with pentane are carried out. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated under reduced pressure. Distillation of the remaining brown liquid at a pressure of < 1 mmHg, using a single receiver cooled at 0°C (fig. 14), gives the crude product which upon redistillation gives 1,3-decadiyne, b.p. 85°C/15 mmHg, $n_D(19°)$ 1.4778, in 55% yield.

5.21 Reaction of Lithium Acetylide with Protected 4-Bromobutanol and Subsequent Deprotection

$$THF + HBr \xrightarrow{40°C} Br(CH_2)_4OH$$

$$Br(CH_2)_4OH + H_2C{=}CHOC_2H_5 \longrightarrow Br(CH_2)_4OCH(CH_3)OC_2H_5 \quad (1)$$

$$(1) + LiC{\equiv}CH \xrightarrow[-33 \rightarrow 10°C]{\text{liq. } NH_3 \rightarrow \text{DMSO}} HC{\equiv}C(CH_2)_4OCH(CH_3)OC_2H_5 \longrightarrow$$

$$\xrightarrow[50°C]{CH_3OH,\ H^+} HC{\equiv}C(CH_2)_4OH$$

Scale: 0.6 molar (HBr).

Apparatus: ring opening: 500-ml round-bottomed flask + gas inlet tube and thermometer (swirling by hand).
protection: fig. 1, 500 ml.
reaction with LiC≡CH: fig. 1; stirrer: fig. 3.
deprotection: one-necked flask, 1 l.

Introduction

The procedure for 5-hexyn-1-ol is an illustration of the use of THF as a building block for the introduction of a $(CH_2)_4OH$ unit. Bromobutanol is formed quantitatively by simply introducing gaseous HBr into THF. The ring opening proceeds easily in the absence of any catalyst (for the reaction with HCl, $ZnCl_2$ is required). Bromobutanol is not suitable for alkylation reactions since nucleophilic reagents immediately cause ring closure to THF. However, protection of the OH group with cheap ethyl vinyl ether, as well as the deprotection

after the coupling reaction, can be carried out quantitatively under mild conditions (note 1). Since the solution obtained by introducing HBr into THF is slightly acidic, its addition to ethyl vinyl ether can be carried out without *p*-toluenesulfonic acid, the usual catalyst for the protection (p. 265) The protected bromobutanol behaves as a normal alkylating agent in the reaction with alkali acetylides.

Procedure

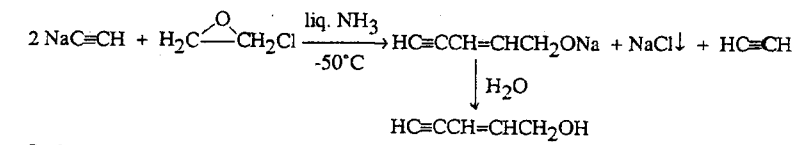
Dry HBr is introduced with manual swirling into 150 ml of THF until the weight increase is 50 g (0.6 mol). The temperature of the solution should be kept below 50°C (preferably around 40°C). The use of a bath with dry ice and acetone (-80°C) permits a rapid introduction of HBr. After standing for an additional 10 min at ~40°C, the almost colourless solution is cooled to -5°C, and then added to 60 g (excess) of freshly distilled ethyl vinyl ether in a number of portions (if there is no clearly observable heating effect after adding the first 10 to 20%, 50-100 mg of *p*-toluenesulfonic acid should be added before continuing the addition). The temperature of the mixture is kept between 5 and -5°C by occasional cooling in a bath with dry ice and acetone. After an additional 20 min at 0°C a few ml of triethylamine are added to neutralize traces of acid. The obtained solution is added (without removing the excess of THF and vinyl ether) over 20 min to an efficiently stirred solution of 0.9 mol of lithium acetylide (p. 17) in 600 ml of liquid ammonia. Subsequently 250 ml of DMSO is cautiously added over a few min and the mixture is stirred for an additional 2 h, and the flask is then placed in a water bath at 40°C (the dropping funnel is replaced by a rubber stopper with a wide hole). The temperature rises gradually while salt separates from the solution. After stirring the mixture for an additional 30 min at ~+10°C, a solution of 25 g of ammonium chloride in 1 l of ice water is slowly added with vigorous stirring. The solution is extracted four times with Et_2O. After washing of the combined organic solutions four times with a saturated solution of NH_4Cl, the solvent is removed using a rotary evaporator (drying is not necessary). Methanol (150 ml) and subsequently 1.5 ml of 36% HCl is added to the remaining liquid. The solution is heated for 15 min at 50°C, and 5 ml of a saturated aqueous solution of KOH is then added. The volatile compounds are removed on the rotary evaporator. The remaining liquid is distilled quickly at < 1 mmHg and collected in a single receiver (fig. 14). Redistillation through a 40-cm Vigreux column gives hexynol, b.p. 75°C/15 mmHg, $n_D(21°)$ 1.4481, in greater than 80% yield.

$CH_3C{\equiv}C(CH_2)_4OH$, b.p. 110°C/10 mmHg, $n_D(19°)$ 1.4663, is obtained in 88% yield by a similar procedure, using a 15% molar excess of $CH_3C{\equiv}CLi$.

Notes

1. Many chemists seem to prefer dihydropyrane as a reagent for the protection. It should be pointed out, however, that both protection and deprotection proceed more satisfactorily using ethyl vinyl ether.

5.22 2-Penten-4-yn-1-ol



Scale: 1.0 molar (epichlorohydrine).

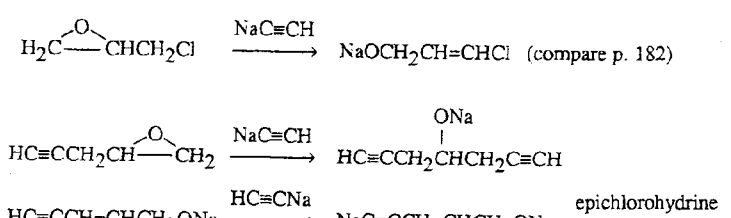
Apparatus: fig. 1, 2 l; cooling vessel: fig. 10; stirrer: fig. 3.

Introduction

English investigators reported [60] the synthesis of the title alcohol from epichlorohydrine and sodium acetylide in liquid ammonia. The synthesis is easily performable on a large scale and gives a useful intermediate. The relatively low yield is explained by the occurrence of a number of other processes, the principal one of which is probably the base-catalysed cyclization of Z-$HC{\equiv}CCH{=}CHCH_2ONa$ to 2-methylfuran, which can be swept along with the ammonia vapour. When the synthesis is carried out with *lithium* acetylide, a mixture of comparable amounts of *E*- and *Z*-pentenynol is obtained in a higher yield [61]. Apparently, the *Z*-lithium alcoholate cyclises less readily.

As mentioned in Section III-1, the formation of the enyne alcoholate may proceed along one or both of two routes: one starting with the nucleophilic displacement of Cl^- by $HC{\equiv}C^-$, the other with the attack of $HC{\equiv}C^-$ on the least substituted C-atom of the epoxide ring. Since alkyl chlorides react very sluggishly with alkali acetylides in liquid ammonia, the reaction path beginning with the attack of $HC{\equiv}C^-$ on CH_2Cl does not seem to have a large contribution in the formation of the pentenynolate. The reaction conditions of exp. 23 show that the ring opening by attack of $HC{\equiv}C^-$ on oxirane is also a rather slow reaction. It might be possible, however, that the analogous ring opening with epichlorohydrine is easier due to inductive influence of the CH_2Cl grouping.

Examples of possible side- or subsequent reactions which might explain the decreased yields, are the following:



→ reactions analogous to main reaction

Procedure

Epichlorohydrine (1.0 mol) is added dropwise over 2 h to a solution of 2.3 mol of sodium acetylide (p. 18) in 1.3 l of liquid ammonia at ~ -55°C (note 1). After an additional 1.5 h (at -55°C) the cooling bath is removed and stirring at -33°C is continued for another 2 h. The auxiliary equipment is then removed and the ammonia is allowed to evaporate overnight (fig. 11). The remaining solid (note 1) is hydrolysed with a saturated aqueous solution of ammonium chloride (500 ml), after which 15 extractions with Et_2O are carried out. The unwashed (note 2) extracts are dried over K_2CO_3 and subsequently concentrated *in vacuo*. The remaining brown liquid is first subjected to a rough distillation at < 0.5 mmHg, through a short Vigreux column. The distillate, collected in a single receiver cooled at < -20°C (fig. 14), is redistilled through a 40-cm Vigreux column to give a mixture of ~85% *E*- and 15% *Z*-pentenynol, b.p. 63-70°C/15 mmHg, $n_D(20°)$ 1.495, in *ca.* 55% yield.

Notes

1. If the reaction with epichlorohydrine is carried out at -33°C and the addition is carried out in only 15 min, much more tar and amorphous black products are formed. Yields are then only 30-35%.
2. The product has a good solubility in water.

Warning

Several people in our laboratory (including the author) who have carried out this synthesis, suffered painful blisters on their hands on the day following this synthesis.

5.23 Reaction of Lithium Alkynylides with Oxirane in Liquid Ammonia

$$RC{\equiv}CLi + \text{oxirane} \xrightarrow[-33°C]{\text{liq. } NH_3} RC{\equiv}CCH_2CH_2OLi \xrightarrow{H_2O} RC{\equiv}CCH_2CH_2OH$$

R = H, CH_3, C_2H_5

Scale: 2.2 molar.

Apparatus: fig. 7, 2 l.

Introduction

Although the reaction of alkali acetylides with oxirane proceeds slowly in liquid ammonia [5], it is an excellent method for preparing "homo-propargylic alcohols" in quantities of 1 mol or more [2]. Since oxirane is very volatile, considerable losses could occur if it is allowed to be swept along with the escaping ammonia vapour. One solution is to carry out the reaction under reflux, using a special condenser filled with dry ice and acetone. This would require regular addition of dry ice over a period of at least 12 h. It is much simpler to mix the acetylide and oxirane in a silvered Dewar flask, which is allowed to stand for several hours. The amount of ammonia that then evaporates is very small (of the order of 10 ml or less per h).

Another way would be to carry out the reaction in DMSO. However, after addition of water it would be extremely difficult or impossible to isolate the water-soluble lower alcohols, $RC{\equiv}CCH_2CH_2OH$, from the mixture of DMSO and water.

In the procedures described below, *lithium* alkynylides are used. When R is CH_3 or higher alkyl, the use of this cation is clearly preferred for several reasons. In particular the sodium alkynylides are poorly soluble in liquid ammonia. The second reason for choosing the lithium compounds is that the reaction of $NaC{\equiv}CH$ with (an excess of) oxirane affords appreciable amounts of the subsequent product $HC{\equiv}CCH_2CH_2OCH_2CH_2OH$.

Procedure

A precooled solution (-45°C) of 2.2 mol of $LiC{\equiv}CH$ or $LiC{\equiv}CR$ is poured into the Dewar flask (if no silvered Dewar flask is available, an unsilvered one may be covered with aluminum foil). After addition of 50 ml of Et_2O (to suppress frothing), oxirane (2.4 mol, cooled to -40°C) is added in 5 equal portions with intervals of 10 min. A rubber stopper with a drying tube filled with KOH pellets is then placed on the flask. After 30-40 h the solution is cautiously poured out into a 3-5 l wide-necked round-bottomed flask. The Dewar flask is rinsed with 100-200 ml of water, which is then retained. After evaporating the ammonia by placing the round-bottomed flask in a water bath at 40°C, 300 ml of water and the rinse solution of the Dewar flask are added. The aqueous solution is subjected to continuous extraction for several hours (when R is C_2H_5, about 15 extractions with Et_2O may be carried out). The Et_2O extract is dried over potassium carbonate and subsequently concentrated *in vacuo* (bath temperature not higher than 25°C). Distillation of the remaining liquid, using a single receiver cooled to 0°C (fig. 14), gives $HC{\equiv}CCH_2CH_2OH$, b.p. 34°C/10 mmHg, $n_D(20°)$ 1.4385, $CH_3C{\equiv}CCH_2CH_2OH$, b.p. 54°C/12 mmHg, $n_D(20°)$ 1.4555, and $C_2H_5C{\equiv}CCH_2CH_2OH$, b.p. 67°C/12 mmHg, $n_D(20°)$ 1.4538, in greater than 80% yields.

5.24 Reaction of Lithium Acetylide with Epoxybutane in DMSO

$$HC{\equiv}CLi + \text{Et-oxirane} \xrightarrow[20°C]{\text{DMSO}} HC{\equiv}CCH_2CH(OLi)C_2H_5 \xrightarrow{H_2O}$$

$$\longrightarrow HC{\equiv}CCH_2CH(OH)C_2H_5$$

Scale: 1.0 molar.

Apparatus: fig. 1, 3 l; stirrer: fig. 3.

Introduction

In the procedure for 5-hexyn-3-ol, the ammonia is replaced by DMSO before the epoxide is added. An advantage of this is that the reaction temperature can be considerably higher than

-33°C. In liquid ammonia the reaction with epoxybutane would be slower than in the case of oxirane. However, the most important effect of the replacement of the NH_3 by DMSO is, that the specific solvatation of the metal ion by DMSO facilitates attack of the acetylide on the ring. The presence of this solvent does not give rise to difficulties during the aqueous work-up of alcohols with a longer carbon chain (compare exp. 23).

Procedure

DMSO (300 ml) is cautiously added over a few min to a solution of lithium acetylide (1.1 mol, p. 17, a small excess is used to compensate for traces of water in the DMSO). In the case of frothing, small amounts of Et_2O should be added. The dropping-funnel inlet combination is replaced by an outlet and the ammonia is evaporated by placing the flask in a water bath, which is gradually heated to 50°C. When the temperature in the flask has risen above 0°C, the equipment on the flask is changed (see fig. 1) and N_2 is introduced. Heating is stopped when the thermometer indicates +10°C. Epoxybutane (1.1 mol) is then added dropwise over 30 min with efficient stirring and cooling between 15 and 20°C. After stirring for an additional 1.5 h at 20°C, 1 l of ice water is added. The solution is saturated with ammonium chloride and then extracted 15 times with Et_2O. The unwashed extracts are dried over potassium carbonate, after which the solvent is removed under reduced pressure. Careful distillation through a 40-cm Vigreux column gives, after a small water-containing first fraction, 5-hexyn-3-ol, b.p. 48°C/10 mmHg, $n_D(20°)$ 1.4428, in > 75% yield.

5.25 Reaction of 1,3-Hexadienyllithium with Oxirane in DMSO

$$C_2H_5C{\equiv}CC{\equiv}CH + LiNH_2 \xrightarrow[-33°C]{\text{liq. } NH_3} C_2H_5C{\equiv}CC{\equiv}CLi + NH_3$$

$$C_2H_5C{\equiv}CC{\equiv}CLi + \text{oxirane} \xrightarrow{DMSO} C_2H_5C{\equiv}CC{\equiv}CCH_2CH_2OLi \xrightarrow{H_2O}$$

$$\longrightarrow C_2H_5C{\equiv}CC{\equiv}CCH_2CH_2OH$$

Scale: 0.50 molar.

Apparatus: fig. 1, 2 l.

Procedure (for Introduction see exp. 24)

1,3-Hexadiyne (0.50 mol, see exp. 9) is added dropwise over 15 min to a suspension of 0.55 mol of lithium amide (see ref. 1 and fig. 6 for the preparation of $LiNH_2$) in 300 ml of liquid ammonia. Dry DMSO (300 ml, for drying see ref. 1) is then added over a few min. The ammonia is then removed by placing the flask in a water bath at 20 to 40°C (the dropping-funnel is temporarily replaced with an outlet). When the temperature of the mixture has risen

above 0°C, the dropping funnel is replaced on the flask and N_2 is introduced again. Heating is stopped as soon as the thermometer indicates 15°C. A mixture of 0.65 mol of oxirane and 50 ml of Et_2O cooled to 0°C is added dropwise over 30 min, while keeping the temperature between 15 and 20°C. After an additional 1h, 1 l of ice water is added and the mixture is extracted 10 times with Et_2O. The combined organic solutions are washed 3 times with a saturated solution of NH_4Cl and subsequently dried over $MgSO_4$. The liquid remaining after removal of the solvent under reduced pressure is distilled through a short column to give the diyne alcohol, b.p. ~90°C/1 mmHg, $n_D(20°)$ 1.5238, in *ca.* 90% yield.

This procedure is also applicable for the hydroxyethylation of $CH_3CH{=}CHC{\equiv}CH$ and higher homogolues and for the hydroxyethylation of 1-pentyne and higher homologues.

5.26 Reaction of Lithium Acetylide with Styrene Oxide in DMSO

$$HC{\equiv}CLi + \text{Ph- oxirane} \xrightarrow[25°C]{DMSO} HC{\equiv}CCH_2CH(OLi)Ph \xrightarrow{H_2O}$$

$$\longrightarrow HC{\equiv}CCH_2CH(OH)Ph$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Procedure (for Introduction see exp. 24)

A solution of 0.30 mol of lithium acetylide in 200 ml of DMSO is prepared as described on p. 21 (after the evaporation of the NH_3, the temperature of the suspension is allowed to rise to 15°C, compare also exp. 24). Freshly distilled styrene oxide (0.20 mol) is added dropwise over 15 min, while keeping the temperature between 20 and 30°C. After stirring the mixture for an additional 2 h at 25°C, 500 ml of ice water is added and six extractions with Et_2O are carried out. After washing the extracts with water and drying over $MgSO_4$, the solvent is removed under reduced pressure. Distillation of the remaining liquid through a short column gives the acetylenic alcohol, b.p. 120°C/mmHg, $n_D(20°)$ 1.5462, in ~70% yield.

5.27 DMSO-Promoted Reaction of Lithium Alkynylides with Oxirane

$$PhC{\equiv}CLi + \text{oxirane} \xrightarrow[45°C]{\text{THF-hexane-DMSO}} PhC{\equiv}CCH_2CH_2OLi \xrightarrow{H_2O}$$

$$\longrightarrow PhC{\equiv}CCH_2CH_2OH$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

The methods described in the previous experiments are less suitable for working on a smaller scale (0.1 molar or less), since it is difficult to maintain absolutely anhydrous conditions while working with liquid ammonia: small traces of moisture cause a relatively large decrease in yield. Oxirane does not react at room temperature with a solution of lithium phenylacetylide in THF and hexane, and the assistance of DMSO as a dipolar aprotic solvent is necessary. In this respect, the ring opening resembles the S_N2 reaction with alkyl halides. In the absence of DMSO, ring opening is assisted to some extent by coordination of Li^+ with the epoxide-oxygen atom. 2-Thienyllithium [1], for example, reacts smoothly in THF with oxirane, but in the case of the weaker base PhC≡CLi, this coordination effect alone appears to be insufficient.

Procedure

Oxirane (0.13 mol), cooled to -20°C, is added in one portion to a solution of lithium phenylacetylide (0.10 mol, see p. 24) in 70 ml of THF and 70 ml of hexane at 10°C. Dry DMSO (30 ml) is added and the temperature is allowed to rise to 45°C. This temperature is maintained for an additional 45 min, then a solution of 20 g of ammonium chloride in 300 ml of water is added to the two-layer system with vigorous stirring. The mixture is extracted five times with Et_2O. The combined organic solutions are washed three times with a saturated solution of ammonium chloride and subsequently dried over $MgSO_4$. The viscous liquid remaining after concentration of the extract under reduced pressure, is distilled through a short column to give $PhC{\equiv}CCH_2CH_2OH$, b.p. ~100°C/0.2 mmHg, $n_D(20°)$ 1.5749, in greater than 90% yield.

A similar procedure may be followed for the hydroxyethylation of the higher homologues of acetylene. In the case of less stable acetylides, *e.g.* $RC{\equiv}CC{\equiv}CLi$, more DMSO is added allowing the reaction to proceed at lower temperatures.

5.28 Ethoxyalkylation of Lithium Alkynylides with α-Chloroethers

$$C_5H_{11}C{\equiv}CLi + ClCH_2OC_2H_5 \xrightarrow[-30\rightarrow +10°C]{\text{THF-hexane}} C_5H_{11}C{\equiv}CCH_2OC_2H_5 + LiCl\downarrow$$

Scale: 0.10 mol.

Apparatus: fig. 1, 1 l.

Introduction

The procedure for 1-ethoxy-2-octyne exemplifies the ethoxy-alkylation of terminal triple bonds by reaction of the metallated acetylene with an α–chloroether. As mentioned in Section III-4, such conversions generally proceed smoothly, even in a poorly polar medium. Lithium as well as Grignard derivatives give excellent results in their reactions with $ClCH_2OR$ and homologues, *e.g.* $CH_3CH(Cl)OR$. Although there is not much difference in the results with

Et_2O and THF, the latter solvent may be preferred in those cases where the metallated acetylene is slightly soluble in Et_2O.

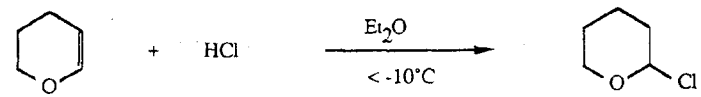
Procedure

Chloromethyl ethyl ether (0.10 mol, note 1) is added over 15 min to a solution of 0.10 mol of heptynyllithium (p. 24) in 70 ml of THF and 70 ml of hexane, while keeping the temperature between -20 and -25°C. The cooling bath is then removed and the temperature allowed to rise to 10°C. After an additional 30 min, the white suspension is cooled to 0°C and 300 ml of ice water is added with vigorous stirring. The layers are separated and three extractions with Et_2O or pentane are carried out. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Careful distillation of the remaining liquid through a 40-cm Vigreux column gives the 2-alkynyl ether, b.p. 78°C/12 mmHg, in ~80% yield. With Et_2O as solvent a similar result is obtained.

Notes

1. HCl is introduced at ~0°C into a stirred mixture of ethanol (0.50 mol) and paraformaldehyde (15 g) until copious fumes escape from the solution. Stirring is stopped and the flask is placed in a bath at -78°C. The clear liquid is decanted from the crust of the bottom of the flask and transferred into a 1-l flask, which is placed in a bath at -20°C. The dissolved HCl is then removed by evacuation (water aspirator). Since α-halocthers are suspected of being carcinogens, care should be taken when working with them.

5.29 Reaction of 2-Chlorotetrahydropyran with Ethynylmagnesium Bromide



Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Procedure (for Introduction see exp. 28)

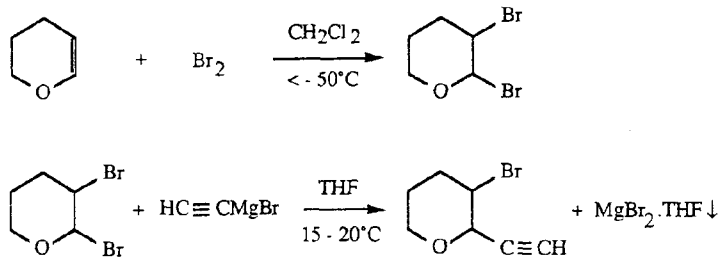
A solution (partly suspension) of ethynylmagnesium bromide is prepared by introducing

acetylene into a solution of ~0.25 mol of ethylmagnesium bromide (prepared from 0.30 mol of ethyl bromide and 0.4 mol of Mg) in 350 ml of THF (p. 27). The Grignard reagent is cooled to -15°C and a mixture of 0.20 mol (short measure) of 2-chlorotetrahydropyran (note 1) and 30 ml of Et_2O is added over 30 min with cooling between -10 and -15°C. After completion of the addition, the cooling bath is removed and the temperature allowed to rise to 20°C. Stirring at this temperature is continued for another 1 h. The suspension is then treated with a solution of 25 g of ammonium chloride in 200 ml of water and, after separation of the layers, four extractions with Et_2O are carried out. The combined organic solutions are dried over $MgSO_4$, after which the greater part of the solvent is distilled off at atmospheric pressure through a 40-cm Vigreux column. Careful distillation of the remaining liquid through the same column gives 2-ethynyltetrahydropyran, b.p. ~35°C/10 mmHg, $n_D(20°)$ 1.4571, in ~70% yield.

Notes

1. Dry gaseous HCl (0.20 mol, measured by weight increase) is introduced at *ca.* -10°C into 0.25 mol of freshly distilled dihydropyran which is contained in a 250 ml one-necked flask. The undistilled product is used for the Grignard reaction.

5.30 Specific Displacement of α-Bromine in α,β-Dibromoethers



Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Introduction

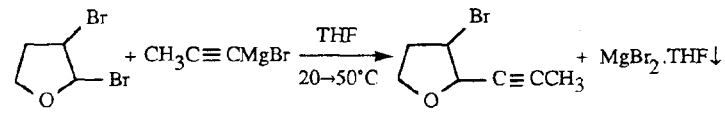
The displacement of the bromine atom in the 2-position of 2,3-dibromotetrahydropyran by ethynyl proceeds with more difficulty than the analogous reaction of ethynylmagnesium bromide with chlorotetrahydropyran (exp. 29). At 20°C a relatively slow conversion takes place. It is not possible to carry out the reaction at a higher temperature, because HC≡CMgBr begins to disproportionate into BrMgC≡CMgBr and acetylene above 30°C.

Procedure

A mixture of 2,3-dibromotetrahydropyran (0.30 mol) and dichloromethane (50 ml) (prepared by adding 0.30 mol of Br_2 to a mixture of 0.35 mol of freshly distilled dihydropyran and 50 ml of CH_2Cl_2, cooled below -50°C; the solution should be used without delay) is added over a few min to a solution of 0.40 ml of ethynylmagnesium bromide in 600 ml of THF (p. 27). During this addition the temperature is kept between 15 and 20°C. After stirring for an additional 2 h at 20°C, the suspension is allowed to stand (or stirred) overnight. A cold solution of 30 g of ammonium chloride in 250 ml of water is then added with vigorous stirring. After separation of the layers and extraction of the aqueous layer with Et_2O, the organic solutions are dried over $MgSO_4$. The liquid remaining after concentration of the solution under reduced pressure is distilled through a short column to give 3-bromo-2-ethynyltetrahydropyran, b.p. ~50°C/0.2 mmHg, $n_D(20°)$ 1.5161, in 78% yield.

$BrCH_2CH(O_2H_5)C{\equiv}CH$, b.p. 64°C/12 mmHg, $n_D(20°)$ 1.4693, was obtained in ~70% yield by a similar procedure from HC≡CMgBr and $BrCH_2CH(Br)OC_2H_5$ (for the addition of Br_2 to $H_2C{=}CHOC_2H_5$, see p. 195)

5.31 3-Bromo-2-(1-propynyl)tetrahydrofuran



Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Introduction

Compared to the reaction in exp. 30, the conversion of 2,3-dibromotetrahydrofuran with *propynyl*magnesium bromide can be carried out at higher temperatures, so that the reaction time can be shortened to 2 h at 50°C. When propynyl*lithium* is used instead of the Grignard reagent, a very impure product is obtained in low yield. Elimination possibly predominates with the more strongly basic lithium alkynylides (compare exp. 28).

Procedure

A solution of 0.20 mol of 2,3-dibromotetrahydrofuran in 40 ml of CH_2Cl_2 is prepared by adding 0.20 mol of Br_2 to a mixture of 0.25 mol of freshly distilled dihydrofuran and 40 ml of CH_2Cl_2 at < -50°C . This solution is added, immediately after its preparation, over a few min to a solution of 0.25 mol of propynylmagnesium bromide (p. 29) in 250 ml of THF. The temperature is allowed to rise to 40-50°C and is kept for an additional 2 h at 45°C. The product (b.p. 65°C/0.2 mmHg, $n_D(20°)$ 1.5140) is isolated in almost 100% yield, in the

manner described in the previous experiment.

5.32 Regiospecific Alkylation of 1,3-Dilithiopropyne with Benzyl Chloride

$$LiCH_2C{\equiv}CLi + PhCH_2Cl \xrightarrow[-10\rightarrow +5^\circ C]{\text{THF-hexane}} PhCH_2CH_2C{\equiv}CH + LiCl\downarrow$$

(after hydrolysis)

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

The regiospecific benzylation of 1,3-dilithiopropyne at the propargylic carbon atom is a useful example of the preparation of a 1-alkyne that is not accessible by alkylation of lithium or sodium acetylide: reaction of $PhCH_2CH_2Br$ with alkali acetylides would result in extensive dehydrohalogenation. Hauser *et al.* showed that reaction of 1,3-dimetallated diketo compounds with equivalent amounts of alkyl halides gives rise to exclusive alkylation at the most strongly basic site [71]. Thus, treatment of $CH_3C(O)CH_2C(O)CH_3$ with two equivalents of alkali amide in liquid ammonia followed by addition of one equivalent of an alkyl halide, affords $RCH_2C(O)CH_2C(O)CH_3$:

$$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{2\,NH_2^-} H_2\underset{O}{\overset{}{C}}\underset{O}{\overset{}{C}}HCCH_3 \xrightarrow{RHal} RCH_2\underset{O}{\overset{}{C}}\underset{O}{\overset{}{C}}HCCH_3$$

The preference of the alkyl halides for reaction at the most strongly basic site in the 1,3-dimetallated 1-alkynes may be compared with the regiospecific alkylation of the "dianions" of the diketones.

Our preference for using benzyl chloride (rather than the bromide) is based on the expectation that side-reactions, such as formation of dibenzyl and the occurrence of lithium-halogen exchange (resulting in $PhCH_2Li$) are less likely (compare ref. 72).

Regiospecific alkylation of 1,3-dilithiated acetylenes is a good method for the preparation of branched 1-alkynes: dilithiation of 1-butyne, for example, followed by alkylation with RBr, gives $HC{\equiv}CCH(R)CH_3$ in good yields [73].

Procedure

Benzyl chloride (0.10 mol) is added dropwise over 30 min to a suspension of 0.22 mol of 1,3-dilithiopropyne in *ca.* 140 ml of THF and 155 ml of hexane (p. 31) with cooling between -10 and -15°C. Stirring at 5°C is continued for an additional 1 h, then the brown reaction mixture is poured into 200 ml of ice water. After vigorous shaking and separation of the layers, three extractions with Et_2O are carried out. The organic solutions are dried over

$MgSO_4$ and subsequently concentrated under reduced pressure. The remaining liquid is carefully distilled through a 40-cm Vigreux column to give 4-phenyl-1-butyne, b.p. 72°C/15 mmHg, $n_D(20^\circ)$ 1.5212, in ~60% yield. There is a small high-boiling residue.

5.33 Regiospecific Hydroxyalkylation of a 1,3-Dilithiated Alkyne with Oxirane

$$C_3H_7CH(Li)C{\equiv}CLi + \text{oxirane} \xrightarrow[-40\rightarrow +10^\circ C]{\text{THF, hexane}} C_3H_7\underset{\displaystyle CH_2CH_2OLi}{\underset{|}{C}}HC{\equiv}CLi \xrightarrow{H_2O}$$

$$\longrightarrow C_3H_7CH(CH_2CH_2OH)C{\equiv}CH$$

Scale: 0.10 molar (hexyne).

Apparatus: fig. 1, 1 l.

Procedure (for Introduction see exp. 31)

A solution of 1,3-dilithiohexyne, prepared from 0.10 mol of 1-hexyne (exp. 10) and 0.23 mol of BuLi.TMEDA in hexane, is cooled to 20°C and THF (150 ml) is added. The brown solution is kept for 1 h at 25-30°C (note 1) and then cooled to -45°C. A mixture of 0.12 mol (note 2) of oxirane and 25 ml of THF is added dropwise over 30 min with cooling between -35 and -45°C. The colour gradually changes into light yellow. After the addition, the cooling bath is removed and the temperature allowed to rise to 10°C. The mixture is then hydrolysed by addition of a cold solution of 25 g of NH_4Cl in 200 ml of water. The organic layer and three ethereal extracts are dried over $MgSO_4$ and subsequently concentrated under reduced pressure. Careful distillation of the remaining liquid through a 40-cm Vigreux column gives 3-ethynyl-1-hexanol, b.p. 80°C/15 mmHg, $n_D(20^\circ)$ 1.4472, in 78% yield.

Notes

1. Any excess of BuLi.TMEDA will be inactivated by the reaction with THF [51].
2. The excess of 0.02 mol does not react with the ethynyl group, see exp. 27.

5.34 Reaction of 1,3-Dipotassiated Methyl Propargyl Ether with Bromohexane

$$KC{\equiv}CCH(K)OCH_3 + C_6H_{13}Br \xrightarrow[-45\rightarrow +10^\circ C]{\text{THF-hexane}} HC{\equiv}CCH(C_6H_{13})OCH_3 + KBr\downarrow$$

(after hydrolysis)

Scale: 0.08 molar.

Apparatus: fig. 1, 1 l.

Introduction (see also exp. 32)

In reactions of nucleophilic reagents with alkyl halides, Li^+ is preferred as a counter ion to K^+ because dehydrohalogenation occurs to a lesser extent with lithium compounds. The reason for carrying out the regiospecific alkylation of dimetallated methyl propargyl ether with the *potassium* derivative is that a high rate of conversion can be attained at low temperatures [74], which is a considerable advantage in view of the low stability of dimetallated propargyl ethers.

Procedure

Hexyl bromide (0.08 mol, short measure) is added dropwise over 10 min to the suspension of dipotassiated methyl propargyl ether in THF and hexane (p. 33) with cooling at ~ -45°C. This temperature is maintained for an additional 15 min, then the cooling bath is removed and the temperature allowed to rise to 10°C. The light-brown suspension is then treated with 300 ml of ice water, after which four extractions with Et_2O are carried out. The organic solutions are dried over $MgSO_4$ and then concentrated under reduced pressure. Distillation through a 40-cm Vigreux column gives the alkylated propargyl ether, b.p. 45°C/0.1 mmHg, $n_D(20°)$ 1.4300, in 70% yield.

5.35 Reaction of 1,4-Dilithiated Isopropenylacetylene with Oxirane and Cyclohexyl bromide

$$LiC{\equiv}CC(CH_2Li){=}CH_2 + \text{oxirane} \xrightarrow[-50°C]{\text{THF-hexane}} HC{\equiv}CC(CH_2CH_2CH_2OH){=}CH_2 \quad \text{(after hydrolysis)}$$

$$LiC{\equiv}CC(CH_2Li){=}CH_2 + c\text{-}C_6H_{11}Br \xrightarrow[-50°C]{\text{THF-hexane}} HC{\equiv}CC(CH_2\text{-}c\text{-}C_6H_{11}){=}CH_2$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction (for the regiospecificity of the reactions see exp. 32)

The reaction of dilithiated isopropenylacetylene with cyclohexyl bromide [46] is an exceptional case of a successful alkylation with a cyclohexyl halide. In reactions with most nucleophilic species, dehydrohalogenation is the main process. Although the reaction conditions for the cyclohexylation are similar to those of other alkylation reactions, the mechanism might differ from the usual S_N2 mechanism in that a single electron transfer (S.E.T.) is involved. It is not possible to predict whether the reaction of a particular nucleophilic species with cyclohexyl halide in an organic solvent or in liquid ammonia will give a good yield of the cyclohexyl derivative or result in dehydrohalogenation of the cycloalkyl halide. Reaction with acetylides, $RC{\equiv}C^-$, and sp^2-nucleophiles, $C{=}C^-$ (vinylic,

aromatic or hetero-aromatic "anions"), probably will only give rise to elimination of hydrogen halide.

It is shown in exp. 27 that lithium acetylides do not react at room temperature with oxirane in a THF-hexane mixture. In contrast, the allylic part of dilithiated isopropenylacetylene is smoothly hydroxyethylated at temperatures in the region of -50°C.

Procedure

Cyclohexyl bromide (0.10 mol) or a mixture of 0.13 mol of oxirane in 30 ml of THF is added dropwise over 15 min to the suspension of 0.10 mol of dilithiated isopropenylacetylene (p. 34) with cooling between -40 and -50°C. After an additional 15 min the cooling bath is removed and the temperature is allowed to rise to 10°C. Ice water (200 ml) is then added with vigorous stirring and the layers are separated. The aqueous layer is extracted four and eight times respectively, with Et_2O. The (unwashed) organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Careful distillation of the remaining liquid through a 30-cm Vigreux column gives:

$HC{\equiv}CC(CH_2\text{-}c\text{-}C_6H_{11}){=}CH_2$, b.p. 70°C/10 mmHg, $n_D(20°)$ 1.4778, in 70% yield, and

$HC{\equiv}CC(CH_2CH_2CH_2OH){=}CH_2$, b.p. 71°C/10 mmHg, $n_D(20°)$ 1.4784, in 92% yield.

5.36 1-Bromopropyne from 1,2-Dibromoethene

$$BrCH{=}CHBr + 2\,LiNH_2 \xrightarrow[-65°C]{\text{liq. } NH_3} BrC{\equiv}CLi + LiBr.NH_3\downarrow + NH_3$$

$$BrC{\equiv}CLi + CH_3I \xrightarrow[-65 \rightarrow -35°C]{\text{liq. } NH_3} BrC{\equiv}CCH_3 + LiI$$

Scale: 0.30 molar.

Apparatus: fig. 1, 1 l.

Introduction

1-Bromopropyne has a b.p. of only *ca.* 65°C at atmospheric pressure. Although the compound presumably can be obtained in a reasonable yield as an ethereal solution from $CH_3C{\equiv}CLi$ and Br_2 in Et_2O (p. 24), its isolation in a pure state would involve a time-consuming distillation. Preparation from an aqueous solution of KOBr and propyne would also not be an attractive method, because the bromination of non-conjugated 1-alkynes proceeds sluggishly. In analogy with the preparation of 1-chloroalkynes (see exp. 15), it has been suggested to prepare derivatives of bromoacetylene (see the chapter on 1-haloalkynes in ref.6) by reacting 1,2-dibromoethene with alkali amides in liquid ammonia and subsequently adding the functionalization reagent. The procedure for 1-bromopropyne seems an obvious example. In view of the possibility of a subsequent attack of amide on bromine in the

intermediate MC≡CBr, it seems advisable to use *lithium* amide, the least reactive alkali amide, and to carry out the dehydrobromination at low temperatures. The use of high-boiling petroleum ether as extraction solvent allows an isolation of the product under mild conditions.

Procedure

A suspension of lithium amide in 500 ml of liquid ammonia is prepared from 0.65 mol of lithium (see refs. 1,3,4). The suspension is cooled to -70°C while N_2 is passed through the apparatus (~500 ml/min) and an *E/Z*-mixture of BrCH=CHBr (0.30 mol) is added dropwise over 15 min with efficient stirring. The flask is occasionally cooled in a bath with liquid N_2 to maintain a temperature between -65 and -75°C during the addition. After an additional 15 min, methyl iodide (0.4 mol) is added dropwise over 15 min, whereby the temperature is kept around -60°C. After this addition, the cooling bath is removed and the temperature is allowed to rise to just below the b.p. (-33°C) of ammonia. Stirring is then continued for 15 min (the excess of CH_3I reacts with ammonia), then 250 ml of high-boiling (b.p. > 170°C) petroleum ether is added (with stirring). The mixture is subsequently poured onto 500 g of finely crushed ice in a 2-l wide-necked conical flask. After melting of the remaining ice and separation of the layers, three extractions with small portions of petroleum ether are carried out. The combined organic solutions are washed with 2 N HCl and subsequently dried over $MgSO_4$. The extract is then heated in the apparatus shown in fig. 14, using a vacuum of 10 to 20 mmHg. The vapour of $CH_3C{\equiv}CBr$ is condensed in a receiver cooled at -78°C. Repeating this operation with the contents of the receiver (but without external heating) gives pure $CH_3C{\equiv}CBr$, $n_D(20°)$ 1.471, in *ca.* 80% yield. The compound should be stored under N_2 in the refrigerator.

5.37 Preparation of Acetylenic Acetals from Alkynylmagnesium Bromide and Ethyl Orthoformate

$$RC{\equiv}CMgBr + HC(OC_2H_5)_3 \xrightarrow[\text{reflux}]{Et_2O} RC{\equiv}CCH(OC_2H_5)_2 + C_2H_5OMgBr\downarrow$$

Scale: 0.50 molar.

Apparatus: 2-l round-bottomed, three-necked flask, equipped with a gas inlet, a mechanical stirrer and a reflux condenser.

Introduction

Although the overall equation representing the title reaction suggests a nucleophilic displacement of OC_2H_5 in the orthoformate by the acetylide grouping, the most favourable reaction conditions are not typical for the familiar S_N-2 displacement. In fact, the conversion proceeds more smoothly in Et_2O than in the more polar THF. With lithium alkynylides in organic solvents, the reaction proceeds sluggishly, while in liquid ammonia the reaction does

not take place at all. These experimental facts strongly suggest the assistance of the Lewis acid ($MgBr_2$) which coordinates with oxygen in the orthoformate, thus facilitating the displacement by the acetylenic group.

Procedure

Freshly distilled ethyl orthoformate (0.7 mol) is added in one portion to a solution of 0.50 mol of the acetylenic Grignard compound in ~800 ml of Et_2O (see p. 29). The temperature rises by only a few degrees (as observed by temporarily placing a thermometer in the liquid). The mixture is heated for several hours (at least 7) under reflux with efficient stirring, during which period a white suspension is formed. After cooling to room temperature, the suspension is cautiously poured (the hydrolysing operation should never be carried out in the inverse sense, as much heat is evolved) into a cold solution of 50 g of NH_4Cl in 300 ml of water. After shaking, the layers are separated and the aqueous layer is extracted three times with Et_2O. The combined solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Careful distillation through a 40-cm Widmer column (for R is CH_3 or C_2H_5) or a 40-cm Vigreux column gives the acetylenic acetals, generally in excellent yields.

Examples:

$CH_3C{\equiv}CCH(OC_2H_5)_2$, b.p. 62°C/12 mmHg, $n_D(20°)$ 1.4261;

$C_2H_5C{\equiv}CCH(OC_2H_5)_2$, b.p. 72°C/10 mmHg, $n_D(20°)$ 1.4290;

$C_4H_9C{\equiv}CCH(OC_2H_5)_2$, b.p. 97°C/10 mmHg, $n_D(20°)$ 1.4342;

$C_2H_5CH{=}CHC{\equiv}CCH(OC_2H_5)_2$, b.p. 96-103°C/12 mmHg (*E/Z* ~ 1:1);

$C_3H_7C{\equiv}CC{\equiv}CCH(OC_2H_5)_2$, b.p. ~100°C/0.5 mm (20-cm Vigreux), $n_D(20°)$ 1.4790.

Chapter IV
Ethynylation and Alkynylation of Carbonyl Compounds

1. Survey of Laboratory Methods

α-Hydroxyacetylenes, compounds which have the general structure $R^1C{\equiv}CC(R^2)(R^3)OH$, are extremely important intermediates and end products in acetylenic chemistry. They are generally prepared by coupling of the acetylene $R^1C{\equiv}CH$ with the carbonyl compound $R^2R^3C{=}O$. Laboratory methods - industrial methods are beyond the scope of this chapter - mostly deal with reactions of an alkali metal alkynylide or Grignard derivative with the carbonyl compound in an organic solvent or in liquid ammonia [5,8,10]:

$$R^1C{\equiv}CM + R^2R^3C{=}O \longrightarrow R^1C{\equiv}CC(R^2)(R^3)OM \xrightarrow{\text{proton donor}} R^1C{\equiv}CC(R^2)(R^3)OH \qquad M = Li, Na, K, MgX$$

In the industrial manufacture of important starting compounds such as $HC{\equiv}CCH_2OH$, $HC{\equiv}CCH(CH_3)OH$, and $HOCH_2C{\equiv}CCH_2OH$, high pressure techniques are employed using alkali hydroxides or copper acetylide as catalyst. For extensive reviews on the alkynylation processes the reader is referred to the book [8] and review of Ziegenbein [6].

The general scheme for preparation in the laboratory has a number of alternatives, the choice of a particular method being determined by the availability of the starting acetylene, $R^1C{\equiv}CH$, the desired scale of the preparation (*e.g.* a few millimoles, 100 mmolar, 1 molar or more) and a number of other factors. The most versatile method, suitable for working on scales varying from a few mmoles to ~0.5 mole, is the reaction of a *lithium* alkynylide with a carbonyl compound in THF(-hexane):

$$R^1C{\equiv}CH \xrightarrow{BuLi} R^1C{\equiv}CLi \xrightarrow[2.\ H_2O]{1.\ R^2R^3C{=}O} R^1C{\equiv}CC(R^2)(R^3)OH$$

If R^1 = H, a complexing agent, *e.g.* $H_2NCH_2CH_2NH_2$ [33] or TMEDA [2] is neccesary to stabilize monolithium acetylide. In some cases, addition of lithium bromide has the favourable effect of solubilizing the lithium alkynylide, and this results in improved yields [47]. The combination of $RC{\equiv}CMgX$ (X is usually Br) and THF is the one which usually guarantees a good result. Et_2O may suffice as well, except in those cases where the metallated acetylene is sparingly soluble and a suspension or oily under-layer is produced.

Reduced yields of acetylenic carbinols are often caused by deprotonation of the carbonyl compound:

$$RC{\equiv}CM + >CH\text{-}C(=O)\text{-} \longrightarrow RC{\equiv}CH + >C=C(\text{-}O^{-}M^{+})\text{-}$$

The extent to which this side-reaction occurs depends upon the acidity of the carbonyl compound, the thermodynamic basicity of the acetylide (related to the pK value) and its kinetic basicity (which decreases in the order K > Na > Li > MgX), and the polarity of the solvent (which also influences the basicity of RC≡CM). Examples of easily enolizable ketones are cyclopentanone, acetophenone, β-ionone and $CH_3C(O)CH_2CH(OCH_3)_2$. The result of their coupling with a metallated acetylene shows a strong dependency upon the reaction conditions. In the polar solvent ammonia, formation of enolates from these ketones is a serious side reaction. The ketones are liberated during the aqueous work-up and have to be separated from the carbinols, mostly *via* fractional distillation. Particularly in the case of ethynyl groups, this distillative separation is difficult due to the small differences in boiling points. Successful couplings in liquid ammonia are mostly confined to less basic acetylides (*e.g.* RC≡CC≡CLi, PhC≡CLi, RSC≡CLi, RSCH=CHC≡CLi, ClC≡CLi) and to non- (or hardly) enolizable carbonyl compounds (*e.g.* PhCH=O, H_2C=CHCH=O, CH_3CH=CHCH=O). An additional competing reaction of aldehydes is the reaction of NH_3 with the C=O group or - in the case of an α,β-unsaturated aldehyde - addition of NH_3 to the C=C system.

In the Favorski reaction [8], ethyne is coupled with a carbonyl compound in the presence of powdered alkali hydroxide suspended in an organic solvent, in which the acetylene has good solubility. Some acetylenic carbinols, derived from ketones, can be obtained in high yields by introducing acetylene at atmospheric pressure. The active intermediate possibly is a metal acetylide formed in low concentration.

$$HC{\equiv}CH + R^2R^3C{=}O \xrightarrow[\text{solvent}]{\text{KOH}} HC{\equiv}CC(R^2)(R^3)OH$$

We found [2] that a number of ketone carbinols can be prepared in excellent yields by adding the ketone to the suspension, prepared by introducing an excess of acetylene into a solution of t-BuOK in THF. This method shows some resemblance with the Favorski preparation. The reactive intermediate is probably potassium acetylide or a complex of it with *t*-BuOH or acetylene.

$$HC{\equiv}CH + R^2R^3C{=}O \xrightarrow[10\text{-}20^{\circ}C]{t\text{-BuOK, THF}} HC{\equiv}CC(R^2)(R^3)OH$$

2. Experiments

All temperatures are internal, unless indicated otherwise

2.1 Reaction of Alkynyllithium with Paraformaldehyde

$$C_4H_9C{\equiv}CLi + (H_2C{=}O)_n \xrightarrow[10\text{-}35^{\circ}C]{\text{THF-hexane}} C_4H_9C{\equiv}CCH_2OH \quad \text{(after hydrolysis)}$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Introduction

Hydroxymethylation of polar organometallic intermediates and Grignard derivatives can be carried out with paraformaldehyde [75] under normal laboratory conditions, using Et_2O or THF as a solvent. This reaction, generally carried out at 20-35°C, is very general and gives excellent yields (particularly with lithium compounds [75], compare Vogel's Textbook [76]). There is not much difference in ease of the reaction with the various organometallic intermediates ranging from acetylides to very strongly basic organometallics. The rate-limiting step is probably the depolymerization of the $-OCH_2-OCH_2-O-$chain, which may be assisted to some extent by interaction between oxygen and the Lewis acid ^{+}MgX or Li^{+}. (The peculiar finding in our laboratory that a few lithium alkynylides, *e.g.* $LiC{\equiv}CC(CH_3){=}CH_2$, give the corresponding alcohols in fair yields upon reaction with paraformaldehyde in liquid ammonia, is not easily explainable with Lewis-acid counter ion interaction). The procedure for 2-heptyn-1-ol presented here is representative. Lower yields may be expected when the metallated acetylene is slightly soluble (in this respect, THF is a better solvent than Et_2O).

Procedure

Dry (note 1) powdered paraformaldehyde (8 g, corresponding to an excess) is added over a few seconds (using a powder funnel) to a solution of 0.20 ml of hexynyllithium (p. 24) in THF (or Et_2O) and hexane, cooled to 0°C. The temperature is then allowed to rise. The heating effect becomes observable in the temperature range 15-25°C. The flask is occasionally cooled in a bath with ice and ice water. When, in the region of 25°C, the evolution of heat has ceased, the reaction mixture is warmed to 35-40°C (in the case of Et_2O gentle reflux). After 1.5 h the mixture is poured into a solution of 25 g of ammonium chloride in 250 ml of water. After vigorous shaking, the layers are separated and the aqueous layer is extracted five times with Et_2O (note 2). The unwashed organic solutions are dried over $MgSO_4$ and subsequently concentrated under reduced pressure. The remaining liquid is first distilled under oil-pump pressure using a short Vigreux column and a single receiver, cooled at a sufficiently low temperature (fig. 14) (note 3). Redistillation through a 30-cm Vigreux column gives 2-heptyn-1-ol, b.p. 83°C/12 mmHg, $n_D(20^{\circ})$ 1.4555, in ~80% yield (note 4).

Notes

1. Azeotropic removal of water with benzene may be envisaged: during the distillation of

the benzene, the suspension should be stirred mechanically or magnetically.

2. In the case of alcohols with a good solubility in water (*e.g.* $H_2C{=}CHC{\equiv}CCH_2OH$) or other alcohols with a limited number of C-atoms, more extractions should be carried out.
3. If one expects the alcohol to have a limited thermal stability (*e.g.* $CH_3C{\equiv}CC{\equiv}CCH_2OH$, $RSC{\equiv}CCH_2OH$), 20-30 ml of paraffin oil should be added (see Chap. I-2.7). The use of a mercury diffusion pump ($p < 0.01$ mmHg) is advised. One should not try to redistil the product at *water-pump* pressure.
4. Examples of other alcohols prepared by this procedure are: $H_2C{=}C(CH_3)C{\equiv}CCH_2OH$, b.p. 70°C/12 mmHg, $n_D(20°)$ 1.4885; $H_2C{=}CHC{\equiv}CCH_2OH$, b.p. 64°C/12 mmHg, $n_D(20°)$ 1.4988; $C_4H_9C{\equiv}CC{\equiv}CCH_2OH$, b.p. 96°C/0.2 mmHg, $n_D(20°)$ 1.5175. Yields are between 75 and 85%.

2.2 General Procedure for the Coupling of Lithium Alkynylides with Aldehydes and Ketones in THF or Et_2O

$$R^1C{\equiv}CLi + R^2R^3C{=}O \xrightarrow[<-30°C]{\text{THF or } Et_2O} R^1C{\equiv}CC(R^2)(R^3)OH \quad \text{(after hydrolysis)}$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Procedure

The aldehyde (0.12 mol, note 1) or ketone (0.12 mol) is added over 5-10 min to a solution of the lithium alkynylide in comparable amounts of THF or Et_2O and hexane (p. 24; for $LiC{\equiv}CH.TMEDA$ see p. 22) with cooling below -50°C (note 2). In the case of slightly soluble $R^1C{\equiv}CLi$ in THF (*e.g.* $CH_3C{\equiv}CLi$, $C_2H_5C{\equiv}CLi$) a solution of anhydrous lithium bromide (0.12 mol, note 3) in 40 ml of THF is added with strong cooling, prior to introducing the carbonyl compound. The reactions generally are extremely fast so that it suffices to remove the cooling bath after completion of the addition and to allow the temperature to rise to -20°C or 0°C. The work up is usually (note 4) carried out by pouring the reaction into ice water (200 ml, which may contain 20-30 g of NH_4Cl), shaking, separating the layers, extracting the aqueous phase with Et_2O (note 5), and drying the combined organic solutions over anhydrous $MgSO_4$ or K_2CO_3 (note 6). The solvent is removed under reduced pressure (rotary evaporator, note 7) after which the remaining liquid is distilled *in vacuo* (note 8). Yields are generally greater than 70% and often excellent.

Examples of carbinols prepared by this procedure:

$HC{\equiv}CCH(Ph)OH$, b.p. 110°C/10 mmHg, $n_D(20°)$ 1.5505, from $LiC{\equiv}CH.TMEDA$-THF-hexane and PhCH=O; aliphatic aldehydes RCH=O, with $R > C_3H_7$ presumably can also be ethynylated with this stabilized acetylide.

$CH_3C{\equiv}CC(CH_2)_4OH$, b.p. 78°C/10 mmHg $n_D(20°)$ 1.4842, from $CH_3C{\equiv}CLi$ + LiBr in THF-hexane and cyclopentanone at -30°C. After an additional period of 20 min (at -30°C) the temperature is allowed to rise to 0°C and the mixture is hydrolysed.

$CH_3C{\equiv}CC(CH_2)_5OH$, b.p. 92°C/10 mmHg, in an analogous way from $CH_3C{\equiv}CLi$ + LiBr in THF-hexane and cyclohexanone.

$Me_2NCH_2C{\equiv}CC(CH_2)_4(OH)$, b.p. 130°C/10 mmHg, from $Me_2NCH_2C{\equiv}CLi$ + LiBr in THF-hexane and cyclopentanone at -40 → -20°C and an additional half hour at -20°C.

$C_2H_5OC{\equiv}CC(CH_3)_2OH$, b.p. 72°C/12 mmHg, $n_D(20°)$ 1.4421, from $C_2H_5OC{\equiv}CLi$ in THF or Et_2O-hexane and acetone at < -40°C. This carbinol is acid-sensitive [77]. The NH_4Cl-solution used for the work-up should contain a small amount of ammonia. All glass-ware should be "rinsed" with gaseous ammonia. A neutral drying agent (Na_2SO_4) is recommended. Bath temperatures during the distillation should not exceed 100°C. Carbinols from ethoxyacetylene and *aldehydes* are even more unstable and distillation should preferably be carried out at very low pressure, using a strongly cooled receiver (fig. 14).

$ClCH_2C{\equiv}CCH(CH_3)OH$, b.p. 86°C/10 mmHg, $n_D(20°)$ 1.4862, from $ClCH_2C{\equiv}CLi$ in Et_2O-hexane and acetaldehyde at ~ -70°C.

$CH_3OCH_2C{\equiv}CCH(OH)CH{=}CH_2$, b.p. 108°C/12 mmHg, $n_D(20°)$ 1.4735, from CH_3O-$CH_2C{\equiv}CLi$ in THF-hexane and (freshly distilled) acroleine at -20 → 0°C and an additional 5 min. The aqueous layer is extracted 10-15 times with Et_2O, the organic solutions are not washed with water.

Notes

1. Only freshly distilled aldehydes should be used. Monomeric acetaldehyde (b.p. 21°C) is prepared 1-2 h in advance by heating the trimer, paraldehyde, with a few ml of 96% sulfuric acid in a distillation apparatus and collecting the acetaldehyde in a cooled receiver. All glassware should be made neutral by successive rinsing with distilled water, and acetone containing a trace of Et_3N, and blowing dry with air. The dropping funnel is treated in the same way.
2. Unstable $LiC{\equiv}CR^1$ should be prepared and converted with >C=O compounds below -70°C. This holds also in the case of reaction of a chloroketone $RCOCH_2Cl$ since the carbinolate $R^1C{\equiv}CC(R)(OLi)CH_2Cl$ may undergo cyclization to an epoxide at higher temperatures.
3. Yields are considerably lower and much ketone is recovered, when this addition is omitted. The beneficial effect of LiBr is strongest in the case of slightly soluble (in THF) $LiC{\equiv}CR^1$. A possible explanation is that LiBr causes solubilization of the alkynylide. The required anhydrous LiBr can be obtained by heating the commerical anhydrous salt (0.14 mol) in a 500-ml round-bottomed flask for 30 min at 150-200°C in a vacuum of 15 mmHg or less. The flask is occasionally swirled by hand. After cooling to 20°C, THF is added and dissolution is effected by vigorous shaking (the heating effect is rather strong).
4. If the carbinol is rather volatile (b.p. < 70°C/15 mmHg) a considerable amount of the

THF and hexane can be removed under reduced pressure using a rotary evaporator. The chance of the retro-reaction (to $R^1C{\equiv}CLi$ and $R^2R^3C{=}O$) is very small if the bath temperature is kept below 45°C. The remaining viscous solution is cooled to 0°C and a cold aqueous solution of NH_4Cl is added. By reducing the amount of THF and hexane, losses of product during the removal of solvent *after* aqueous work up are minimized. The procedure seems risky when $R^1 = C_2H_5O$ or Me_3Si.

5. Repeated extraction is necessary in the cases of carbinols with a short carbon chain, alkoxy- or dialkylamino groups.
6. K_2CO_3 is more effective, $MgSO_4$ should not be used if acid-sensitive groups (e.g. C≡C-O, C-O-CH-O) are present in the carbinol.
7. If the b.p. of the product is lower than 70°C/15 mmHg, the bath temperature should not be higher than 40°C.
8. It is generally advisable to first carry out a "rough" distillation at oil-pump or mercury diffusion-pump pressure, collecting the products in a strongly cooled single receiver (fig. 14).

2.3 Coupling of Monolithium Diacetylide with Acetone

$$HC{\equiv}CC{\equiv}CLi + (CH_3)_2C{=}O \xrightarrow[2.\ H_2O]{1.\ \text{THF-hexane, -70°C}} HC{\equiv}CC{\equiv}CC(CH_3)_2OH$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

The preparation of butadiynyl carbinols needs a prior explanation. Especially those carbinols derived from aldehydes have limited thermostability and bath temperatures higher than 100°C should be avoided. Distillation of amounts larger than 15 g involves the risk of explosive decomposition at the last stage. It is therefore essential that the undistilled product is sufficiently pure. If equivalent amounts of BuLi and diacetylene are used in the preparation of the lithium compound, there is a great chance that *diols* are formed from $LiC{\equiv}CC{\equiv}CLi$:

$$HC{\equiv}CC{\equiv}CH \xrightarrow{\text{BuLi, THF}} LiC{\equiv}CC{\equiv}CH + LiC{\equiv}CC{\equiv}CLi$$

The formation of the diols can be effectively suppressed by using a large excess (~ 50%) of diacetylene.

Procedure

A solution of 0.10 mol of BuLi in 70 ml of hexane is added over 10 min to a solution of 0.15 mol of freshly prepared diacetylene (p. 179) in 80 ml of THF, while keeping the temperature

below -50°C. The mixture (partly suspension) is cooled to -70 → -80°C and acetone (0.10 mol) is added over 5 min. The cooling bath is removed and the suspended material disappears within a few min. After an additional 10 min a solution of 10 g of NH_4Cl in 100 ml of water is added with vigorous stirring. After separation of the layers, three extractions with Et_2O are carried out. The unwashed organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*, leaving practically pure carbinol in > 90% yield. Distillation of the light-brown liquid from a relatively big flask (500 ml), using a short Vigreux column and a single receiver cooled below -20°C, gives the pure carbinol, b.p. ~ 40°C/1 mmHg, $n_D(20°)$ 1.4886, in 85-90% yield. During the distillation, the bath temperature should be kept as low as possible. The distillate rapidly turns dark upon standing at room temperature.

2.4 Coupling of Lithium Acetylide with Butanal

$$HC{\equiv}CLi + C_3H_7CH{=}O \xrightarrow[2.\ H_2O]{1.\ NH_3(liq.) \rightarrow THF} HC{\equiv}CCH(OH)C_3H_7$$

Scale: 1.5 molar.

Apparatus: fig. 1, 3 l; stirrer: fig. 3.

Introduction

Reaction of aliphatic aldehydes with alkali acetylides in liquid ammonia gives the carbinols in very small amounts, even when the aldehyde is added to a strongly cooled solution of lithium acetylide. The predominant reaction presumably is formation of the enolate and the aldol condensation product. As shown on p. 21, a suspension of $LiC{\equiv}CH$ in THF can be obtained by gradually replacing the ammonia of an ammoniacal solution of the acetylide by THF. The lithium acetylide obtained in this way probably thanks its stability to the complexed ammonia. In the procedure described below, butanal is added to the suspension to give the acetylenic carbinol in a reasonable yield. Since this compound is rather volatile, it is essential to remove the greater part of the THF, before the hydrolysis is carried out. The main solvent which then has to be removed in the isolation procedure is the diethyl ether, used for the extractions. During the addition of the aldehyde, acetylene is introduced to suppress the formation of the diol $RCH(OH)C{\equiv}CCH(OH)R$.

Procedure

A suspension of 1.5 mol of lithium acetylide in 600 ml of THF (p. 21) is cooled to -10°C. Acetylene is then introduced at a rate of 500 ml/min with vigorous agitation. After 10 min the rate is adjusted to ~300 ml/min and 1.5 mol of freshly distilled butanal is added dropwise over 30 min, while keeping the temperature between -10 and 0°C. The bath is then removed and stirring and introduction of acetylene are continued for an additional 10 min. The equipment is removed and two stoppers are placed on the outer necks. The greater part of the THF is

distilled off on the rotary evaporator, raising the bath temperature gradually (in the beginning some acetylene may escape from the solution) to 45°C. The brown viscous liquid is then hydrolysed with a cold (-5°C) solution of 100 g of NH_4Cl in 500 ml of water (vigorous shaking or mechanical stirring). The solution is extracted at least 7 times with Et_2O. The combined (unwashed) extracts are dried over potassium carbonate and subsequently concentrated *in vacuo*. The remaining liquid is then first distilled at 10-20 mmHg, using a short Vigreux column and a *single* receiver, cooled below 0°C (fig. 14). The viscous residue is discarded. Redistillation through a 40-cm Widmer column gives the carbinol, b.p. ~50°C/20 mmHg, $n_D(20°)$ 1.4379, in ~60% yield.

2.5 Coupling of Propynyllithium with Ketobutyraldehyde Dimethylacetal

$$CH_3C{\equiv}CLi + CH_3COCH_2CH(OCH_3)_2 \xrightarrow[10°C]{NH_3 \rightarrow THF} CH_3C{\equiv}C{-}\underset{\displaystyle OH}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}{-}CH_2CH(OCH_3)_2$$

(after hydrolysis)

Scale: 1.5 molar.

Apparatus: fig. 1, 3 l.

Introduction

The procedure for the carbinol from propyne and ketobutyraldehyde dimethylacetal, an intermediate in a new synthesis of Vitamine A aldehyde [78] is similar to the one in exp. 4. Attempts to couple propyne with the acetal via the lithium or sodium compound in liquid ammonia give poor results: most of the ketone is converted into brown products of unknown composition. Although the suspension of propynyllithium in THF obtained by replacing the ammonia by this solvent probably still contains ammonia (complexed to $CH_3C{\equiv}CLi$), an excellent result is obtained in the reaction with the ketone, if this is used in a short measure. The ketone is extremely base-sensitive and it is essential that it does not flow along the glass wall during its addition: in that case a brown colour will apear immediately and the yield is considerably lower. This procedure really is a good opportunity to make (justified) anti-propaganda for round-bottomed flasks with slanting necks (fig. −1), an apparatus that ought to be banned).

Procedure

Ketobutyraldehyde dimethylacetal (1.5 mol, commercially available) is added dropwise over 1.5 h to a suspension of 2.0 mol of propynyllithium (p. 21) in 1.2 l of THF. The temperature of the mixture is kept between 10 and 15°C. A brown solution is gradually formed. After completion of the addition , two stoppers are placed on the outer necks and most of the THF is distilled off on the rotary evaporator (bath temperature not higher than 65°C). The remaining viscous liquid is quickly hydrolysed with a cold (-5°C) solution of 120 g of NH_4Cl

in 500 ml of water (vigorous swirling and shaking), after which ten extractions with Et_2O are carried out. The (unwashed) organic solutions are dried over $MgSO_4$ and then concentrated *in vacuo*. Distillation of the remaining brown liquid gives the carbinol, b.p. 100°C/12 mmHg, $n_D(20°)$ 1.4520, usually in greater than 80% yield.

2.6 Reaction of Acroleine and Crotonaldehyde with Lithium Acetylide in Liquid Ammonia

$$LiC{\equiv}CH + RCH{=}\dot{C}HCH{=}O \xrightarrow[-75°C]{liq.\ NH_3} HC{\equiv}CCH(OLi)CH{=}CHR \xrightarrow[-33°C]{NH_4Cl}$$

$$\longrightarrow HC{\equiv}CCH(OH)CH{=}CHR \qquad R = H \text{ or } CH_3$$

Scale: 2.5 molar (aldehyde).

Apparatus: fig. 5, 3 l; stirrer: fig. 3.; cooling vessel: fig. 10, liquid N_2 is used for cooling.

Introduction

The correct performance of the procedures for 1-penten-4-yn-3-ol and 4-hexen-1-yn-3-ol requires considerable experimental skill. First a concentrated (~ 2 mol/l) solution of lithium acetylide in liquid ammonia has to be made by introducing acetylene into a suspension of lithium amide, using triphenylmethane as an indicator (p. 19). Subsequently the solution has to be cooled to a temperature in the region of -75°C, using a bath with liquid nitrogen. Efficient stirring is necessary to prevent solidification of the ammonia on the bottom of the flask: for this reason cooling should be applied only occasionally. It is very important that the aldehyde from the stem of the dropping funnel flows directly into the suspension: this conditon can be met only when the apparatus shown in fig.5 is used. A vigorous stream of nitrogen is introduced during the addition of the aldehyde in order to ensure that prior contact with the ammonia vapour does not occur. When the reactions are carried out at the b.p. of ammonia, yields are considerably lower, probably as a result of a competitive reaction of the aldehydes with ammonia.

Although deprotonation at the methyl group in crotonaldehyde by $LiC{\equiv}CH$ seems thermodynamically possible, this reaction does not take place under the reaction conditions applied. In this respect is is interesting that hexanal $C_5H_{11}CH{=}O$ and $LiC{\equiv}CH$ give only traces of the carbinol under similar conditions. The main reaction probably is formation of the enolate $C_4H_9CH{=}CHOLi$.

Procedure (compare [79,81])

Freshly distilled acroleine or crotonaldehyde (2.5 mol) is added dropwise over 20 min to a vigorously stirred suspension of 3.0 mol of lithium acetylide in 1.5 l of liquid ammonia (p. 19). During this addition the temperature of the suspension is kept between -70 and -78°C,

while N_2 is introduced (1.5 - 2 l/min). After an additional 15 min (without cooling) the reaction mixture is cautiously poured into a 5-l wide-necked round-bottomed flask. The reaction flask is rinsed twice with a small amount of liquid ammonia and the rinsings poured into the round-bottomed flask. Powdered ammonium chloride (150 g) is introduced in small portions with occasional manual swirling. The ammonia is then evaporated by placing the flask in a water bath at 50-60°C. The remaining mass is dissolved in the minimal amount of water (~250 ml) and the solution extracted with Et_2O: 15-20 times in the case R = H and 10-15 times in the case R = CH_3 (note 1). The combined ethereal solutions are dried over K_2CO_3 after which most of the ether is distilled off at normal pressure through a 40-cm Vigreux column. The remaining liquid is subsequently distilled in a water-pump vacuum, the receiver being cooled in a bath at -70°C (fig. 14). The temperature of the heating bath should not exceed 100°C in the case R = H. A viscous residue remains after the distillation of the acroleine carbinol. An additional small amount of carbinol may be obtained from this residue by lowering the pressure to < 2 mmHg (oil-pump) (note 2). Careful redistillation through a 40-cm Vigreux column gives the carbinols: R = H, b.p. 40°C/15 mmHg, $n_D(20°)$ 1.4522 and R = CH_3, b.p. 60°C/12 mmHg, $n_D(20°)$ 1.4650, in greater than 75% yields. The products contain 2-5% water.

The carbinol HC≡CC(OH)(CH_3)CH=CH_2, b.p. 30°C/12 mmHg, $n_D(20°)$ 1.4452, is obtained in ~60% yield by a similar procedure, with the difference that only 1.5 mol of (freshly distilled and water-free) methyl vinyl ketone is added to 3.0 mol of LiC≡CH. There remains a considerable amount of viscous residue after the distillation.

Notes

1. Saturation of the solution with K_2CO_3 may reduce the number of extractions necessary. Otherwise continuous extraction may be considered (after addition of more water).
2. Especially the acrolein carbinol has a limited thermal stability. Bath temperatures higher than 90°C during distillation should be avoided.

2.7 Reaction of Sodium Acetylide with Saturated Ketones

$$HC{\equiv}CNa + R^1R^2C{=}O \xrightarrow[-33°C]{\text{liq. } NH_3} HC{\equiv}CC(R^1)(R^2)ONa \xrightarrow{NH_4Cl} HC{\equiv}CC(R^1)(R^2)OH$$

Scale: 2.0 molar (ketone).

Apparatus: fig. 1, 3 l; stirrer: fig.3.

Introduction

Couplings of alkali acetylides with carbonyl compounds in liquid ammonia often give reduced yields. In many cases, the rates of carbinolate- and enolate formation (the alkali acetylide being the deprotonating agent) are comparable. In the subsequent hydrolysis, the carbonyl compound is liberated together with a corresponding amount of the acetylene. In some cases distillative separation of the desired product from the (recovered) starting compound(s) is difficult (*e.g.* when ethynyl or propynyl β-ionol, prepared from LiC≡CH or LiC≡CCH_3 and β-ionone, is to be separated from the β-ionone reformed from the enolate). The previous procedure describes the preparation in excellent yields of carbinols from LiC≡CH and acrolein or crotonaldehyde; carbonyl compounds that are not or are difficultly (respectively) enolizable. With a number of aliphatic saturated ketones, high yields can be obtained in the reaction with lithium or sodium acetylide in liquid ammonia, provided that during the addition of this ketone, acetylene is introduced to suppress the subsequent formation of diols:

$$HC{\equiv}CC(R^1)(R^2)OM \xrightarrow[HC{\equiv}CM]{R^1R^2C{=}O} HO\text{-}\underset{R^2}{\overset{R^1}{C}}\text{-}C{\equiv}C\text{-}\underset{R^2}{\overset{R^1}{C}}\text{-}OH \quad \text{(after hydrolysis)}$$

Ethynylation of cyclohexanone and cycloheptanone with lithium acetylide afforded yields between 50 and 60%. Appreciable amounts of the ketones were recovered indicating an appreciable degree of enolate formation. Under similar conditions the more easily enolizable cyclopentanone gave the ethynyl carbinol in a poor (~20%) yield [2].

Procedure

A (concentrated) solution of 2.3 mol of sodium acetylide in ~ 1.5 l of liquid ammonia is prepared as described on p. 19. The ketone (2.0 mol) is added dropwise over 30 min with vigorous agitation and introduction of acetylene (500 ml/min). After an additional 10 min stirring and introduction of acetylene are stopped and the ammonia is allowed to evaporate overnight (fig. 11). The solid residue is treated with a solution of 200 g of NH_4Cl in 400 ml of water. Five extractions (ten in the case of $R^1 = R^2 = CH_3$) with Et_2O are carried out. The (unwashed) extracts are dried over a large amount of $MgSO_4$ (100 g, stirring for 30 min). After filtration through a sintered-glass funnel and rinsing of the drying agent with Et_2O, most of the solvent is slowly distilled off through a 40-cm Vigreux column. Continuation of the distillation gives, after a small water-containing first fraction, the carbinols: $R^1 = R^2 = CH_3$: b.p. 102°C/760 mmHg, $n_D(20°)$ 1.4211; $R^1 = CH_3$, $R^2 = C_2H_5$: b.p. 120°C/760 mmHg, $n_D(20°)$ 1.4330; $R^1 = R^2 = C_2H_5$ b.p. 137°C, $n_D(20°)$ 1.4383. Yields are usually higher than 80% (including the aqueous fraction, which is dried over a small amount of $MgSO_4$ and subsequently redistilled). The (solid) residue consists mainly of the diol.

2.8 Reaction of Lithium Chloroacetylide with Acetone in Liquid NH_3

$$ClCH{=}CHCl + 2\,LiNH_2 \xrightarrow[-35\ to\ -40°C]{liq.\ NH_3} LiC{\equiv}CCl + LiCl\downarrow + NH_3$$

$$LiC{\equiv}CCl + (CH_3)_2C{=}O \xrightarrow[-35\ to\ -40°C]{} (CH_3)_2C(OLi)C{\equiv}CCl\downarrow \xrightarrow{NH_4Cl}$$

$$\longrightarrow (CH_3)_2C(OH)C{\equiv}CCl$$

Scale: 0.5 molar (dichloroethene).

Apparatus: fig. 1, 2 l; cooling vessel: fig. 10; stirrer: fig. 3.

Introduction

In contrast to many acetylenes RC≡CH, chloroacetylene can be successfully coupled with ketones in liquid ammonia via the lithium compound [80,85]. The excellent yield in the reaction with acetone indicates that practically no formation of enolate occurs. Similar good results have been obtained with lithiated ethynyl thioethers, (LiC≡CSR), lithiated enyne thioethers, (LiC≡CCH=CHSR), lithiated 1,3-diynes (RC≡CC≡CLi), and lithiated arylacetylenes (LiC≡CAryl)[2]. A possible explanation for the small extent of enolization of the ketone is that all these acetylides are less basic due to some stabilization of the anion.

Procedure (for precautions during working with chloroacetylides see p. 56!)

A solution of 0.5 mol of lithium chloroacetylide in ~0.7 l of liquid ammonia is prepared as described on p. 56. Acetone (0.6 mol) is added dropwise over 20 min, while stirring at a moderate rate (but nevertheless efficiently) and introducing N_2 at a rate of ~500 ml/min. During this addition the temperature of the thick suspension is kept between -35 and -40°C. After an additional 5 min the dropping funnel is replaced with a stopper and the thermometer-outlet combination removed. The rate of introduction of N_2 is increased to 1.5 l/min. Acetone is sprayed onto the upper surface of the flask (especially into the necks) in order to convert any remaining traces of LiC≡CCl into the carbinol. The introduction of N_2 is then stopped and powdered NH_4Cl (40 g) is introduced in small portions with stirring at a moderate rate (the cooling bath is no longer used). The ammonia is then allowed to evaporate (fig.11). After dissolving the salt in a small (~300 ml) amount of water, the solution is extracted 10 times with Et_2O. The (unwashed) extracts are dried well over $MgSO_4$ (a relatively large amount is used). After removing the Et_2O under reduced pressure (bath temperature is not allowed to exceed 25°C, in view of the volatility of the product), the product is distilled through a 40-cm Vigreux column and collected in a *single* receiver cooled at 0°C (fig. 14). The carbinol, b.p. 45°C/10 mmHg, $n_D(20°)$ 1.4515, is obtained in greater than 80% yield.

2.9 Reaction of Disodium Diacetylide with Acetone in Liquid NH_3

$$ClCH_2C{\equiv}CCH_2Cl + 4\,NaNH_2 \xrightarrow[-40°C]{liq.\ NH_3} NaC{\equiv}CC{\equiv}CNa + 2\,NaCl\downarrow + 2\,NH_3$$

$$NaC{\equiv}CC{\equiv}CNa + 2\,(CH_3)_2C{=}O \xrightarrow[-35\ to\ -40°C]{liq.\ NH_3} (CH_3)_2C(OH)\text{-}C{\equiv}CC{\equiv}C\text{-}C(OH)(CH_3)_2$$

(after hydrolysis)

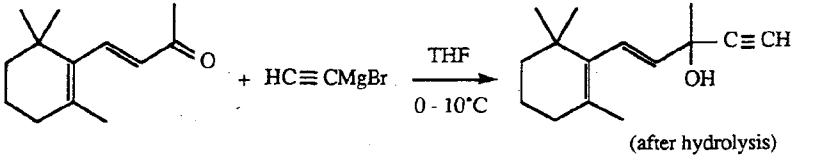
Scale: 0.20 molar (dichlorobutyne).

Apparatus: fig. 1, 1 l.

Procedure (for Introduction see exp. 8)

Acetone (0.50 mol) is added dropwise over a few min to a solution of disodium diacetylide in about 400 ml of liquid ammonia, prepared from 0.20 mol of 1,4-dichlorobutyne and 0.80 mol of sodamide (p. 46). During the addition of acetone the temperature of the mixture is kept between -35 and -40°C. After an additional 5 min, stirring is stopped and the cooling bath removed. The ammonia is allowed to evaporate overnight (fig. 11). The remaining solid mass is shaken with ice water (300 ml), after which four extractions with Et_2O are carried out. The combined ethereal solutions are washed once with water and subsequently dried over $MgSO_4$. The brown solid remaining after concentration of the solution under reduced pressure, ≥ 95% diol) is recrystallized from a 1:1 mixture of Et_2O and pentane to give a pure sample with m.p. 129-130°C.

2.10 Reaction of β-Ionone with Ethynylmagnesium Bromide



(after hydrolysis)

Scale: 0.20 molar (β-ionone).

Apparatus: fig. 1, 1 l.

Introduction

β-Ionone is very readily converted into the enolate -C-C(OM)=CH_2 by basic reagents, especially under polar conditions. Attempts to ethynylate this ketone with lithium- or sodium

acetylide in liquid ammonia gave the carbinol in moderate yields, along with much β–ionone, reformed from the enolate produced during the reaction with the alkali acetylide. Grignard reagents are highly reactive in additions to carbonyl groups, but show a slight tendency to deprotonate ketones or aldehydes at the α-position of the C=O group. Therefore, they are the reagents of choice if base-sensitive compounds such as β-ionone are to be alkynylated.

Procedure

A solution (partly suspension) of ethynylmagnesium bromide is prepared by introducing acetylene into a solution of 0.25 mol of C_2H_5MgBr in 350 ml of THF (p. 27 and fig. 16). After cooling to 0°C, freshly distilled β-ionone (0.20 mol) is added over a few min. The reaction is weakly exothermic. After an additional 15 min the cooling bath is removed and stirring is continued for 1 h. The solution is then poured into 200 ml of a concentrated aqueous solution of NH_4Cl. After vigorous shaking and separation of the layers, three extractions with Et_2O are carried out. The solvent is removed under reduced pressure and the remaining viscous liquid distilled through a short column to give ethynyl β–ionol, b.p. 100°C/0.2 mmHg, in 87% yield. There is a small high-boiling residue which decomposes during attempts to distill it.

Benzaldehyde or hexanal and HC≡CMgBr (additions at -20°C, then allowing the temperature to rise to 20°C), give the carbinol in 85-90% yields.

Coupling of β-ionone with $BrMgC{\equiv}CCH{=}C(CH_3)CH{=}CHOCH_3$ in THF under conditions similar to those described above, give the carbinol in an excellent yield (distillation is not possible). This carbinol can be converted into Vitamine A aldehyde *via* reduction with $LiAlH_4$ and subsequent treatment with dilute acid.

2.11 Ethynylation of Ketones with *t*-BuOK and Acetylene in THF

$$HC{\equiv}CH + R^1R^2C{=}O \xrightarrow[10\text{-}15^\circ C]{t\text{-BuOK, THF}} HC{\equiv}CC(R^1)(R^2)OH \quad \text{(after hydrolysis)}$$

Scale: 0.50 molar.

Apparatus: fig. 5, 1 l; stirrer: fig. 3.

Introduction

A number of saturated aliphatic and cycloaliphatic ketones can be ethynylated with excellent results by adding the ketone to a suspension of potassium acetylide in THF, while continuously introducing acetylene. The potassium acetylide is first generated by introducing acetylene through a solution of *t*-BuOK in THF.

$$HC{\equiv}CH + t\text{-BuOK} \rightleftharpoons HC{\equiv}CK\downarrow + HOt\text{-Bu}$$

The formation of potassium acetylide is presumably an equilibrium: yet it appears to be possible to convert the ketones completely into the ethynyl carbinols in greater than 90% yield, using a 1:1 molar ratio of *t*-BuOK and ketone. In the case of cyclohexanone even a 1:2 molar ratio gave > 85% yield of ethynylcyclohexanol, suggesting that a catalytic amount of starting base may suffice. However, the formation of acetylene *diols* appears to become increasingly important as the ratio *t*-BuOK/ketone is diminished.

The method gives unsatisfactory results in the cases of β-ionone and acetophenone, $PhCOCH_3$, (extensive formation of enol *etc.*) and is totally unsuitable for the ethynylation of benzaldehyde (Cannizarro reaction ?).

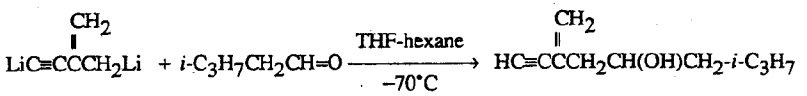
Procedure

Potassium *tert*-butoxide (0.50 mol) is dissolved in 600 ml of THF. A vigorous stream of acetylene (1.5-2 l/min) is introduced with efficient stirring and cooling in a bath with ice water. A jelly-like suspension is formed and the temperature may rise above 30°C (stirring may become less efficient). When no further rise in temperature is observed (after some 10 min), the flow of acetylene is adjusted to ~600 ml/min and the temperature of the suspension brought to 15°C. The ketone (0.50 mol) is then added dropwise over 20 min with vigorous agitation. The suspension gradually disappears. The temperature of the reaction mixture is maintained between 10 and 20°C. Stirring and introduction of acetylene are continued for an additional 10 min, then the light-brown solution is *cautiously* (some acetylene may escape) poured into a solution of 50 g of ammonium chloride in 200 ml of water. After vigorous shaking, the layers are separated and the aqueous layer is extracted four times (at least) with Et_2O. The combined organic solutions are washed twice with 100 ml portions of a saturated aqueous solution of NH_4Cl and subsequently dried over a large amount (~100g) of $MgSO_4$ (stirring for 30 min). After filtration through sintered glass and thorough rinsing of the drying agent with Et_2O, the greater part of the solvent is distilled off at atmospheric pressure through a 40-cm Vigreux column. After cooling, the remaining liquid is carefully distilled *in vacuo* through the same column. The following carbinols are obtained in 90% yield:

$R^1 = CH_3$, $R^2 = C_6H_{13}$, b.p. 87°C/15 mmHg, $n_D(20^\circ)$ 1.4921;
$R^1R^2C = (CH_2)_4C$ (cyclopentanone carbinol), b.p. 57°C/15 mmHg $n_D(19^\circ)$ 1.4742;
$R^1 = CH_3$, R^2 = *iso*-butyl, b.p. 75°C/18 mmHg, $n_D(22^\circ)$ 1.4328;
$R^1R^2C = (CH_2)_5C$, b.p. 75°C/15 mmHg (solid fraction);
$R^1R^2C = (CH_2)_6C$, b.p. 88°C/15 mmHg, $n_D(20^\circ)$ 1.4897;
$R^1 = CH_3$, $R^2 = t\text{-}C_4H_9$, b.p. 64°C/15 mmHg.

In all cases small high-boiling residues of the diol are left behind: the amount of residue is significant when the ketone has been added at too fast a rate.

2.12 Regiospecific Mono-Hydroxyalkylation of Dilithiated Isopropenylacetylene with Isovaleraldehyde (Preparation of a Precursor of a Bark-Beetle Pheromone)



Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

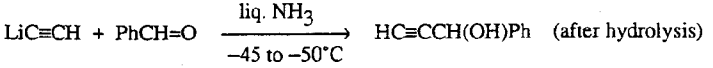
The procedures on p. 73,74 are examples of regiospecific *alkylation* at the most strongly basic centre in dimetallated acetylenes. The dilithio derivative of isopropenyl- acetylene $LiC{\equiv}CC(CH_2Li){=}CH_2$ shows this regiospecificity in reactions with most types of "electrophiles"; if one equivalent "E^+" is added to the dilithium compound, the primary product is $LiC{\equiv}CC(CH_2E){=}CH_2$: in the last stage of the addition some $EC{\equiv}CC(CH_2E){=}CH_2$ may also be formed.

The procedure of exp. 12 exemplifies the regiospecific reaction of dilithiated isopropenyl acetylene with carbonyl compounds. This example is significant in that the coupling product is a precursor of an aggregation pheromone of the bark beetle: treatment with activated zinc powder in ethanol gives ipsenol $H_2C{=}CHC(=CH_2)CH_2CH(OH)CH(CH_3)_2$ in almost quantitative yield. [46]

Procedure

Freshly distilled isovaleraldehyde (0.10 mol), diluted with 20 ml of THF is added dropwise over 15 min to a suspension of dilithiated isopropenylacetylene (0.10 mol) in THF and hexane (p. 34) maintained between -65 and -75°C. After the addition the cooling bath is removed and the temperature is allowed to rise to -40°C. Water (150 ml) is then added with vigorous stirring. After separation of the layers, five extractions with Et_2O are carried out. The unwashed extracts are dried over $MgSO_4$ and subsequently concentrated under reduced pressure. Careful distillation of the remaining liquid through a 30-cm Vigreux column gives the carbinol, b.p. 47°C/0.1 mmmHg, $n_D(20°)$ 1.4756, in 70% yield. The residue consists mainly of the diol (reaction at both negative centres).

2.13 Reaction of Lithium Acetylide with Benzaldehyde in Liquid Ammonia



Scale: 0.50 molar.

Apparatus: fig. 16, 2 l; after the introduction of acetylene, the gas inlet tube is removed and the benzaldehyde is introduced using a syringe.

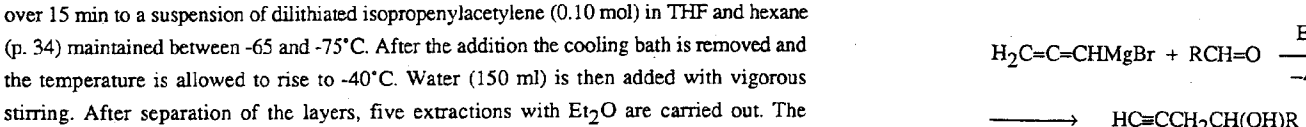
Introduction

The non-enolizable benzaldehyde can be ethynylated with excellent results by simply introducing it into a cooled solution of lithium acetylide in liquid ammonia which contains an excess of dissolved acetylene. The advantage of cooling the ammoniacal solution below its b.p. (-33°C) is that the acetylene gas need not be introduced continuously during the addition of the aldehydes; several liters of acetylene dissolve in the ammonia at temperatures below -40°C. Formation of the diol $PhCH(OH)C{\equiv}CCH(OH)Ph$ is effectively suppressed by the excess of acetylene, and therefore a rapid addition of the aldehyde is possible.

Procedure

A solution of 0.7 mol of lithium acetylide (p. 17) in about 500 ml of liquid ammonia is cooled to between -45 and -50°C. A rapid flow (~2 l/min) of acetylene is introduced with vigorous stirring during 5 min, while keeping the temperature between -45 and -50°C. Subsequently, a mixture of 0.50 mol of freshly distilled benzaldehyde and 40 ml of THF is introduced over 5 min. The cooling bath and the equipment are then removed. The greater part of the ammonia is removed by placing the flask in a water bath at 40°C. A solution of 25 g of NH_4Cl in 500 ml of water is then cautiously added and 5 extractions with Et_2O are carried out. The extracts are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Careful distillation through a 30-cm Vigreux column gives the carbinol, b.p. 110°C/15 mmHg $n_D(20°)$ 1.5517, in 79% yield. There remains 4 g of viscous residue.

2.14 Reaction of Allenylmagnesium Bromide with Aldehydes



Scale: 0.50 molar.

Apparatus: fig. 1.

Procedure

A solution of about 0.5 mol of allenylmagnesium bromide in ~400 ml of Et_2O, prepared as described on p. 35, is cooled to ~ -40°C. The aldehyde (0.50 mol, freshly distilled, note 1) is then added dropwise over 20 min with vigorous stirring. After the addition, the temperature is allowed to rise from -40 to +10°C. In most cases a coarse suspension is formed. The reaction

mixture is hydrolysed by pouring it into a solution of 50 g of ammonium chloride in 300 ml of ice water (note 2) after which the small amount of suspension remaining in the flask is treated with the NH_4Cl solution. After swirling and (subsequent) vigorous shaking, the layers are separated and the aqueous phase is extracted with Et_2O (note 3). The unwashed organic solution is dried over 25 to 50 g of $MgSO_4$ (shaking or mechanical stirring for 10 min) after which the drying agent is filtered off on a sintered-glass funnel and rinsed with Et_2O. The solvent is removed under reduced pressure (note 4) and the remaining liquid distilled through a 30 to 40-cm Vigreux column under water-pump or oil-pump pressure (depending on the volatility of the product). Yields are generally good to excellent.

Examples of alcohols prepared in this way:

R = n-C_3H_7, b.p. 58°C/12 mmHg, $n_D(20°)$ 1.4438;

R = $CH{=}CH_2$, b.p. 55°C/12 mmHg, $n_D(20°)$ 1.4592;

R = E-$CH{=}CHCH_3$, b.p. 68°C/12 mmHg, $n_D(20°)$ 1.4668.

Notes

1. Especially the lower aliphatic aldehydes tend to trimerize or polymerize. This process is accelerated by (traces of) acid. Redistillation is absolutely necessary: the indication of the supplier on the flask "acetaldehyde or propionaldehyde, 99%", should never be believed! Prior to carrying out the redistillation, all parts of the distillation apparatus should be rinsed with gaseous ammonia and subsequently with air. In this way, traces of acid adhering to the glass are neutralized. The volatile aldehydes are collected in a receiver, cooled at 0°C. The best way to prepare acetaldehyde is to add (with continuous swirling) 1 ml of 96% H_2SO_4 to 100 ml of the cyclic trimer ("paraldehyde") and to subsequently distill the volatile monomer (b.p. between 20 and 25°C)) through a 40-cm Widmer column. Exhaustive distillation should not be attempted since this may result in a vigorous decomposition of the residue. The redistilled aldehydes should be used without delay.
2. If the hydrolysis is carried out by inversed addition, much heat is evolved which may result in the loss of part of the ethereal solution.
3. Frequent extraction is necessary in the cases of the lower homologues.
4. In the case of carbinols from acetaldehyde and propionaldehyde, the Et_2O should be distilled off at atmospheric pressure.

Chapter V
Carboxylation, Acylation, and Related Reactions

1. Introduction

Acetylenic derivatives in which the triple bond is conjugated with a C=O group are versatile intermediates in organic synthesis, especially in cycloaddition reactions. A number of these systems have been prepared by transformation of other functional groups: acetylenic aldehydes $RC{\equiv}CCH{=}O$, for example can be obtained by acid hydrolysis of acetylenic acetals $RC{\equiv}CCH(OC_2H_5)_2$, which, in their turn, are accessible from acetylenic Grignard reagents $RC{\equiv}CMgBr$ and ethyl orthoformate $HC(OC_2H_5)_3$. Acetylenic ketones $RC{\equiv}CCOR'$ are formed by oxidation of the carbinols $RC{\equiv}CCH(OH)R'$ with chromic acid [83]. In most cases, however, the C=O function can be introduced in a direct manner and this chapter gives several excellent procedures for the introduction of this functionality. These procedures generally use an organic solvent; THF and Et_2O are the most favoured ones, though THF is often preferred for reasons of solubility. While the use of strongly polar solvents such as DMSO and HMPT, does not offer special advantages - the acylation and carboxylation reactions proceed at a convenient rate in THF or Et_2O - it could give rise to difficulties in the purification of the desired compounds. Liquid ammonia is generally unsuitable due to the ammonia-sensitivity of the functionalization reagent or of the product. For most derivatizations of acetylides Li^+ is preferred to Na^+, K^+ or XMg^+ as a counter ion, mainly because of better solubility of the acetylide. The general experience is that lithium compounds react more satisfactorily than do the Grignard derivatives.

2. Carboxylations

The usual procedure for carboxylation consists of pouring the solution of the organometallic intermediate onto powdered dry ice, covered with the organic solvent (Et_2O or THF). In the reaction of metallated acetylenes with CO_2, there is no danger of attack by the acetylide on the acetylenic carboxylate, and therefore this quenching procedure is unneccesary. An advantage of introducing gaseous CO_2 is that anhydrous conditions can be maintained more easily. It can generally be said that for the preparation of acetylenic carboxylic acids THF is the best solvent and Li^+ the best counter ion of the acetylenic anion. Yields are mostly excellent and often quantitative [2].

$$RC{\equiv}CLi \xrightarrow{CO_2,THF} RC{\equiv}CCOOLi \xrightarrow[H_2O]{H^+} RC{\equiv}CCOOH$$

3. Acylations and Related Reactions

Introduction of the following groups can be accomplished by reaction of a metallated acetylene with an easily available reagent: CH=O, RC=O, COOR, RN(H)C=O, RN(H)C=S, R_2NC=O.

A formyl group can be introduced by reacting the metallated acetylene (M = Li or MgX) with a *N,N*-disubstituted formamide or with a formic ester [84-86]:

$$RC{\equiv}CM + HC(=O)NR'_2 \xrightarrow{Et_2O \text{ or THF}} RC{\equiv}CC(OM)(H)NR'_2 \xrightarrow[H_2O]{H^+} RC{\equiv}CCH{=}O$$

$$RC{\equiv}CM + HCOOR' \xrightarrow{Et_2O \text{ or THF}} RC{\equiv}CC(H)(OM)OR' \longrightarrow RC{\equiv}CCH{=}O$$

Reaction of a metallated acetylene with a *N,N*-disubstituted formamide gives an adduct which is reasonably stable in the reaction solvent. Further attack of the acetylide on this adduct does not occur. A subsequent acid hydrolysis has to be carried out to liberate the aldehyde. Especially the reaction with lithium alkynylides gives excellent yields, provided that suitable conditions for the reaction and the aqueous work-up are chosen. With Grignard compounds yields are somewhat lower [84]. Although the use of formyl*piperidine* has been proposed [86], we obtained similar results with *N,N*-dimethylformamide [2]. The disadvantage of using formic esters HCOOR' lies in the fact that OR' is a better leaving groups than NR'_2. The adduct RC≡CCH(OM)OR' immediately eliminates R'OM from the aldehyde which may undergo further attack by RC≡CM to give a dialkynyl carbinol $(RC{\equiv}C)_2CHOH$. It is obvious that inversed-order addition has to be applied (using an excess of HCOOR') in order to limit the formation of this carbinol. This is also the case in the preparation of acetylenic esters from alkynylides and chloroformic esters; here, trialkynyl carbinols may be formed.

$$RC{\equiv}CM + ClCOOR' \xrightarrow{THF \text{ or } Et_2O} RC{\equiv}CCOOR' \ (M = Li \text{ [preferably]})$$

$$RC{\equiv}CCOOR' \xrightarrow{RC{\equiv}CM} RC{\equiv}CCOC{\equiv}CR \xrightarrow{RC{\equiv}CM} (RC{\equiv}C)_3COM$$

These subsequent reactions can be avoided by adding the lithiated acetylene to a large excess of chloroformate, and in this way, excellent yields can be obtained [2].

For the introduction of keto-functions, a number of variants are available which complement or overlap each other as to their scope. Although some methods seem to be less attractive than others, their use in special cases will become clear after comparision of the scope and limitations of the various methods. A few are represented below (for other variants see refs. 88-93).

$$RC{\equiv}CLi + R'C(=O)NR_2'' \longrightarrow RC{\equiv}CC(OLi)(R')NR_2'' \xrightarrow[H_2O]{H^+} RC{\equiv}CCOR'$$

$$RC{\equiv}CZnCl + R'C(=O)Cl \xrightarrow{(Pd^0)} RC{\equiv}CCOR'$$

$$RC{\equiv}CLi + (R'CO)_2O \longrightarrow RC{\equiv}CCOR'$$

$$RC{\equiv}CBF_3Li + R'C(=O)OR'' \longrightarrow RC{\equiv}CCOR'$$
$$(\text{or } R'C(=O)NR_2'')$$

$$RC{\equiv}CCu + R'C(=O)Cl \longrightarrow RC{\equiv}CCOR'.$$

For syntheses on a relatively small scale, *lithium* alkynylides are the most convenient starting compounds: they can be used as such or transformed into other organometallic intermediates.

A number of acetylenic methyl and phenyl ketones can be prepared with excellent yields from a lithium alkynylide and CH_3CONMe_2 or $PhCONMe_2$ (first equation [2]). Weakly basic acetylides such as PhC≡CLi and RC≡CC≡CLi gave unsatisfactory results (incomplete conversion) with CH_3CONMe_2. Also the amides from other aliphatic carboxylic acids, *e.g.* *t*-$BuCONMe_2$ and $C_3H_7CONMe_2$ react incompletely [2]. Good results are reported, however, if the lithium alkynylide is first treated with $BF_3.Et_2O$ and then carboxylic *esters* as well as acid amides can be employed [92]. Acid anhydrides, *e.g.* $(CH_3CO)_2O$, give fair yields (60-65%) in couplings with lithium alkynylides, provided that the acetylide is added to an excess of the anhydride. In our opinion, the acylation of alkynylzinc chloride with acyl halides is the most versatile method [2]. The organozinc intermediates can be prepared simply and quantitatively by an exchange reaction, using good quality zinc chloride. The reactions with benzoyl chloride and unsaturated acid halides, *e.g.* $H_2C{=}CHC(=O)Cl$ and RC≡CC(=O)Cl are very slow, probably because of mesomeric stabilization of the positive charge on the carbonyl carbon atom. In the presence of a catalytic amount of $Pd(PPh_3)_4$, however, a smooth conversion can be effected (compare also [94]). Thus, ketones with the systems C=CC(=O)C≡C and C≡CC(=O)C≡C (interesting substrates for the synthesis of cyclic compounds) are accessible in a direct way. Although this method seems to overshadow the acylation *via* copper acetylides [93], the latter variant could have significance as a mild method for the preparation of sensitive ketones.

Mono- and disubstituted acetylenic amides can be obtained in high yields by reacting metallated acetylenes with isocyanates and dialkylcarbamoyl chloride [95-98]:

$$RC{\equiv}CLi + R'N{=}C{=}O \xrightarrow{THF} RC{\equiv}CC(OLi){=}NR' \xrightarrow{H_2O,\ H^+} RC{\equiv}CCONHR'$$

$$RC{\equiv}CLi + ClC(=O)NR'_2 \xrightarrow{THF} RC{\equiv}CC(=O)NR'_2$$

Isothiocyanates give *N*-substituted thioamides:

$$RC{\equiv}CLi + R'N{=}C{=}S \xrightarrow{THF} RC{\equiv}CC(SLi){=}NR' \xrightarrow{H_2O,\ H^+} RC{\equiv}CCSNHR'$$

4. Experiments

All temperatures are internal, unless indicated otherwise

4.1 General Procedure for the Carboxylation of Acetylenes

$$RC{\equiv}CLi + CO_2 \xrightarrow[<0°C]{THF,\ hexane} RC{\equiv}CCOOLi \xrightarrow{H_2O,\ H^+} RC{\equiv}CCOOH$$

Scale: 0.30 molar.

Apparatus: fig. 16, 1 l.

Procedure (for Introduction see Section 2)

Dry carbon dioxide is introduced at a rate of 0.5-1 l/min into a vigorously agitated solution of 0.30 mol of lithium alkynylide in 210 ml of hexane and about 150 ml of THF (p. 24), which is kept between 0 and -10°C (or preferably lower temperature) by cooling in a bath with dry ice and acetone. After 10 to 20 min (depending upon the rate of introduction) the exothermic reaction has ceased. The resulting solution is then cautiously poured into 200 ml of ice water. After vigorous swirling and subsequently shaking, the layers are separated. The organic layer is extracted twice with 40-ml portions of water and then discarded. The aqueous washings are combined with the first aqueous layer. Concentrated hydrochloric acid is added in small portions with cooling in an ice bath and swirling until a pH of 1 has been reached. The mixture is then extracted with Et_2O, the number of extractions depending upon the solubility of the carboxylic acid (in the case of $CH_3C{\equiv}CCOOH$ and $C_2H_5C{\equiv}CCOOH$ several extractions are needed, consult p. 10!). The unwashed extracts are dried over a large amount (~100 g) of $MgSO_4$ (stirring for half an hour), after which the drying agent is filtered off on a sintered-glass funnel and rinsed well with Et_2O. After concentration of the solution under reduced pressure, the residue is distilled through a short Vigreux column to give (after a small forerun) $CH_3C{\equiv}CCOOH$, b.p. 85°C/15 mmHg, $C_2H_5C{\equiv}CCOOH$, b.p. 103°C/12 mmHg, $C_3H_7C{\equiv}CCOOH$, b.p. 118°C/15 mmHg, *E* + *Z*- $CH_3CH{=}CHC{\equiv}CCOOH$, b.p. 120°C/12 mmHg. The products solidify upon standing or during the distillation in the condenser (the use of an air condenser is recommended).

In the cases of $PhC{\equiv}CCOOH$ and $C_4H_9C{\equiv}CC{\equiv}CCOOH$, the residue remaining after concentration of the extract *in vacuo* is heated for 1-2 h at ~70°C in a vacuum of 1 mmHg or better. The products are subsequently crystallized from Et_2O or pentane, respectively (at -25°C). $PhC{\equiv}CCOOH$ has m.p. 132-133°C; $C_4H_9C{\equiv}CC{\equiv}CCOOH$, m.p. 38-40°C. Yields are generally higher than 95%.

4.2 Acetylenic Esters from Lithium Alkynylides and Alkyl Chloroformates

$$RC{\equiv}CLi + ClCOOR' \xrightarrow[<-10°C]{THF\text{-}hexane} RC{\equiv}CCOOR' + LiCl\downarrow$$

Scale: 0.30 molar.

Apparatus: fig. 1, 1 l.

Procedure (for Introduction see Section 3)

A solution of 0.30 mol of the lithiated acetylene (when R = CH_3 partly suspension) in 200 ml of THF (p. 24) is added in 10 equal portions to a mixture of 0.60 mol of the chloroformic ester and 50 ml of THF. During this addition, which is carried out over 30 min, the temperature is kept between -25 and -35°C. Stirring at this temperature is continued for another 30 min, then the cooling bath is removed and the temperature allowed to rise to +10°C. The reaction mixture (fine suspension or solution) is then poured into 800 ml of a saturated aqueous solution of NH_4Cl. After vigorous shaking and separation of the layers, three extractions with Et_2O are carried out. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. In the case of R being CH_3, however, the greater part of the solvent is distilled off at atmospheric pressure through a 40-cm Vigreux column. Careful distillation of the remaining liquid through a 40-cm Vigreux column at reduced pressure gives the following esters: $CH_3C{\equiv}CCOOCH_3$, b.p. 45°C/15 mmHg, $n_D(20°)$ 1.4348; $C_3H_7C{\equiv}CCOOC_2H_5$, b.p. 76°C/12 mmHg, $n_D(20°)$ 1.4398; $C_4H_9C{\equiv}CCOOC_2H_5$ b.p. 90°C/12 mmHg, $n_D(20°)$ 1.4448; $H_2C{=}C(CH_3)C{\equiv}CCOOCH_3$, b.p. 65 °C/15 mmHg, $n_D(20°)$ 1.4660. Yields are between 78 and 85%.

$ClCH_2C{\equiv}CCOOCH_3$ b.p. ~40°C/0.5 mmHg, $n_D(23°)$ 1.4783, is obtained in 67% yield (compare ref. 99) by adding 0.20 mol of $ClCOOCH_3$ in one portion to a solution of 0.10 mol of $LiC{\equiv}CCH_2Cl$ (p. 25.) cooled to -95°C. The temperature is then maintained for 1.5 h at -40°C and subsequently allowed to rise to 15°C. The brown reaction mixture is hydrolysed and the work-up is carried out as described above.

$HC{\equiv}CC{\equiv}CLi$ and $CH_3C{\equiv}CC{\equiv}CLi$ (in THF-hexane) unexpectedly gave very intractable black reaction mixtures.

When alkynyl magnesium halides are used in the reaction with ClCOOR yields are considerably lower.

4.3 General Procedure for the Formylation of Acetylenes with DMF

$$RC{\equiv}CLi + HC(=O)NMe_2 \xrightarrow[-60\rightarrow+15^\circ C]{Et_2O} RC{\equiv}CC(H)(NMe_2)OLi \xrightarrow[pH\ 2 \rightarrow 6\ to\ 7]{H_2O,\ H^+} RC{\equiv}CCH{=}O$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Introduction

Additions of polar organometallic intermediates to the C=O group in *N,N*-disubstituted formamides proceed less easily than the reactions with aldehydes. Whereas (soluble) lithium alkynylides react almost instantaneously with aldehydes, even at temperatures in the region of -70°C, the adduct formation from *N,N*-dimethylformamide and RC≡CLi at -70 to -50°C in THF or Et_2O is slow. This is reflected in the low yield of aldehyde obtained from the subsequent acid hydrolysis. Although upon mixing a THF or Et_2O solution of RC≡CLi and dimethylformamide at -60°C a significant heating effect is observed (in the case of poorly soluble alkynyllithium the solution becomes clear upon addition of DMF), practically no acetylenic aldehyde is formed when the mixture is treated with dilute acid after a few minutes. For obtaining optimal yields of RC≡CCH=O, it is necessary to allow the temperature to rise to +10-20°C prior to the hydrolysis. If during the hydrolysis the pH rises above 7, the amine liberated may add to the α,β-unsaturated system. It is therefore essential to add the organic solution of the adduct from RC≡CLi and the formamide to a slight excess of dilute acid. The pH is then brought to 6-7 by controlled addition of sodium hydrogen carbonate.

Procedure

Dimethylformamide (or formylpiperidine) (0.25 mol) is added over a few min to a solution or suspension of 0.20 mol of alkynyllithium in Et_2O (p. 24), cooled to -70°C. The cooling bath is then removed and the temperature allowed to rise. Stirring at +10 to 15°C is continued for an additional 20 min, then the (almost) clear solution is added over a few min to a vigorously stirred mixture of 250 ml of ice water and 45 g (slight excess) of 36% aqueous hydrochloric acid (addition with the aid of syringe may be convenient). Subsequently, a concentrated aqueous solution of $NaHCO_3$ is added dropwise with vigorous stirring until a pH between 6 and 7 has been reached. The layers are separated, after which the aqueous layer is extracted four times with pentane or Et_2O. The combined organic solutions are dried over $MgSO_4$ and then concentrated under reduced pressure. Vacuum distillation gives the aldehydes in 80% or higher yields: $C_4H_9C{\equiv}CCH{=}O$, b.p. 58°C/15 mmHg, 1-cyclohexenyl- -C≡CCH=O (from ethynylcyclohexene), b.p. 105°C/10 mmHg (partial polymerization), $n_D(18°)$ 1.5505; PhC≡CCH=O, b.p. *ca.* ~70°C/0.5 mmHg, $n_D(18°)$ 1.6032; $Me_3SiC{\equiv}C$- -CH=O, b.p. 30°C/10 mmHg, $n_D(20°)$ 1.4420. The solution of $Me_3SiC{\equiv}CLi$ is obtained by adding at ~

-40°C a solution of $C_2H_5Li.LiBr$ (prepared from C_2H_5Br and Li, see ref. 1) to a mixture of a slight excess of $Me_3SiC{\equiv}CH$ in Et_2O.

$CH_3C{\equiv}CC{\equiv}CCH{=}O$ is obtained in ~75% yield (undistilled) from $CH_3C{\equiv}CC{\equiv}CLi$ and DMF in a THF-hexane mixture and subsequent treatment with dilute aqueous acid. The aldehyde is solid at room temperature. Attempts to distil this compound resulted in a vigorous decomposition.

Reaction of $LiC{\equiv}CCH_2Cl$ with DMF led to the formation of an intractable suspension containing brown, amorphous and tarry material. Subsequent acid hydrolysis did not give the aldehyde.

It should be pointed out that the use of a (commercially available) solution of BuLi in *hexane* gives rise to problems during the isolation of *volatile* (b.p. up to 40°C/10 mmHg) aldehydes. In these cases, one should use $C_2H_5Li.LiBr$ in Et_2O for the metallation of the acetylene. The aldehydes $CH_3C{\equiv}CCH{=}O$ and $C_2H_5C{\equiv}CCH{=}O$, for example, should be preparable in good yields from the reaction of $CH_3C{\equiv}CLi$ and $C_2H_5C{\equiv}CLi$ in Et_2O (containing LiBr) with DMF. Several extractions with pentane or Et_2O have to be carried out after hydrolysis. The solvent is then slowly distilled off through an efficient column at atmospheric pressure.

4.4 Methyl Alkynyl Ketones from Alkynyllithium and Dimethylacetamide

$$RC{\equiv}CLi + CH_3C(=O)NMe_2 \xrightarrow{Et_2O(or\ THF)} RC{\equiv}CC(CH_3)(NMe_2)OLi \xrightarrow[pH\ 2\rightarrow 6\ to\ 7]{H_2O,\ H^+} RC{\equiv}CCOCH_3$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Procedure (for Introduction see exp. 3)

N,N-Dimethylacetamide (0.25 mol) is added over a few min to a solution of 0.20 mol of alkynyllithium in 140 ml of hexane and 140 ml of Et_2O (p. 24, THF is preferred when the alkynyllithium derivative is only slightly soluble in Et_2O), cooled to -60°C. The temperature is allowed to rise to 15-20°C and stirring is continued for an additional half hour. The solution is then hydrolysed with a slight excess of dilute hydrochloric acid, as described in the previous experiment. Working up (see also exp. 3) gives the following ketones in greater than 90% yields: 1-cyclohexenyl-$C{\equiv}CCOCH_3$, b.p. ~50°C/0.5 mmHg, $n_D(17°)$ 1.5283; $C_4H_9C{\equiv}C$-$COCH_3$, b.p. 60°C/10 mmHg, $n_D(17°)$ 1.4482.

With PhC≡CH, a 3:2 mixture of $PhC{\equiv}CCOCH_3$ and PhC≡CH is obtained. Also 1,3-diynes $RC{\equiv}CC{\equiv}CH$ react very incompletely with CH_3CONMe_2. *t*-$BuCONMe_2$ does not react with a solution of $C_2H_5C{\equiv}CLi$ in THF-hexane. Under similar conditions the much

stronger base 2-thienyllithium and *t*-BuCONMe$_2$ gave 2-thienylCO*t*-Bu in an excellent yield (after hydrolytic work-up). The reaction of $C_2H_5C{\equiv}CLi$ with *n*-$C_4H_9CONMe_2$ "stopped" after ~50% conversion.

4.5 Acylation with *N,N*-Dimethylbenzamide

$$CH_3C{\equiv}CLi + PhCONMe_2 \xrightarrow{\text{THF-hexane}} CH_3C{\equiv}CC(OLi)(Ph)\text{—}NMe_2 \xrightarrow[\text{pH 2}\rightarrow\text{6-7}]{H^+,\ H_2O} CH_3C{\equiv}CCOPh$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Procedure

This preparation is carried out in a manner similar to that described in exp. 4. $PhCONMe_2$ (0.10 mol) is added at -20°C to a suspension of 0.12 mol (excess is used to avoid separation problems) $CH_3C{\equiv}CLi$ (p. 24) in 84 ml of hexane and 80 ml of THF. The suspension clears, gradually. After stirring for an additional hour at + 15°C, the reaction mixture is worked up to give $PhCOC{\equiv}CCH_3$, b.p. ~80°C/0.5 mmHg, $n_D(24°)$ 1.5433, in 80% yield.

4.6 Acylation with Acid Anhydrides

$$RC{\equiv}CLi + (CH_3CO)_2O \xrightarrow{Et_2O\text{-hexane}} RC{\equiv}CCOCH_3 + CH_3COOLi\downarrow$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Procedure

A solution of the alkynyllithium derivative (0.10 mol, p. 24) in 70 ml of Et_2O and 70 ml of hexane is added over 30 min to a mixture of 0.20 mol of pure acetic anhydride and 50 ml of Et_2O with cooling between -60 and -70°C. After an additional 15 min the cooling bath is removed and the temperature of the suspension allowed to rise to 0°C. A solution of 30 g of NH_4Cl in 200 ml of water is then added followed by dropwise addition of 15 ml of concentrated aqueous ammonia over 30 min with vigorous stirring. The layers are separated and the aqueous layer extracted four times with Et_2O. The combined organic solutions are washed with concentrated aqueous NH_4Cl, dried over $MgSO_4$ and then concentrated *in vacuo*. The remaining liquid is distilled at ≤ 0.5 mmHg through a very short column and the distillate collected in a *single* receiver, cooled below -30°C (fig. 14). The contents of the

receiver are redistilled through a 20-cm Vigreux column (note 1). The following ketones are obtained: $C_4H_9C{\equiv}CCOCH_3$, b.p. 68°C/12 mmHg, $n_D(20°)$ 1.4462, yield 60%; *Z*-C_3H_7-$CH{=}CHC{\equiv}CCOCH_3$, b.p. *ca.* 50°C/0.5 mmHg, $n_D(20°)$ 1.4760, yield 80%; $C_3H_7C{\equiv}C$-$C{\equiv}CCOCH_3$ (purity ~94%), b.p. *ca.* 55°C/0.5 mmHg, $n_D(20°)$ 1.5134, yield 64%.

Notes

1. Bath temperatures should be kept below 90°C. Especially those ketones with systems $C{=}CC{\equiv}C$ and $C{\equiv}CC{\equiv}C$ have limited thermal stability.

4.7 Reaction of Alkynylzinc Chloride with Acyl Halides

$$RC{\equiv}CZnCl + R'COCl \xrightarrow{\text{THF-hexane}} RC{\equiv}CCOR' + ZnCl_2$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

Although it should be possible to prepare acetylenic ketones in moderate to reasonable yields by controlled addition of alkynyllithium to an excess of acyl halide, this procedure does not seem very attractive for sensitive products. It is very difficult to prevent the subsequent reaction of the ketones with alkynylllithium which results in the formation of dialkynyl carbinols. These will accumulate in the distillation residue and may give rise to explosive decomposition. Normant [93] used the reaction of copper alkynylides (generated *in situ* from alkynyllithium or alkynyl Grignard reagents and copper(I)halide) with acyl halides to synthesise acetylenic ketones. Here too, problems may arise during the work-up and isolation: removal of the copper salts requires the use of alkali cyanide. The alkaline conditions during the work-up may cause further reactions of the acetylenic ketone, for example Michael additions or base-catalysed isomerization. Another way to "tame" alkynylides is to convert them into alkynylzinc halides by addition of an equivalent amount of zinc halide. The zinc salts are easily removed during the work-up. The alkynylzinc method appears to give very good results with saturated aliphatic acyl halides (compare ref. 94).

Procedure

The acyl halide (0.10 mol, freshly distilled) is added dropwise over 15 min to a solution (sometimes two-layer system) of 0.10 mol of alkynylzinc halide (p. 36) in THF and hexane, maintained between 5 and 10°C. After the addition, the cooling bath is removed and the temperature allowed to rise. Stirring is continued for 45 min at 20°C, then the mixture is cooled to -10°C and a solution of 20 g of NH_4Cl in 200 ml of water is added with vigorous stirring After separation of the layers, three extractions with Et_2O are carried out. The combined organic solutions are washed four times with a saturated aqueous solution of

NH_4Cl (to remove traces of zinc salts) and subsequently dried over $MgSO_4$. The liquid remaining after concentration of the solution *in vacuo* is distilled under low pressure (see previous experiment). The following ketones are prepared in 70 to 80% yields: $CH_3C{\equiv}CCOC_3H_7$, b.p. 55°C/15 mmHg, $n_D(20°)$ 1.4447; $PhC{\equiv}CCOCH_3$, b.p. ~80°C/0.5 mmHg, $n_D(20°)$ 1.572; $C_3H_7C{\equiv}CC{\equiv}CCOCH_3$, b.p. ~70°C/0.3 mmHg, $n_D(20°)$ 1.5120.

4.8 Pd^0-Catalysed Coupling of Alkynylzinc Chlorides with Acyl Halides

$$C_2H_5C{\equiv}CZnCl + C_2H_5C{\equiv}CC(=O)Cl \xrightarrow[Pd(PPh_3)_4]{\text{THF-hexane}} C_2H_5C{\equiv}C{-}\overset{O}{\overset{\|}{C}}{-}C{\equiv}CC_2H_5 + ZnCl_2$$

$$C_5H_{11}C{\equiv}CZnCl + H_2C{=}CHC(=O)Cl \longrightarrow C_5H_{11}C{\equiv}C{-}\overset{O}{\overset{\|}{C}}{-}CH{=}CH_2 + ZnCl_2$$

Scale: 0.10 molar.

Apparatus: fig. 1, 11.

Introduction

Unsaturated acyl halides, such as pentynoyl chloride and acryloyl chloride, as well as benzoyl chloride, are much less reactive towards alkynylzinc halide than the saturated ones. Attempts to prepare the unsaturated ketones at higher temperatures gave only "polymeric" products [2]. The palladium complex $Pd(PPh_3)_4$ shows a strong catalytic effect, allowing the reactions to proceed in a short time under mild conditions. Although the reactions seem to proceed cleanly, it turns out to be difficult in practice to obtain yields higher than 80%. Use of too high a temperature or too long a reaction time involves a high risk of subsequent reactions under the influence of the palladium catalyst. In the usual small-scale procedures small amounts of palladium or organopalladium compounds are removed by subjecting the extract to column "chromatography". For working on a 0.1 molar scale, this is not a very practical solution. Fortunately, very small amounts of the Pd-catalyst are sufficient in the procedures for the acetylenic ketones. Since during the aqueous work-up most of the palladium compounds precipitate, only traces remain during distillation. Yet it is advisable to carry out the distillation as quickly as possible at a very low pressure (preferably less then 0.1 mmHg) avoiding high bath temperatures. A wide and very short distillation column is indispensable!

Procedure

A solution of 0.7 g of $Pd(PPh_3)_4$ [100] in 15 ml of THF is added to a solution of 0.11 mol of the alkynylzinc chloride (p. 36) in THF and hexane cooled to 0°C. Pentynoyl chloride (0.11 mol, see below) or acryloyl chloride (0.12 mol freshly distilled, commercially available) is then added dropwise over 2 min, while keeping the temperature between 0 and 5°C. After an additional 5 min (at 5-10°C) 300 ml of pentane is added and the reaction mixture is poured

into a saturated aqueous solution of NH_4Cl (250 ml). After vigorous shaking, the layers are separated and the aqueous layer is extracted once with 100 ml of pentane. The combined organic solutions are washed four times with 150-ml portions of a saturated aqueous solution of NH_4Cl (note 1) and subsequently dried over $MgSO_4$. The light-brown liquid remaining after concentration of the organic solution under reduced pressure is distilled from a 100-ml flask, using a 10-cm Vigreux column (B-29 glass is recommended) and a mercury-diffusion pump. The pressure should be 0.01 mmHg or lower. The product is collected in a *single* receiver, cooled at -78°C. A small brown, viscous residue remains in the distillation flask. Redistillation at oil-pump pressure gives $(C_2H_5C{\equiv}C)_2C{=}O$, b.p. ~70°C/0.5 mmHg, $n_D(20°)$ 1.4930 and $C_5H_{11}C{\equiv}CCOCH{=}CH_2$, b.p. ~60°C/0.5 mmHg, $n_D(20°)$ 1.4710, in yields varying between 46 and 82% (note 2).

Benzoyl chloride (0.12 mol) reacts smoothly at 10-15°C. After an additional 15 min (at 25°C) pentane is added and the reaction mixture is poured into an aqueous solution of NH_4Cl containing a small amount of ammonia (to remove the excess of benzoyl chloride). The ketone $PhCOC{\equiv}CC_2H_5$, b.p. ~90°C/0.5 mmHg, $n_D(20°)$ 1.5570, is obtained in 83% yield.

Pentynoyl chloride is prepared as follows: Pentynoic acid (0.20 mol, see exp. 1) and dichloromethane (20 ml) are placed in a 250-ml two-necked flask, equipped with a dropping funnel and a reflux condenser. The mixture is warmed in a bath at 80°C and 0.20 mol of freshly distilled $SOCl_2$ is added dropwise over 15 min with occasional swirling. After heating the mixture for an additional half hour at ~80°C (while introducing N_2) a careful distillation is carried out, giving the acid chloride, b.p. 35°C/10 mmHg, $n_D(20°)$ 1.4670, in ~75% yield.

Notes

1. It seems essential to remove traces of zinc salts.
2. The procedures have been carried out only a few times. More research may result in improved yields. Short reaction times seem to be essential for obtaining good yields.

4.9 Reaction of Butynyllithium with Dimethylcarbamoyl Chloride

$$C_2H_5C{\equiv}CLi + Me_2NC(=O)Cl \xrightarrow[-40 \rightarrow +20°C]{\text{THF-hexane}} C_2H_5C{\equiv}CC(=O)NMe_2 + LiCl$$

Scale: 0.10 molar.

Apparatus: fig. 1, 11.

Introduction

N,N-disubstituted acid amides are often prepared by reaction of acyl halides with secondary amines. This method is attractive when the acyl halide is readily available. This is not the case with pentynoyl chloride, which has to be synthesised by a two-step procedure from butyne (see exp. 8). In analogy with the carboxyalkylation with alkyl chloroformates (exp. 2), an

acid amide group can be introduced in a one-step operation, using a dialkylcarbamoyl chloride [97] (commercially available and inexpensive). The usual procedure involves addition of the organometallic intermediate to a solution of an excess of the carbamoyl halide. Applying the normal addition procedure in the case of the reaction of 1-butynyllithium with dimethylcarbamoyl chloride, we obtained a mixture of the desired product $C_2H_5C{\equiv}CC(=O)NMe_2$ and $(C_2H_5C{\equiv}C)_2C{=}O$.

Warning! Dimethylcarbamoyl chloride is said to be carcinogeneous.

Procedure

A solution of 0.10 mol of butynyllithium in 80 ml of THF and 70 ml of hexane (p. 24) is placed in the dropping funnel. The solution is added over 30 min to a mixture of 0.2 mol of dimethylcarbamoyl chloride and 40 ml of THF, while keeping the temperature of the reaction mixture between -25 and -30°C. After completion of the addition, the cooling bath is removed and the temperature allowed to rise to 10-15°C. Ice water (50 ml) is then added with vigorous stirring and cooling in an ice bath. After separation of the layers, the aqueous layer is extracted three times with small portions of *THF*. The combined organic solutions are dried (without previous washing) over $MgSO_4$ and subsequently concentrated under reduced pressure. Distillation of the remaining liquid through a 20-cm Vigreux column gives the acid amide, b.p. 85°C/1 mmHg, $n_D(20°)$ 1.4832, in 85% yield.

LiC≡CH.TMEDA in THF-hexane and Me_2NCOCl gave only black tars.

4.10 Addition of Propynyllithium to Phenyl Isocyanate

$$CH_3C{\equiv}CLi + PhN{=}C{=}O \xrightarrow[-40\rightarrow +10°C]{\text{THF-hexane}} CH_3C{\equiv}CC(OLi){=}NPh \xrightarrow{H_2O,\ H^+} CH_3C{\equiv}CC(=O)NHPh$$

Scale: 0.10 molar.

Apparatus: fig. 1, 11.

Introduction

A general reaction of polar organometallic and Grignard compounds is their addition to heterocumulenes [72], the most familiar reaction of this group being carboxylation *i.e.* addition to CO_2 (exp. 1). Additions to other types of heterocumulenes (RN=C=O, RN=C=S, RN=S=O, CS_2, SO_2) have been studied less extensively [72] and additions of metallated acetylenes to these heterocumulenes have been reported only incidentally [94-96,98]. Metallated acetylenes generally are less reactive than the more strongly basic metallated aromatic and heteroaromatic compounds and in some cases they show unexpected behaviour: we were unable to prepare acetylenic dithioates RC≡CC(=S)SLi (or -MgBr) from metallated

acetylenes and carbon disulfide. The procedures in exps. 10, 11 and 12 show typical reaction conditions for the addition of lithiated acetylenes to isocyanates, isothiocyanates and sufinylamines. The limited thermal stability of the products does not allow distillative purification without considerable losses, therefore we have chosen the examples where the products can be obtained in a crystalline state.

Procedure

Freshly distilled phenyl isocyanate (0.10 mol) is added in one portion to a suspension of 0.11 mol of propynyllithium (p. 24) in 80 ml of THF and 77 ml of hexane at -60°C. The cooling bath is removed and the temperature allowed to rise. The heating effect is weak. The suspension gradually becomes a little gelatinous. After stirring for an additional 15 min at +10°C, a mixture of 12 g (~0.10 mol) of 36% aqueous HCl and 100 ml of water is added with vigorous stirring. After separation of the layers, three extractions with Et_2O are carried out. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated under reduced pressure. The brown residue is dissolved in a 2:1 mixture of pentane and Et_2O and the solution allowed to stand at -25°C for 12 h. The light-brown crystalline mass is rinsed with cold pentane and dried *in vacuo*. From the concentrated mother liquor a second crop of crystals is obtained, bringing the yield to 88%. The m.p. (after a second crystallization from pentane: Et_2O) is 111-112°C.

4.11 Reaction of *t*-Butylethynyllithium with Methyl Isothiocyanate

$$t\text{-}C_4H_9C{\equiv}CLi + CH_3N{=}C{=}S \xrightarrow[-10\rightarrow 15°C]{\text{THF-hexane}} t\text{-}C_4H_9C{\equiv}C{-}C(SLi){=}NCH_3 \xrightarrow{H_2O,\ H^+} t\text{-}C_4H_9C{\equiv}CC(=S)NHCH_3$$

Scale: 0.10 molar.

Apparatus: fig. 1, 11.

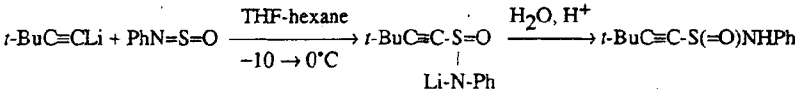
Procedure (for Introduction see exp. 10)

A solution of 0.10 mol of methyl isothiocyanate in 30 ml of THF is added over a few min to a solution of 0.11 mol of t-butylethynyllithium (p. 24) in 80 ml of THF and 77 ml of hexane, cooled to -10°C. The cooling bath is removed and the temperature allowed to rise. The light-yellow solution gradually turns brown. After stirring for an additional 45 min at 15°C, the solution is cooled to -20°C and a mixture of 12 g (0.10 mol) of 36% aqueous HCl and 100 ml of water is added with vigorous stirring. After separation of the layers, three extractions with Et_2O are carried out. The combined solutions are dried over $MgSO_4$ and subsequently concentrated under reduced pressure. Crystallization (at -25°C) from a 2:1 mixture of pentane and Et_2O gives the thioamide (m.p. 87-88°C) in 74% yield.

$CH_3C{\equiv}CLi$ and $C_2H_5C{\equiv}CLi$ react with $CH_3N{=}C{=}S$ under similar conditions to give viscous brown liquids, reasonably pure thioamides according to ^1H NMR. $HC{\equiv}CLi.TMEDA$ in THF-hexane and $CH_3N{=}C{=}S$ give an intractable, dark reaction mixture.

Phenyl isothiocyanate reacts less readily with alkynyllithium than methyl isothiocyanate. The thioamide from the reaction of $CH_3C{\equiv}CLi$ with $PhN{=}C{=}S$ is not easy to obtain in a crystalline state.

4.12 Reaction of *t*-Butylethynyllithium with Phenylsulfinylamine



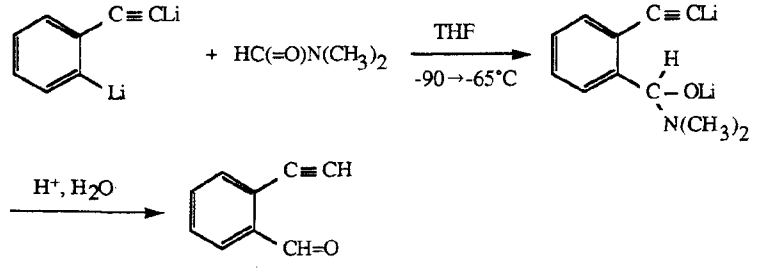
Scale: 0.10 molar.

Apparatus: fig. 1, 1 l; stirrer fig. 3.

Procedure (for Introduction see exp. 10)

A mixture of 0.10 mol of $PhN{=}S{=}O$ [232] and 100 ml of Et_2O is added over 15 min to a vigorously agitated solution of 0.11 mol of *t*-$BuC{\equiv}CLi$ (p. 24) in 80 ml of THF and 77 ml of hexane, maintained between -10 and 0°C. A thick white suspension is formed. After stirring without external cooling for an additional 5 min (when the yellow colour has disappeared completely) the mixture is treated with dilute HCl as described in the previous experiments. Isolation of the product, a light-brown syrup, is also carried out as described in these experiments. The product is dissolved in 50 ml of Et_2O (reflux), after which 100 ml of pentane is added. After cooling to below -30°C white crystals separate from the solution. Suction filtration followed by rinsing with cold pentane and drying of the crystals *in vacuo* gives the pure sulfinamide in 92% yield. The m.p. is 68-69°C.

4.13 *ortho*-Ethynylbenzaldehyde from Dimetallated Phenylacetylene and DMF



Scale: 0.10 molar ($PhC{\equiv}CH$).

Apparatus: fig. 1, 1 l.

Introduction (compare ref. 1)

In the introduction of exp. 3 it is mentioned that lithiated acetylenes react very slowly at -70°C with dimethylformamide. However, lithiated *benzene* derivatives in most cases add very quickly to DMF at these low temperatures. This difference in basicity may explain the specific reaction of the *ortho*-aryl negative center in dilithiated phenylacetylene with dimethylformamide.

Procedure

THF (100 ml) is added to a solution of 0.22 mol of butyllithium in 150 ml of hexane, cooled to -50°C. Phenylacetylene (0.10 mol, p. 168) is added over 10 min to the solution, while keeping the temperature below -20°C. The solution is then cooled to -65°C and a solution of 0.12 mol of potassium *tert*-butoxide in 100 ml of THF is added dropwise over 30 min while maintaining the temperature of the red suspension between -60 and -65°C. After completion of the addition, the cooling bath is removed and the temperature is allowed to rise to 0°C. A solution of 0.13 mol of anhydrous lithium bromide (note 1) in 40 ml of THF is then added over a few seconds with vigorous stirring. The colour changes to pink. The mixture is cooled to -90°C and dimethylformamide (0.15 mol) is added over 5 min. The mixture is stirred for an additional 10 min at -65°C, after which the light-yellow to nearly white suspension is cautiously poured into a vigorously stirred mixture of 1 l of ice water and 40 ml of 36% aqueous HCl. After standing for 15 min, the layers are separated and four extractions with pentane are carried out. The combined organic solutions are washed with a saturated solution of NH_4Cl and subsequently dried over $MgSO_4$. The light yellow liquid remaining after removal of the solvent under reduced pressure is distilled through a 20-cm Vigreux column at oil-pump pressure (1 mmHg or less). The use of an air condenser is recommended. The solid distillate is crystallized from a 4:1 mixture of pentane and Et_2O to give *o*-ethynyl benzaldehyde, m.p. 67°C, in ~55% yield.

Notes

1. The commercial anhydrous salt (0.15 mol) is heated during 30 min in a 250-ml round-bottomed flask, evacuated at < 15 mmHg. After cooling to room temperature dry N_2 is admitted and the salt is dissolved in the THF.

Chapter VI
Silylation*, Stannylation, and Phosphorylation

1. Introduction

Silylated acetylenes are useful synthetic intermediates. Numerous examples are mentioned in the reviews [28,101]. One can subdivide the applications into three groups. In the first one, the silyl function merely serves as a protector which is removed in the last step of the synthesis. An example is the silylation of a diyne RC≡CC≡CH to give RC≡CC≡CSiMe$_3$ [226], which by partial reduction with Pd/H$_2$ or activated zinc in ethanol, gives *Z*-RCH=CHC≡CSiMe$_3$. Treatment of this enyne with $^-$OH in methanol or silver nitrate and cyanide finally gives *Z*-RCH=CHC≡CH. Another type of application concerns reactions in which the silyl group is substituted by another functionality, *e.g.* RC(=O) or halogen. These transformations are often catalysed by Lewis acids [101]. In the third category can be placed conversions in which the acetylenic function itself undergoes a transformation. The function of the silyl group may be either an active one, in that the regiochemistry of the process is influenced, or rather that of a companion which can fulfill its useful task after the crucial operation has been carried out .

Stannylated and phosphorylated acetylenes have, so far, found relatively few applications as synthetic intermediates. One serious disadvantage of many organotin compounds is their low volatility and poor propensity to crystallize. This makes them less attractive for working on a somewhat larger scale.

2. Reaction Conditions for Silylation, Stannylation and Phosphorylation

An excellent review by Cadiot and Chodkiewicz has appeared in the book "Chemistry of Acetylenes" [6]. The introduction of the heteroatom may be represented by the following, general scheme:

$$(m\text{-}n)\ RC{\equiv}CM + R'_nYX_{m-n} \longrightarrow (RC{\equiv}C)_{m-n}YR'_n + (m\text{-}n)XM$$

Y = Si, Sn or P; m = 4 or 3 (valency of Y); X is usually Cl.

The reactions, usually carried out in organic solvents, proceed under mild conditions and often give high yields of the desired compounds. Compounds in which the hetero-atom bears one alkynyl group are better known than the "poly"-alkynyl derivatives. This can be explained in part by the readier availability of the mono-halogeno compounds R'$_n$YX and by a lower

*Carefulness sometimes can be irrelevant: a large number of (organic) chemists store trimethylchlorosilane in the refrigerator!

stability of the "poly"-alkynyl compounds: triethynylphosphine, for example, decomposes explosively upon heating.

3. The Choice of Reaction Conditions for Silylations

Silylation of a metallated organic compound is a reaction that is familiar to modern synthetic organic chemists since it is often used to determine the efficiency (yield) of a preceding metallation. In this quenching procedure, a relatively large excess of the silylating agent is used to ensure complete silylation. It might therefore be tempting to also use an excess of Me_3SiCl in a preparative procedure. One should realize, however, that this will give rise to the formation of $Me_3SiOSiMe_3$ during the aqueous work-up. This compound has a b.p. in the region of 100°C, and its presence may cause serious difficulties in the purification of silylated derivatives with a comparable volatility. Such a consideration may result in the use of a short measure of silylating agent. If the starting acetylenic compound has a high molecular weight, the increase in boiling point upon silylation will be relatively small. In such cases one should consider the use of an excess of metallating agent and a corresponding excess of silyl halide. Treatment of some acetylenic compounds RC≡CH with an excess of a strongly basic reagent, however, may give rise to subsequent reactions such as dimetallation and dimerization or oligomerization. The best solution then is to carry out the metallation of RC≡CH with C_2H_5MgBr, which is a weak base in a kinetic sense. Although THF is the best solvent for metallation and silylation, Et_2O may be preferred when the silyl derivative to be prepared is rather volatile, *e.g.* when the b.p. at atmospheric pressure is lower than 150°C. The only way to remove the THF without significant loss of product is to distill it off at atmospheric pressure; this is only allowed if the product is sufficiently stable. For similar reasons one may decide to use a solution of EtLi.LiBr in Et_2O (made from C_2H_5Br and Li) instead of the commercially available solution of butyllithium in (the less volatile) hexane.

The experimental part of this chapter contains a few procedures with typical combinations of reaction conditions which should enable the user of this book to derive the experimental parameters for a particular conversion. Of course, the remarks mentioned above are also valid for some other functionalizations, *e.g.* stannylation.

4. Experiments

4.1 Ethynyl Trimethylsilane

$$HC{\equiv}CH + C_2H_5MgBr \xrightarrow[20\text{-}25^\circ C]{THF} HC{\equiv}CMgBr + C_2H_6\uparrow$$

$$HC{\equiv}CMgBr + Me_3SiCl \xrightarrow[-10\rightarrow 20^\circ C]{THF} HC{\equiv}CSiMe_3 + BrMgCl.THF\downarrow$$

Scale: 4.0 molar (Me_3SiCl), (note 1).

Apparatus: fig. 1, 10 l; cooling vessel: fig. 10; stirrer: fig. 3.

Introduction

Although the procedure for this extremely useful compound (see Chap. X) can also be carried out with smaller amounts, we prefer to do it on a large scale, mainly for reasons of efficiency. The whole preparation will take at least three days, even for an experienced experimentalist: the first day is necessary for the preparation of the solution of ethylmagnesium bromide, the second day for making ethynylmagnesium bromide and for its reaction with trimethylchlorosilane (this reagent is added late in the day), and the third (long) day is to be spent for the work-up and isolation. The effort for making, for example, 1 mole is only slightly less (note 2).

The heating effect of the trimethylsilylation is not very strong, yet it is essential to keep the temperature below 25°C in view of the chance of disproportionation of HC≡CMgBr into acetylene and BrMgC≡CMgBr. The manner of working-up is rather peculiar: water (containing ammonium chloride) is used as extraction solvent for the removal of the undesired organic component THF! One might experience this extraction as a boring operation (taking ~1.5 h) but one should keep in mind that it saves about 24 h of time which otherwise would be necessary to separate the 4 liters of THF, b.p. 66°C, from only some 350 g of $Me_3SiC{\equiv}CH$ (b.p. 53°C) by fractional distillation. It will be clear that a large (10 l) separating funnel is required, at least for the first five extractions. In order to limit the losses due to evaporation, a cold (0°C) solution of NH_4Cl should be used. For the same reason it is advisable to continue with a smaller separating funnel after some 5 extractions have been carried out and the volume has decreased considerably. After some 10 extractions the amount of THF which is still present in the organic layer, is about 10%. Further extraction is then not very effective. Pure $Me_3SiC{\equiv}CH$ can be obtained by careful fractional distillation of this layer through a 50 to 60-cm Widmer column (taking ~5 h!). Persons with a practical mind might consider carrying out a quick distillation (to separate $Me_3SiC{\equiv}CH$ + THF from possible higher-boiling products) and use this mixture of $Me_3SiC{\equiv}CH$ and (5-15%) THF for their syntheses.

Procedure

A suspension of ethynylmagnesium bromide in about 4 l of THF is prepared as described in Organic Syntheses [35], starting from 4.6 mol of ethyl bromide and 5.5 mol of magnesium (note 3). Trimethylchlorosilane (4.0 mol, carefully distilled, note 4) is added with efficient stirring over 45 min, while keeping the temperature between 5 and 10°C (a bath with dry ice and acetone is indispensable). The heating effect is easily observable, but, taking into account the large scale, rather modest, so that the reaction can be easily kept under control. Ten minutes after completion of the addition, the cooling bath is removed and the temperature is allowed to rise to 15-20°C. If the temperature rises too fast, temporary strong cooling should

be applied. When in the range of 15-20°C, no further significant evolution of heat is observed, stirring is stopped and the thick suspension is allowed to stand at room temperature overnight. A cold (-5°C) solution of 300 g of ammonium chloride in 2 l of water is then poured onto the thick mass (note 5) which gradually dissolves. Dissolution is completed by vigorous stirring during 1-2 min. The layers are then transferred into the separating funnel, the flask being rinsed with a small amount of THF. The layers are separated as sharply as possible, the aqueous layer being discarded. The THF-layer is first extracted five times with 1-l portions of an aqueous NH_4Cl solution (4 mol/l) cooled to -5°C (note 6) and subsequently ten times with cold 2 N HCl, containing NH_4Cl, 2 mol/l (portions of 300 to 500 ml). The remaining organic layer is dried over $MgSO_4$ (note 7), carefully decanted from the drying agent and then slowly distilled through a 50 to 60-cm Widmer column (or other efficient column). Pure $Me_3SiC{\equiv}CH$, b.p. 53°C/760 mmHg, $n_D(20°)$ 1.3912, is obtained in at least 80% yield.

Notes

1. This procedure is a good excercise in *planning*: insufficient planning may give rise to undesired delay during the various operations, which may be a major cause of decreased yields. To give only one example: one should control the pressure of the acetylene cylinder in advance. At least 100 liters of this gas are needed, and if the manometer on a 10 or 20-l cylinder indicates a pressure of only a few atmospheres, one is likely to be confronted with the extremely unpleasant fact that the acetone in the cylinder wants to keep the acetylene for itself! (If you are lucky, there is another acetylene cylinder in the lab!)
2. An additional advantage of preparing a large amount is that you are in a position to oblige colleagues in your research group who may occasionally need a sample. They will undoubtedly be grateful, especially when you show them the catalogue price for $Me_3SiC{\equiv}CH$!
3. The "yield" of C_2H_5MgBr may be ~95%, if the Grignard preparation is carried out carefully. There should be, in any case, a small excess of $HC{\equiv}CMgBr$ to guarantee that all Me_3SiCl has reacted: reaction with water during the work-up would give volatile $Me_3SiOSiMe_3$. The use of an excess of magnesium is prescribed to ensure the complete conversion of C_2H_5Br (b.p. 38°C, this is only 15°C lower than the b.p. of $Me_3SiC{\equiv}CH$!).
4. The undistilled compound may contain hydrogen chloride and $Me_3SiOSiMe_3$.
5. The salt MgBrCl forms a rather strong complex with THF. The additional enthalpy due to complexation with water is not large. If Et_2O had been the solvent, this way of carrying out the hydrolysis would probably have resulted in the loss of all product!
6. It is advisable to take a smaller separating funnel as soon as the volume of the layers permits: one should realize that several grams of product may get lost, when a large volume of air becomes saturated (after shaking) with the vapour of this volatile compound. These losses will become more serious as the concentration of $Me_3SiC{\equiv}CH$ in the organic layer increases.
7. Shaking with a few grams of $MgSO_4$ is sufficient to effect disappearance of the turbidity. The best way to remove dissolved water, however, is to cool the liquid below -60°C. The water crystallizes out and the ice collects on the bottom. The cold, supernatant liquid is then decanted. The remaining ice suspension is immediately shaken with a very small amount of $MgSO_4$, just sufficient to absorb the ice.

4.2 Bis(trimethylsilyl)acetylene

$$BrMgC{\equiv}CMgBr + 2\ Me_3SiCl \xrightarrow[50\text{-}60°C]{THF} Me_3SiC{\equiv}CSiMe_3 + 2\ MgBrCl.THF\downarrow$$

Scale: 1.0 molar (Me_3SiCl).

Apparatus: fig. 1, 2 l; at a later stage the thermometer is replaced with a reflux condenser.

Introduction

The trimethylsilylation of the di-Grignard derivative of acetylene has to be carried out at temperatures that are considerably higher than those necessary for the silylation of ethynyl mono-magnesium bromide. This decreased reactivity may be ascribed to the slight solubility of the intermediate.

Procedure

Trimethylchlorosilane (1.0 mol, freshly distilled, see exp. 1, note 4) is added dropwise over 20 min to a suspension of 0.5 mol of acetylene dimagnesium bromide in ~1200 ml of THF (p. 28), which is kept between 50 and 55°C by occasional cooling or heating. The suspension disappears gradually. After completion of the addition, the thermometer-outlet combination is replaced with a reflux condenser and the mixture is heated to 60-65°C for an additional period of 2 h. The mixture is then cooled to *ca.* 30°C and subsequently poured into a solution of 100 g of NH_4Cl in 1 l of water. After vigorous shaking, the aqueous layer is extracted twice with 150-ml portions of pentane. The combined organic solutions are washed ten times with 150 ml portions of a saturated aqueous solution of NH_4Cl in order to remove as much of the THF as possible. The organic layer is then dried over $MgSO_4$. Distillation through a 40-cm Vigreux column at 760 mmHg gives $Me_3SiC{\equiv}CSiMe_3$ in greater than 80% yield. The product distills between 128 and 138°C and solidifies upon standing.

4.3 Bis(trimethylsilyl)butadiyne

$$HC{\equiv}CC{\equiv}CH + 2\ BuLi \xrightarrow[-40°C]{Et_2O\text{-hexane}} LiC{\equiv}CC{\equiv}CLi\downarrow + 2\ C_4H_{10}$$

$$LiC{\equiv}CC{\equiv}CLi + 2\,Me_3SiCl \xrightarrow[-10 \rightarrow 20^\circ C]{} Me_3SiC{\equiv}CC{\equiv}CSiMe_3 + 2\,LiCl\downarrow$$

Scale: 0.10 molar ($LiC{\equiv}CC{\equiv}CLi$).

Apparatus: fig. 1, 1 l.

Procedure

Freshly distilled trimethylchlorosilane (0.22 mol, see exp. 1, note 4) is added dropwise over 20 min to a suspension of 0.10 mol of dilithium diacetylide in 200 ml of Et_2O and 140 ml of hexane (see p. 27). During this addition the temperature is kept between -10 and -20°C. After an additional 15 min the cooling bath is removed and the temperature is allowed to rise to 20°C. Stirring is then continued for an additional half hour, after which the suspension is poured into 200 ml of ice water. After vigorous shaking, the layers are separated and the aqueous layer is extracted once with Et_2O. The light-brown to white cyrstalline mass remaining after careful removal of the solvent and volatile products is almost pure $Me_3SiC{\equiv}CC{\equiv}CSiMe_3$. The yield is essentially quantitative.

4.4 Mono(trimethylsilyl)butadiyne

$$HC{\equiv}CC{\equiv}CH + EtLi \xrightarrow[< -40^\circ C]{Et_2O} LiC{\equiv}CC{\equiv}CH + C_2H_6$$

$$LiC{\equiv}CC{\equiv}CH + Me_3SiCl \xrightarrow[-30 \rightarrow 20^\circ C]{} Me_3SiC{\equiv}CC{\equiv}CH + LiCl\downarrow$$

Scale: 0.30 molar (EtLi).

Apparatus: fig. 1, 1 l.

Introduction (see also Section 3)

Although it is much more convenient to use a commercially available hexane solution of butyllithium in the preparation of $Me_3SiC{\equiv}CC{\equiv}CH$, we prefer to carry out the mono-metallation of diacetylene with a solution of $C_2H_5Li.LiBr$ in Et_2O. In view of the limited thermal stability of mono-substituted 1,3-diynes, the distillative separation of the product and the solvent has to be carried out under mild conditions, applying a partial vacuum and avoiding strong heating.

A serious side reaction is the formation of the bis-silylated diyne, which may result from trans-metallation of the primary product by $LiC{\equiv}CC{\equiv}CH$ and subsequent silylation. This reaction can be suppressed to some extent by using a 100% excess of diacetylene.

Procedure

A solution of 0.30 mol of ethyllithium in *ca.* 300 ml of Et_2O (see ref. 1) is added over 15 min to a solution of 0.60 mol of diacetylene in 75 ml of Et_2O (freshly prepared from 1,4-dichlorobutyne, see p. 000; storage at -80°C for a few days is feasible). During this addition the temperature is kept below -40°C. Subsequently 0.30 mol of freshly distilled (see exp. 1, note 4) trimethylchlorosilane is added in one portion. The temperature is allowed to rise to -20°C and is maintained there for 30 min. A white suspension is gradually formed. The cooling bath is then removed and the temperature allowed to rise to 20°C. After an additional 30 min (at 20°C) the suspension is poured into 300 ml of ice water. After vigorous shaking and extracting the aqueous layer twice with small portions of Et_2O, the combined solutions are dried over $MgSO_4$. The greater part of the Et_2O is then distilled off at normal pressure (in the beginning N_2 is introduced at a rate of ~500 ml/min, because some butadiyne vapour may pass over) through a 40-cm Vigreux column keeping the bath temperature below 90°C. After cooling to room temperature, the remaining liquid is distilled *in vacuo* using a single receiver cooled in a bath with ice and ice water. The mono-silylated diacetylene, b.p. ~28°C/20 mmHg, $n_D(20°)$ 1.4664, is obtained in 62-68% yield. The residue (*ca.* 9 gram) is almost pure $Me_3SiC{\equiv}CC{\equiv}CSiMe_3$.

4.5 Ethynyl Tributyltin

$$HC{\equiv}CMgBr + Bu_3SnCl \xrightarrow[5 \rightarrow 25^\circ C]{THF} HC{\equiv}CSnBu_3 + BrMgCl.THF\downarrow$$

Scale: 0.20 molar (Bu_3SnCl).

Apparatus: fig. 1, 1 l.

Procedure (see also Section 3)

A solution of 0.30 mol of ethynylmagnesium bromide in 350 ml of THF (p. 27) is cooled to 5-10°C. A vigorous stream (1.5 - 2 l/min) of acetylene is introduced for 3 min, while keeping the temperature between 5 and 10°C. Subsequently, 0.20 mol of tributyltin chloride is added over a few min. After an additional 30 min, the cooling bath is removed and the temperature allowed to rise. Stirring at ~25°C is continued for another 1 h, then the suspension (or solution) is cautiously poured into a solution of 30 g of NH_4Cl in 250 ml of water. After vigorous shaking, the layers are separated and the aqueous layer is extracted twice with small portions of Et_2O. The combined organic solutions are dried over $MgSO_4$ and then concentrated *in vacuo*. Distillation of the remaining liquid through a very short Vigreux column gives ethynyl tributyltin, b.p. ~90°C/0.1 mmHg, $n_D(20°)$ 1.4767, in ~80% yield. There is a small residue of $Bu_3SnC{\equiv}CSnBu_3$.

4.6 Butadiynyl Tributyltin

$$HC{\equiv}CC{\equiv}CLi + Bu_3SnCl \xrightarrow[-40\rightarrow0^\circ C]{THF} HC{\equiv}CC{\equiv}CSnBu_3 + LiCl\downarrow$$

Scale: 0.10 molar (Bu_3SnCl).

Apparatus: fig. 1, 1 l.

Introduction (see also Section 3)

In some derivatization reactions with mono-metallated butadiyne, considerable amounts of disubstituted diacetylene are formed. Their presence can hamper the purification of the desired mono-substitution products, particularly when the boiling point is high and the thermal stability limited. The formation of disubstitution products can be effectively suppressed, however, by using a large excess of butadiyne. The preparation of butadiynyl tributyltin is an illustrative example.

Procedure

A solution of 0.13 mol of BuLi in 90 ml of hexane is added dropwise over 20 min to a mixture of 0.25 mol of diacetylene (freshly prepared or stored as a THF solution at -80°C, see p. 84) and 100 ml of THF. During this addition the temperature is kept below -40°C. Tributyltin chloride (0.10 mol) is then added at -30°C over 10 min, after which the cooling bath is removed. The mixture is stirred for an additional 1 h at 0°C, then the mixture is poured into a solution of 25 g of NH_4Cl in 200 ml of water. After separation of the layers, one extraction with pentane is carried out. The organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. The last traces of volatile components are removed in a vacuum of 0.5 mmHg or less. The residue is the product, $Bu_3SnC{\equiv}CC{\equiv}CH$ (yield ~100%), which is indicated as being pure by ^1H NMR. Distillation is not carried out.

4.7 1-(Trimethylsilyl)propyne

$$CH_3C{\equiv}CH + C_2H_5Li \xrightarrow[-50^\circ C]{Et_2O} CH_3C{\equiv}CLi\downarrow + C_2H_6\uparrow$$

$$CH_3C{\equiv}CLi\downarrow + Me_3SiCl \xrightarrow[reflux]{Et_2O} CH_3C{\equiv}CSiMe_3 + LiCl\downarrow$$

Scale: 1.0 molar.

Apparatus: 2-l three-necked flask (fig. 1); after the addition of Me_3SiCl the thermometer is replaced with a reflux condenser.

Introduction

It will be immediately clear from the boiling point of trimethylsilylpropyne (96°C at atmospheric pressure) that the use of a hexane solution of BuLi for the lithiation of propyne is not advisable. The best way is to metallate propyne with a solution of ethyllithium in Et_2O, prepared from C_2H_5Br and lithium. *Butyl*lithium in Et_2O would be less suitable, because of the formation of small amounts of octane (b.p. 128°C) during its preparation (Würtz-coupling).

Procedure (see also Section 3)

A cold (< -30°C) mixture of 1.2 mol of propyne (compare Chap. IX, exp.1) and 100 ml of dry Et_2O is added over 10 min to a solution of 1.0 mol of ethyllithium in ~900 ml of Et_2O [1]. A cooling bath with liquid N_2 is used to keep the temperature below -40°C and to allow rapid addition. Freshly distilled trimethylchlorosilane (0.9 mol, note 4 of exp. 1) is then added in one portion to the white suspension and the cooling bath is removed. The thermometer is replaced with a reflux condenser. The suspension is first stirred at room temperature for 1 h (a bath with ice water should be kept in readiness for occasional cooling) and subsequently for 4 h under reflux. After cooling to ~0°C the mixture is cautiously poured into 200 ml of water with occasional swirling. After separating the layers and extracting the aqueous layer twice with small portions of Et_2O, the combined solutions are washed with a saturated solution of NH_4Cl and subsequently dried over $MgSO_4$. Careful distillation through a 40-cm (or longer) Widmer column gives the desired product, b.p. 96°C/760 mmHg, $n_D(20^\circ)$ 1.4163, in > 80% yield.

4.8 Trimethylsilylation of Propargyl Chloride

$$LiC{\equiv}CCH_2Cl + Me_3SiCl \xrightarrow[-60\rightarrow0^\circ C]{Et_2O\text{-}HMPT} Me_3SiC{\equiv}CCH_2Cl + LiCl\downarrow$$

Scale: 0.45 molar.

Apparatus: fig. 1, 1 l.

Introduction

In view of the limited stability of the "carbenoid" $LiC{\equiv}CCH_2Cl$, functionalization reactions have to be carried out at temperatures that are as low as possible. Silylations of metallated acetylenes are usually rather slow in Et_2O at temperatures below -20°C. A small amount of HMPT appears to cause a considerable enhancement of the rates of silylation with trimethylchlorosilane. It is not known whether this effect is only due to the typical properties of HMPT as a dipolar aprotic solvent (also shown in alkylation with alkyl halides) or whether it is a result of active participation of this solvent in the reaction as depicted in the following equations:

$$[(CH_3)_2N]_3P{=}O + Me_3SiCl \longrightarrow [(CH_3)_2N]_3\,P^+\text{-}OSiMe_3\ Cl^-$$

$$[(CH_3)_2N]_3P^+\text{-}OSiMe_3\ Cl^- + LiC{\equiv}CR \longrightarrow HMPT + LiCl + Me_3SiC{\equiv}CR$$

Procedure (see also Section 3)

Freshly distilled trimethylchlorosilane (0.45 mol, see exp. 1, note 4) is added over a few min to a solution of 0.50 mol of lithiated propargyl chloride (p. 25) with cooling between -75 and -85°C. A mixture of 35 ml of dry HMPT (see ref. 1, Chap. I) and 20 ml of Et_2O is then added dropwise over 10 min with vigorous stirring and cooling between -70 and -80°C. The temperature is then allowed to rise over 1 h to +10°C (occasionally removing the cooling bath). A white suspension is gradually formed. The reaction mixture is worked up by pouring it into 200 ml of ice water and extracting the aqueous layer twice with Et_2O. The combined solutions are washed four times with water (to remove some HMPT), subsequently dried over $MgSO_4$ and finally concentrated by distilling off most of the solvent at atmospheric pressure through a 40-cm Vigreux column (bath temperature ≤ 110°C). After cooling to room temperature, the remaining liquid is carefully distilled at reduced pressure to give the silylated propargyl chloride, b.p. 45°C/15 mmHg, $n_D(20°)$ 1.4546, in 85% yield.

4.9 Trimethylsilylation of Propargyl Bromide

$$LiC{\equiv}CCH_2Br + Me_3SiCl \xrightarrow[-85 \rightarrow 10°C]{Et_2O\text{-}HMPT} Me_3SiC{\equiv}CCH_2Br + LiCl\downarrow$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Procedure (for Introduction see exp. 8)

Freshly distilled trimethylchlorosilane (0.40 mol, excess, see exp. 1, note 4) is added over 5 min to a solution of 0.20 mol of lithiated propargyl bromide in 200 ml of Et_2O and 140 ml of hexane (p. 26) cooled to between -80 and -90°C. Subsequently a mixture of 30 ml of dry HMPT (ref. 1, Chap. I and note 1) and 30 ml of Et_2O is added dropwise with vigorous stirring while carefully keeping the temperature within this range. After this addition the cooling bath is occasionally removed and the temperature is allowed to rise gradually over 30 min to -40°C, and subsequently to 10°C. The white suspension is then poured into 500 ml of 2N aqueous HCl and the product is isolated as described in exp. 8 (the solvent and volatile components are removed under reduced pressure). Careful distillation through a 40-cm Vigreux column gives the desired compound, b.p. 58°C/15 mmHg, $n_D(18°)$ 1.4778, in ~80% yield. If no HMPT is used, the product is obtained in a moderate yield.

Notes

1. DMSO can be used instead of HMPT.

4.10 Trimethylsilylation of Vinylacetylene

$$H_2C{=}CHC{\equiv}CLi + Me_3SiCl \xrightarrow{Et_2O} H_2C{=}CHC{\equiv}CSiMe_3 + LiCl\downarrow$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Procedure (for Introduction see Section 3, compare also exp.4)

Trimethylchlorosilane (0.10 mol, freshly distilled, see exp. 1, note 4) is added over 15 min to a solution of $H_2C{=}CHC{\equiv}CLi$ in *ca.* 130 ml of Et_2O (prepared by adding 0.11 mol of EtLi.LiBr in Et_2O at <-50°C to a mixture of 0.13 mol of vinylacetylene and Et_2O), cooled to between -20 and -30°C. After this addition, the cooling bath is removed and stirring at 10-20°C is continued for an additional 1 h. The white suspension is then poured into 200 ml of ice water and the product is isolated as described in exp. 4. $H_2C{=}CHC{\equiv}CSiMe_3$, b.p. *ca.* 40°C/25 mmHg, $n_D(20°)$ 1.4492, is obtained in ~90% yield.

4.11 Trimethylsilylation of 1-Bromo-5-hexyne

$$HC{\equiv}C(CH_2)_4Br + BuLi \xrightarrow[-60°C]{THF\text{-}hexane} LiC{\equiv}C(CH_2)_4\,Br + C_4H_{10}$$

$$LiC{\equiv}C(CH_2)_4Br + Me_3SiCl \longrightarrow Me_3SiC{\equiv}C(CH_2)_4Br + LiCl\downarrow$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Procedure (for Introduction see Section 3)

Trimethylchlorosilane (0.13 mol) is added over a few min to a solution of 0.10 mol of lithiated bromohexyne (p. 26) cooled to -40°C. The cooling bath is removed allowing for a fast temperature rise. After 20 min at +10°C, 200 ml of ice water is added to the vigorously stirred suspension. The product, b.p. 100°C/10 mmHg, $n_D(21°)$ 1.4748, is obtained in almost 100% yield (for the work-up and isolation see exp. 9).

$PhC{\equiv}CSiMe_3$, b.p. 90°C/10 mmHg, $n_D(18°)$ 1.5277, is obtained in almost 100% yield by a similar procedure.

$Me_3SiC{\equiv}COC_2H_5$, b.p. 37°C/10 mmHg, $n_D(20°)$ 1.4255, is obtained in 78% yield from $LiC{\equiv}COC_2H_5$ and a 10% (molar) short measure of Me_3SiCl. The aqueous work-up is

carried out with a solution of NH_4Cl in H_2O to which 10 ml of a concentrated aqueous solution of NH_3 has been added.

4.12 Trimethylsilylation of 1,3-Decadiyne

$$HC{\equiv}CC{\equiv}CC_6H_{13} + C_2H_5MgBr \xrightarrow[-10 \rightarrow +10^\circ C]{THF} BrMgC{\equiv}CC{\equiv}CC_6H_{13} + C_2H_6\uparrow$$

$$BrMgC{\equiv}CC{\equiv}CC_6H_{13} + Me_3SiCl \xrightarrow[-10 \rightarrow +20^\circ C]{} Me_3SiC{\equiv}CC{\equiv}CC_6H_{13} + BrMgCl.THF\downarrow$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Procedure (for Introduction see Section 3)

1,3-Decadiyne (0.10 mol, see p. 60) is added in one portion to a solution (partly suspension) of 0.13 mol of ethylmagnesium bromide in *ca.* 120 ml of THF, cooled to -20°C. The cooling bath is removed and the temperature allowed to rise to 10°C. After an additional 45 min at 10°C, the solution is again cooled to -20°C and 0.15 mol of Me_3SiCl (freshly distilled, see exp. 1, note 4) is added in one portion. The cooling bath is removed and the temperature allowed to rise to 20°C. After 30 min at about 20°C, a solution of 20 g of NH_4Cl in 100 ml of water is added to the thick suspension. The organic layer and one ethereal extract are dried over $MgSO_4$ and subsequently concentrated under reduced pressure. Distillation of the remaining liquid through a 20-cm Vigreux column gives the silylated diyne (b.p. ~70°C/0.2 mmHg), $n_D(18^\circ)$ 1.4867, in almost quantitative yield.

4.13 Ortho-(trimethylsilyl)phenylacetylene

$$PhC{\equiv}CH + 2\,BuLi + 2\,t\text{-}BuOK \xrightarrow[-70^\circ C]{THF\text{-}hexane} o\text{-}C_6H_4(C{\equiv}CK)K + 2\,t\text{-}BuOLi$$

$$o\text{-}K\text{-}C_6H_4C{\equiv}CK + 2\,Me_3SiCl \xrightarrow[-40 \rightarrow 20^\circ C]{} o\text{-}C_6H_4(SiMe_3)C{\equiv}CSiMe_3 + 2\,KCl\downarrow$$

$$o\text{-}C_6H_4(SiMe_3)C{\equiv}CSiMe_3 \xrightarrow{KOH,\ CH_3OH} o\text{-}C_6H_4(SiMe_3)C{\equiv}CH$$

Scale: 0.10 molar (PhC≡CH).

Apparatus: fig. 1, 1 l.

Introduction

Metallated phenylacetylene is readily potassiated in the *ortho*-position of the benzene ring using the super base BuLi.*t*-BuOK [1,44,52,53]. One would expect, in analogy with the regiospecific fuctionalizations of "di-anions" of 1,3-diketones, that the negative center in the benzene ring (which is generated under more strongly basic conditions) would be much more reactive than the acetylide. It appears, however, that the reaction with *one* equivalent of Me_3SiCl is completely unselective. The desired *o*-trimethylsilyl-phenylacetylene can be prepared in excellent yields by first silylating both "negative" centers and subsequently heating the bis-silyl derivative with potassium hydroxide in methanol. Under these conditions the silyl group on the benzene ring is not removed.

Procedure

Phenylacetylene (0.10 mol, see Chap. IX) is added to a solution of 0.22 mol of BuLi in 154 ml of hexane and 100 ml of THF, kept between -80 and -90°C. Subsequently, a solution of 0.22 mol of *t*-BuOK in 50 ml of THF is added dropwise over 30 min with cooling between -70 and -75°C. A red suspension is formed. After an additional 1 h at -70°C, 0.22 mol of Me_3SiCl is added with vigorous stirring. The cooling bath is removed and the temperature allowed to rise to 20°C. Water (200 ml) is then added and, after separation of the layers, two extractions with Et_2O are carried out. The combined organic solutions are concentrated *in vacuo* (drying is not necessary). The remaining liquid is heated for 30 min at 50°C with a solution of 10 g of KOH in 50 ml of methanol. Most of the methanol is then distilled off using a rotary evaporator. After addition of 150 ml of water to the remaining viscous liquid, three extractions with Et_2O are carried out. The combined extracts are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Distillation of the remaining liquid through a 20-cm Vigreux column gives *o*-(trimethylsilyl)phenylacetylene, b.p. 85°C/10 mmHg, $n_D(20^\circ)$ 1.5279, in ~90% yield.

4.14 Dibutyl Ethynylphosphine

$$(C_4H_9)_2PCl + HC{\equiv}CMgBr \xrightarrow{THF} (C_4H_9)_2PC{\equiv}CH + BrMgCl\downarrow$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Procedure (note 1)

In a solution of ~0.3 mol of ethynylmagnesium bromide in ~400 ml of THF [p. 27] with cooling at -15°C acetylene is introduced (100 ml/min) for 15 min. Chlorodibutylphosphine (0.20 mol, see [102,238]) is added over 15 min to this suspension, now cooled between -20 and -30°C. After this addition, the cooling bath is removed and the temperature allowed to rise to +10°C. A solution of 20 g of NH_4Cl in 200 ml of water is then added over a few min with

vigorous stirring. After separation of the layers and extraction of the aqueous layer with Et_2O, the extracts are dried over $MgSO_4$ (note 2) and subsequently concentrated under reduced pressure. Distillation through a 30-cm Vigreux column gives the ethynylphosphine, b.p. 85°C/10 mmHg, $n_D(20°)$ 1.4765, in 75% yield (note 3). Crystallization of the solid residue from Et_2O gives a small amount of $Bu_2PC{\equiv}CPBu_2$, m.p. 32-33°C.

Notes

1. In view of the oxygen-sensitivity of phosphines all operations must be carried out in a nitrogen atmosphere.
2. The amount of $MgSO_4$ should be as small as possible. Instead of being filtered, the organic solution is carefully decanted from the drying agent, which is rinsed a few times with Et_2O.
3. After termination of the distillation *nitrogen* must be admitted!

4.15 Diethynyl Phenylphosphine

$$2\ HC{\equiv}CMgBr + PhPCl_2 \xrightarrow[-20 \rightarrow 0°C]{THF} (HC{\equiv}C)_2PPh + 2\ BrMgCl{\downarrow}$$

Scale: 0.10 molar ($PhPCl_2$).

Apparatus: fig. 1, 1 l.

Procedure (see exp. 14, note 1!)
Acetylene (1 l/min) is introduced for 5 min in a suspension of 0.25 mol of ethynylmagnesium bromide in 350 ml of THF (p. 27) cooled to between -20 and -30°C. Subsequently dichlorophenylphosphine (0.10 mol, commercially available) is added dropwise over 15 min while keeping the temperature between -10 and -20°C. After an additional 30 min the cooling bath is removed and the temperature allowed to rise to 0°C. The suspension is then treated with a solution of NH_4Cl in water as described in exp. 14. The work-up is also carried out in a similar way. Distillation of the remaining brown liquid through a very short and wide column (preferably B-29 glass joints) in a high-vacuum (mercury-diffusion pump, pressure 0.01 mmHg or lower) gives the acetylenic phosphine, b.p. ~50-60°C/0.01 mmHg, $n_D(20°)$ 1.5941, in 52% yield. The temperature of the heating bath should not exceed 80°C since the residue may decompose vigorously upon excessive heating.

4.16 Tri(1-propynyl)phosphine

$$3\ CH_3C{\equiv}CMgBr + PCl_3 \xrightarrow[-90 \rightarrow 0°C]{THF} (CH_3C{\equiv}C)_3P + 3\ BrMgCl{\downarrow}$$

Scale: 0.10 molar (PCl_3).

Apparatus: fig. 1, 1 l.

Procedure (compare [103]; note 1)
A solution of 0.45 mol of propynylmagnesium bromide in 350 ml of THF (p. 29) is added dropwise over 30 min to a mixture of 0.10 mol of freshly distilled PCl_3 and 100 ml of THF. Occasional cooling in a bath with liquid N_2 is applied to keep the temperature between -70 and -90°C. After the addition has been completed, the temperature of the reaction mixture is allowed to rise gradually over 3-4 h to 0°C. Stirring at 0°C is continued for another 1 h. The brown suspension is then poured into a concentrated aqueous solution of NH_4Cl. After vigorous shaking and separation of the layers, the aqueous layer is extracted with Et_2O. The organic solution is dried over $MgSO_4$ and subsequently concentrated under reduced pressure, giving reasonably pure (~94%) tripropynylphosphine. Recrystallization from Et_2O gives pure tripropynylphosphine in ~80% yield, m.p. 95-96°C.

Notes

1. All operations must be carried out under nitrogen.

4.17 Reaction of Allenylmagnesium Bromide with Trimethylchlorosilane

$$H_2C{=}C{=}CHMgBr + Me_3SiCl \xrightarrow[-10°C]{Et_2O} HC{\equiv}CCH_2SiMe_3 + MgBrCl{\downarrow}$$
$$(+\ 8\%\ Me_3SiCH{=}C{=}CH_2)$$

Scale: 0.50 molar.

Apparatus: fig.1; stirrer: fig. 3.

Introduction
Reaction of the Grignard reagent from propargyl bromide with electrophilic reagents in principle may give both an allenic and an acetylenic derivative. The ratio of the products formed appears to vary considerably with the electrophilic reagent. Whereas aldehydes give exclusively acetylenic products (see p. 95), with tributyltin chloride a 93:7 mixture of the allenic and acetylenic derivative is obtained [4]. From the reaction with trimethyl- chlorosilane the acetylenic product is obtained predominantly. However, it is not possible to separate this from other products by distillation. Upon hydrolysis unconverted trimethyl- chlorosilane forms $Me_3SiOSiMe_3$ which has a b.p. very close to that of the desired product. One should therefore be sure that an excess of Grignard reagent is present!

Procedure

A solution of allenyl magnesium bromide in ~400 ml of Et_2O, prepared from 0.75 mol of propargyl bromide (see p. 35) is cooled to -10°C. Freshly distilled trimethylchlorosilane (0.50 mol, note 1) is added dropwise over 20 min with efficient stirring while maintaining the temperature between -5 and -15°C. A thick suspension is formed. After an additional 15 min, as much of the suspension as possible is poured into a solution of 100 g of ammonium chloride in 200 ml of water. The suspension remaining in the flask can be hydrolysed by addition of aqueous NH_4Cl (note 2). After vigorous shaking, the layers are separated. The combined organic layer and one extract, using only a small amount of Et_2O, are dried over $MgSO_4$, after which a very careful distillation through a 40 to 50-cm Widmer column is carried out. The propargylsilane (containing ~8% of allenylsilane), b.p. ~92°C/760 mmHg, is obtained in 75% or higher yields.

Notes

1. The undistilled compound may contain small amounts of $Me_3SiOSiMe_3$ and dissolved hydrogen chloride.
2. One should never add the solution of NH_4Cl when all of the suspension is still in the flask, since the hydrolysis is then very vigorous.

Chapter VII
Sulfenylation and Related Reactions

1. Methods for the Direct Introduction of Sulfur, Selenium or Tellurium

The most practical methods for compounds containing the system C≡C-S (and the Se- or Te-analogues) consist of reacting a metallated acetylene with elemental sulfur (Se or Te) or a sulfenyl derivative with a suitable leaving group L. Sulfoxides may be prepared by analogous coupling reactions. The various methods can be represented by the following schemes (Y = S, Se, Te):

RC≡C-M	+ "Y"	⟶	RC≡C-YM ⟶ ("E^+")	RC≡C-YE	[104]
RC≡C-M	+ R'SL	⟶	RC≡C-SR' + ML		[105]
2 RC≡C-M	+ SCl_2	⟶	$(RC{\equiv}C)_2S$ + 2 MCl		[106]
2 RC≡C-M	+ $SOCl_2$	⟶	$(RC{\equiv}C)_2S{=}O$ + 2 MCl		[106]
RC≡C-M	+ R'S(=O)Cl	⟶	RC≡C-SOR' + MCl		[2]

The insertion of a sulfur atom into the ≡C-metal bond is analogous to the well-known formation of alkali thiocyanate from alkali cyanide and sulfur. The insertion reaction has been successfully applied to introduce sulfur (or Se and Te) into an aromatic or heteroaromatic ring system [72]. The reaction of a metallated acetylene with the elements S, Se and Te constitutes a ready access to several derivatives with the C≡C-Y systems. Although derivatization of the mesomeric anion $RC{\equiv}C\text{-}Y^- \leftrightarrow R\underline{C}{=}C{=}Y$ with an "electrophilic" reagent "E^+" in principle may give products from both structures, the only type of derivative isolated is RC≡C-YE. In the case of selenium and tellurium, yields are significantly better than with sulfur. The reactions with sulfur and subsequent derivatizations usually give appreciable amounts of high-boiling residues, which might in part result from further reactions of the thioketenes RC(E)=C=S. The insertions proceed most easily in liquid ammonia. However, functionalizations in this solvent are confined to alkylation reactions. Reactions in THF or Et_2O are generally carried out with the *lithium* alkynylides, which react much more smoothly than sodium- or potassium derivatives, because their solubility is better. A wide variety of derivatives with the structure system C≡C-Y is accessible *via* the lithium chalcogenates RC≡C-YLi in organic solvents.

Alkali acetylides react very easily with disulfides, R'SSR', thiocyanates, R'SC≡N, and thiosulfonates, $R'SSO_2R'$. The reactions can be carried out in liquid ammonia as well as in organic solvents and generally give excellent yields of the acetylenic sulfides, RC≡CSR' [2,105]. Although sulfenyl halides seem suitable reagents for the introduction of alkylthio- or arylthio groups, they are seldom used for this reaction, because of their sensitivity and the

chance of further reaction with the products.

Di(1-alkynyl)sulfides are formed in excellent yields, if (freshly distilled) sulfur dichloride is added to a solution or suspension of a lithium alkynylide in Et_2O [106]. In an analogous manner, di(1-alkynyl)sulfoxides are formed from thionyl chloride and an alkynyllithium [106], while sulfinyl chlorides R'S(=O)Cl may be used to prepare the sulfoxides RC≡CS(=O)R'. Preliminary experiments suggest that interaction between alkynyllithium and sulfonyl chlorides $R'SO_2Cl$ can give both sulfones $RC{\equiv}CSO_2R'$ and chloroalkynes RC≡CCl [2].

2. Experiments

All temperatures are internal, unless indicated otherwise

2.1 Reaction of Metallated Acetylenes with Disulfides or Thiocyanates or Thiosulfonates in Liquid Ammonia

$$RC{\equiv}CM + R'SX \xrightarrow[-33^\circ C]{\text{liq. } NH_3} RC{\equiv}CSR' + MX\downarrow \qquad \begin{matrix} M = Li \text{ or } Na \\ X = SR', SO_2R' \text{ or } C{\equiv}N \end{matrix}$$

Scale: 0.20 molar.

Apparatus: fig. 4, 1 l.

Introduction

A convenient and quick method to prepare acetylenic sulfides consists of adding a disulfide, thiosulfonate or thiocyanate to a lithium or sodium alkynylide in liquid ammonia. The reaction proceeds almost instantaneously, except in the case of di-*t*-butyl disulfide (reaction with RC≡CLi in an organic solvent at higher temperatures, or the use of *t*-BuSC≡N may be considered). *Ethynyl* sulfides HC≡CSR' cannot be obtained using this method, since they are immediately deprotonated by alkali acetylide MC≡CH and then a second R'S group is introduced with the formation of R'SC≡CSR' [2]. Sulfides with conjugated unsaturated systems, *e.g.* $H_2C{=}CHC{\equiv}CSR'$ and $RC{\equiv}CC{\equiv}CSR'$, readily undergo nucleophilic addition of thiolate $R'S^-$. Therefore, thiocyanates or thiosulfonates should be used for the sulfenylation of alkali compounds from 1,3-enynes and 1,3-diynes and also in those cases in which there is a chance of a subsequent reaction of the product with thiolate.

Procedure

A solution or suspension of 0.22 mol of the lithium or sodium alkynylide in 300 ml of liquid ammonia is prepared as described on p. 20. The disulfide, thiosulfonate or thiocyanate (0.20 mol, diluted with 50 ml of Et_2O, is added dropwise over 10 min with efficient stirring. In many cases a rather thick suspension is formed: an additional volume of ~100 ml of liquid

ammonia may then be introduced. The ammonia may either be removed by placing the flask in a water bath at 40°C (after having replaced the equipment on the outer necks with gas outlets) or allowed to evaporate (fig. 11). After addition of 200 ml of Et_2O to the solid residue, 300 ml of ice water is added with vigorous stirring or swirling by hand. After separation of the layers, the aqueous phase is extracted with Et_2O, and the organic solution dried over $MgSO_4$. The solvent is removed under reduced pressure and the remaining liquid distilled *in vacuo*. The following examples give an impression of the scope:

$C_3H_7C{\equiv}CSCH_3$, b.p. 50°C/12 mmHg, $n_D(20^\circ)$ 1.4900, yield 90%, from $C_3H_7C{\equiv}CLi$, and $CH_3SC{\equiv}N$;

1-cyclohexenyl-$C{\equiv}CSCH_3$, b.p. 120°C/12 mmHg, $n_D(20^\circ)$ 1.5729, in 85%, yield from 1-cyclohexenyllithium and CH_3SSCH_3;

$CH_3C{\equiv}CC{\equiv}CSCH_3$, b.p. 80°C/12 mmHg, $n_D(20^\circ)$ 1.5993, in 82%, yield from $CH_3C{\equiv}C{-}C{\equiv}CLi$ and $CH_3SSO_2CH_3$;

$CH_3C{\equiv}CS(CH_2)_4Cl$, b.p. ~90°C/1 mmHg, $n_D(20^\circ)$ 1.5129, yield 84%, from $CH_3C{\equiv}CLi$ and $Cl(CH_2)_4SC{\equiv}N$;

$CH_3SC{\equiv}CSCH_3$, b.p. 72°C/10 mmHg, $n_D(20^\circ)$ 1.5982, yield ~90%, from $HC{\equiv}CNa$ and $CH_3SC{\equiv}N$.

2.2 C-Thiomethylation of Acetylenic Alcohols in Liquid Ammonia

$$LiC{\equiv}C(CH_2)_mOH + CH_3SC{\equiv}N \xrightarrow[-33^\circ C]{\text{liq. } NH_3} \underset{\text{(after hydrolysis)}}{CH_3SC{\equiv}C(CH_2)_mOH} + LiC{\equiv}N\downarrow \qquad m = 1 \text{ or } 2$$

Scale: 0.20 molar.

Apparatus: fig. 4, 1 l.

Procedure

Propargyl alcohol (0.20 mol) or homopropargyl alcohol (0.20 mol, see p. 64) is added dropwise over 10 min to a vigorously stirred suspension of 0.50 mol of lithium amide [1] in 500 ml of liquid ammonia. Most of the suspended material disappears. Methylthiocyanate (0.30 mol [1,3]) is then added dropwise over 10 min. The ammonia is subsequently removed by placing the flask in a water bath at 40°C, stirring being continued as long as possible (the other equipment is removed). To the remaining dark residue 200 ml of ice water is added, whereupon five to ten extractions with Et_2O are carried out. The unwashed organic solution is dried over $MgSO_4$ and subsequently concentrated *in vacuo* using a rotary evaporator. Distillation of the remaining liquid through a 30-cm Vigreux column gives $CH_3SC{\equiv}C{-}CH_2OH$, b.p. ~60°C/0.2 mmHg, $n_D(20^\circ)$ 1.546 in ~70% yield (redistillation gives b.p. 95°C/12 mmHg, $n_D(19^\circ)$ 1.5455) and $CH_3SC{\equiv}CCH_2CH_2OH$, b.p. 108°C/15 mmHg, $n_D(18^\circ)$ 1.5351, in 80% yield.

2.3 Alkylthiolation of Acetylenes in Et_2O or THF

$$RC{\equiv}CLi + CH_3SX \xrightarrow{Et_2O \text{ or THF}} RC{\equiv}CSCH_3 + LiX \qquad X = CH_3S,\ C{\equiv}N \text{ or } CH_3SO_2$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Procedure (for Introduction see exp.1)

The sulfenyl compound (0.10 mol, [1,3,4] is added over a few min to a solution or suspension of 0.11 mol of $RC{\equiv}CLi$ in Et_2O or THF (see p. 24 and 25), cooled to -80 or -70°C (in the case of X is C≡N or CH_3SO_2) or -40°C (when X = CH_3S). The cooling bath is removed and the temperature allowed to rise to 0°C. If a very thick suspension is formed, an additional amount of Et_2O or THF should be added. Work-up is carried out by adding 100 ml of ice water to the vigorously stirred reaction mixture, extracting the aqueous layer with Et_2O and drying the organic solvent over $MgSO_4$. The following compounds have been prepared in yields of at least 80%:

n-$C_4H_9C{\equiv}CSCH_3$, b.p. 65°C/12 mmHg, $n_D(20°)$ 1.4878 (CH_3SSCH_3-method); $(CH_3O)_2CHC{\equiv}CSCH_3$, b.p. 86°C/12 mmHg, $n_D(18°)$ 1.4900 ($CH_3SC{\equiv}N$-method); $CH_3SC{\equiv}CCH_2Cl$, b.p. 65°C/15 mmHg, $n_D(20°)$ 1.5500 ($CH_3SSO_2CH_3$-method).

$CH_3C{\equiv}CSCH_2CH_2Cl$, b.p. 78°C/15 mmHg, $n_D(18°)$ 1.5258, is obtained in an excellent yield from $CH_3C{\equiv}CLi$ in THF-hexane (-70°C) and $N{\equiv}CSCH_2CH_2Cl$.

2.4 1-Ethylthio-3-buten-1-yne, 1-Methylseleno-3-buten-1-yne and 1-Methyl-telluro--3-buten-1-yne

$$E\text{-}ClCH_2CH{=}CHCH_2Cl + 3\ NaNH_2 \xrightarrow[-40°C]{\text{liq. } NH_3} H_2C{=}CHC{\equiv}CNa + 2\ NaCl{\downarrow}$$

$$H_2C{=}CHC{\equiv}CNa + \text{"Y"} \longrightarrow H_2C{=}CHC{\equiv}C\text{-}YNa$$

$$H_2C{=}CHC{\equiv}C\text{-}YNa + CH_3I \longrightarrow H_2C{=}CHC{\equiv}C\text{-}YCH_3 + NaI{\downarrow}$$

$$H_2C{=}CHC{\equiv}C\text{-}YNa + C_2H_5Br \longrightarrow H_2C{=}CHC{\equiv}C\text{-}YC_2H_5 + NaBr{\downarrow}$$

(Y = S, Se or Te)

Scale: 0.20 molar (dichlorobutene).

Apparatus: fig. 1, 1 l; for the addition of the elements the dropping funnel is replaced with a powder funnel.

Introduction

AlkylSe and alkylTe groups can be introduced by reaction with diselenides and ditellurides, but the desired products can be prepared in a more practical and economical way by successive addition of the elements and the alkyl halide. The insertion of the elements proceeds most easily in liquid ammonia, provided that *grey* Te powder and *red* Se powder is used (black Te powder, obtained by precipitation is unreactive, probably because of the presence of an oxide coating, while the black modification of Se,"selenium nigrum" is also less reactive). In Et_2O or THF, temperatures in the range 0-20°C are necessary for the dissolution of the elements.

Procedure

E-1,4-Dichloro-2-butene (0.20 mol, commercially available, note 1) is added dropwise over 15 min to a suspension of 0.60 mol of sodamide in 500 ml of liquid ammonia [1] with cooling between -35 and -40°C. After an additional 15 min the dropping funnel is replaced by a powder funnel and dry, powdered sulfur (6.0 g) , red selenium (14.0 g) or grey tellurium (24 g) is introduced in small portions over 15 min, while maintaining the temperature between -35 and -40°C. Small amounts of the elements in the funnel and the neck are rinsed into the reaction mixture with Et_2O (20-40 ml). After an additional 15-30 min, when the powder has dissolved completely (note 2), the reaction mixture is cooled to -55°C. Methyl iodide (0.25 mol) or ethyl bromide (0.35 mol) is added over a few seconds with a syringe. After an additional 10 min, the cooling bath is removed and the mixture is stirred for one hour. The ammonia is then allowed to evaporate (fig. 11). After addition of water to the remaining salt mass, the product is isolated by extraction with Et_2O, drying the extracts over $MgSO_4$ and concentrating the organic solution *in vacuo* (note 3). Distillation of the remaining liquid at <0.5 mmHg, using a *single* receiver, cooled in a bath at < -20°C (fig.14), gives $H_2C{=}CH\text{-}C{\equiv}CSeCH_3$, $n_D(20°)$ 1.5867, in ~80% and $H_2C{=}CHC{\equiv}CTeCH_3$, $n_D(20°)$ 1.6628 (yellowish-brown liquid), in ~70% yield. Pure $H_2C{=}CHC{\equiv}CSC_2H_5$, b.p. 47°C/10 mmHg, $n_D(20°)$ 1.5412, is obtained in ~55% yield by careful redistillation of the contents of the receiver.

Notes

1. The reaction of the *Z*-isomer with $NaNH_2$ proceeds less satisfactorily, and gives a considerable amount of resinous product.
2. A small amount of coarse Te powder may remain undissolved.
3. The tellurium compound is air-sensitive, and the work-up should therefore be carried out under nitrogen.

2.5 1-Ethylseleno-1-propyne and 1-Ethyltelluro-1-propyne

$$CH_3CHBrCH_2Br + 3\ NaNH_2 \xrightarrow[-40°C]{\text{liq. } NH_3} CH_3C{\equiv}CNa{\downarrow} + 2\ NaBr{\downarrow}$$

$CH_3C{\equiv}CNa$ + "Y" ⟶ $CH_3C{\equiv}CYNa$ (Y = Se or Te)

$CH_3C{\equiv}CYNa + C_2H_5Br$ ⟶ $CH_3C{\equiv}CYC_2H_5 + NaBr\downarrow$

Scale: 0.20 molar (dibromopropane).

Apparatus: fig. 1, 1 l.

Procedure (compare exp. 4)

1,2-Dibromopropane (0.20 mol, see p. 195) is added dropwise over 15 to 20 min to a suspension of 0.60 mol of sodamide [1] in *ca.* 600 ml of liquid ammonia with cooling between -35 and -40°C. After an additional 15 min, red selenium powder (14.0 g) or grey tellurium powder (24.0 g) is introduced over 15 min through a powder funnel which temporarily replaces the dropping funnel. During this addition the temperature of the reaction mixture is maintained between -35 and -40°C. Small amounts of powder in the funnel or in the neck are rinsed into the flask with 50 ml of Et_2O. After 15 to 30 min, the Se or Te has disappeared (a small amount of coarse Te powder may remain unconverted). Ethyl bromide (0.3 mol) is then added dropwise over 15 min without external cooling. After an additional 1 h stirring is stopped and the ammonia is allowed to evaporate (fig. 11). The remaining salt is dissolved by addition of 200 ml of water, after which the mixture is extracted four times with Et_2O (portions of 150 and 50 ml for the first and second extraction). After drying the organic solution over $MgSO_4$, the solvent is removed by evacuation and the remaining liquid distilled through a 30-cm Vigreux column.

$CH_3C{\equiv}CSeC_2H_5$, b.p. 44°C/10 mmHg, $n_D(20°)$ 1.5245, and $CH_3C{\equiv}CTeC_2H_5$, b.p. 66°C/10 mmHg, $n_D(20°)$ 1.5946, are obtained in yields of ~85 and 75%, respectively.

2.6 Reaction of Sodium Acetylide in Liquid Ammonia with Selenium and Subsequent Ethylation. Formation of Bis(ethylseleno)acetylene

$HC{\equiv}CNa$ + "Se" $\xrightarrow[-33°C]{\text{liq. } NH_3}$ $HC{\equiv}CSeNa$

$HC{\equiv}CSeNa + C_2H_5Br$ ⟶ $HC{\equiv}CSeC_2H_5 + NaBr\downarrow$

2 $HC{\equiv}CSeC_2H_5$ $\xrightarrow{NaOC_2H_5}$ $C_2H_5SeC{\equiv}CSeC_2H_5\downarrow + HC{\equiv}CH\uparrow$

Scale: 0.20 molar ($HC{\equiv}CNa$).

Apparatus: fig. 15, 1 l.

Introduction

Ethynyl selenides very readily disproportionate into bis(alkylseleno)acetylenes and acetylene under the catalytic influence of nucleophilic reagents, a property which they have in common with ethynyl phosphines [40,103]. Attempts to prepare ethylselenoacetylene by reaction of alkali acetylide in liquid ammonia with selenium and subsequent addition of ethyl bromide, give bis(ethylseleno)acetylene as the main product. Small traces of nucleophiles, possibly also $HC{\equiv}CSe^-$, catalyze the disproportionation. The disproportionation can be represented as an equilibrium, which gradually shifts to the side of the bis-selenide and acetylene by the slight solublilty of the bis-selenide in liquid ammonia and the escape of acetylene from the solution. The reaction is considerably facilitated by addition of small amounts of sodium ethoxide. The mechanism of the disproportionation has not been investigated. Ethynyl *sulfides* do not undergo this reaction.

Procedure

A solution of 0.20 mol of sodium acetylide (or $LiC{\equiv}CH$) in 300 ml of liquid ammonia is prepared as described on p. 17 (no excess of acetylene is introduced). Powdered red selenium (16.0 g) is then introduced in small portions over 15 min. During this addition the solution is cooled between -35 and -40°C. After an additional 10 min (when the Se has dissolved completely) ethyl bromide (0.25 mol) is added over 15 min while maintaining the temperature between -35 and -40°C. The cooling bath is then removed and after an additional 30 min a few ml of a concentrated solution of sodium ethoxide in ethanol is added. Stirring is continued for another 2 h (or longer). The remaining ammonia is allowed to evaporate overnight (fig. 11). After addition of 200 ml of water to the remaining salt mass, the product is extracted with Et_2O. The organic solution is dried over $MgSO_4$ and subsequently concentrated under reduced pressure. Distillation of the remaining liquid through a short column gives bis-(ethylseleno)ethyne, b.p. 118°C/10 mmHg, $n_D(20°)$ 1.6105, in yields between 70 and 80%.

Warning

Rubber gloves should be worn during the work-up, because the compound has a very persisting (evil) smell.

2.7 Reaction of Alkynyllithium in THF with Sulfur or Selenium and Subsequent Alkylation with Bromochloromethane

$RC{\equiv}CLi$ + "Y" $\xrightarrow{\text{THF-hexane}}$ $RC{\equiv}CYLi$

$RC{\equiv}CYLi + BrCH_2Cl$ ⟶ $RC{\equiv}CYCH_2Cl + LiBr$ (Y = S or Se)

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Procedure

Dry, powdered sulfur (6.4 g) or red selenium (16.0 g) is added over a few min to a solution of RC≡CLi (0.20 mol in 140 ml of THF and 140 ml of hexane, see p. 24), cooled at -40°C. The cooling bath is removed and the temperature allowed to rise to 15°C. After an additional period of 15-30 min (when the powder has dissolved) 0.60 mol (a large excess) of bromochloromethane is added over a few seconds. In the case of the preparation of sulfides, the brown solution is allowed to stand for 12-15 h at room temperature, the alkyneselenolates react faster so that a period of about 4 h is sufficient. The reaction mixture is poured into 300 ml of ice water and, after vigorous shaking, the layers are separated. The organic layer and three ethereal extracts are dried over $MgSO_4$ and subsequently concentrated under reduced pressure. The remaining liquid is first distilled at low (< 0.5 mmHg) pressure through a very short column and the distillate collected in a *single* receiver cooled below -30°C (fig.14). Redistillation gives the following products:

$C_2H_5C{\equiv}CSCH_2Cl$, b.p. 65°C/12 mmHg, $n_D(20°)$ 1.5205;
$CH_3C{\equiv}CSCH_2Cl$, b.p. 58°C/12 mmHg, $n_D(20°)$ 1.5322;
t-$C_4H_9C{\equiv}CSCH_2Cl$, b.p. 70°C/12 mmHg, $n_D(20°)$ 1.4930;
$Me_3SiC{\equiv}CSCH_2Cl$, b.p. 78°C/12 mmHg, $n_D(20°)$ 1.4988;
$C_2H_5C{\equiv}CSeCH_2Cl$, b.p. 35°C/0.01 mmHg, $n_D(20°)$ 1.5482.

Yields of the sulfides are between 55 and 64%, the selenium compound is obtained in 72% yield.

2.8 Reaction of Alkynethiolates with Acetyl Bromide and Ethyl Chloroformate

$$RC{\equiv}CSLi + CH_3C(=O)Br \xrightarrow{Et_2O} RC{\equiv}CSC(=O)CH_3 + LiBr$$

$$RC{\equiv}CSLi + ClCOOC_2H_5 \longrightarrow RC{\equiv}CSCOOC_2H_5 + LiCl$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Procedure (compare [107])

A suspension or solution of 0.20 mol of alkynyllithium in 140 ml of Et_2O and 140 ml of hexane (see pag. 24) is cooled to -40°C and 6.4 g dry, powdered sulfur is added over 1 min. The cooling bath is removed and the temperature allowed to rise to 15-20°C. In all cases brown solutions are formed. Stirring at 15-20°C is continued for about 1 h until all sulfur has dissolved. The solution is then transferred into the dropping funnel and added over 30 min to a mixture of 0.22 mol of freshly distilled acetyl bromide or 0.25 mol of ethyl chloroformate, and 200 ml of Et_2O. During, and for 30 min after this addition, the temperature of the mixture

is maintained between -30 and -40°C. The cooling bath is then removed and the temperature allowed to rise to 0°C. Ice water (100 ml) is then added with vigorous stirring and cooling at ~0°C. The layers are then separated and extraction with Et_2O is carried out (note 1). After drying over $MgSO_4$, the solvent is removed under reduced pressure. The remaining lachrymatory liquid is first distilled at < 0.5 mmHg pressure through a very short column and the distillate collected in a single receiver cooled below -30°C. Redistillation through a 20-cm Vigreux column gives the desired products (note 2).

Examples: $C_4H_9C{\equiv}CSCOCH_3$, b.p. 100°C/10 mmHg, $n_D(20°)$ 1.4997, yield ~50%; $C_2H_5C{\equiv}CSCOOC_2H_5$, b.p. 88°C/10 mmHg, $n_D(20°)$ 1.4824, yield ~53%.

Notes

1. Since the products are water sensitive [108] ($C_4H_9C{\equiv}CSCOCH_3$ is converted into $C_4H_9COCH_2SCOCH_3$), the work-up should be carried out without delay.
2. Part of the sulfur is converted into Li_2S, while a corresponding part of RC≡CLi remains in the reaction mixture. With CH_3COCl and $ClCOOC_2H_5$, $RC{\equiv}CCOCH_3$ and $RC{\equiv}CCOOC_2H_5$ are formed. Careful distillation is necessary to separate these more volatile byproducts from the desired compounds. Too strong heating during the distillation should be avoided as the compounds have limited thermal stability.

2.9 Preparation of 1-Alkynyl Thiocyanates from Alkynethiolates and Cyanogen Chloride

$$RC{\equiv}CSLi + ClC{\equiv}N \xrightarrow[-40°C]{Et_2O\text{-hexane}} RC{\equiv}CSC{\equiv}N + LiCl\downarrow$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Procedure (compare [110])

A solution or suspension of 0.20 mol of lithium alkynethiolate in 140 ml of hexane and 200 ml of Et_2O (compare p. 24 and exp.8) is added over 30 min to a solution of 0.30 mol of cyanogen chloride (note 1) in 100 ml of Et_2O. After the addition, which is carried out with cooling between -30 and -40°C (note 2), the cooling bath is removed and the temperature allowed to rise to 10°C. The reaction mixture is then poured into 200 ml of ice water and after vigorous shaking and separation of the layers, two extractions with Et_2O are carried out. The organic solution is dried over $MgSO_4$ and the liquid remaining after concentration of the solution under reduced pressure is subjected to a "rough" distillation at < 0.5 mmHg. The distillate, collected in a strongly cooled, *single* receiver (fig. 14) is carefully redistilled at water-pump pressure (note 3) to give $CH_3C{\equiv}CSC{\equiv}N$, b.p. 40°C/12 mmHg, $n_D(20°)$ 1.5041 and *t*-$BuC{\equiv}CSC{\equiv}N$, b.p. 60°C/12 mmHg, $n_D(20°)$ 1.4748, in 45 and 64% yields,

respectively (note 4).

Notes

1. Cyanogen chloride, an extremely poisonous gas, is commercially available in cylinders (expensive!). It can be prepared from chlorine and sodium cyanide in carbon tetrachloride [109] (see also p. 156)
2. Since alkynethiolates can react with alkynylthiocyanates, yields may be lower when the addition is carried out too quickly.
3. The small amount of unconverted alkynyllithium (see exp. 8, note 2) may react with ClC≡N to give RC≡CC≡N. This has to be separated from the desired product by careful distillation.
4. See note 3 of exp. 10.

2.10 1-Trimethylsilylthio-1-propyne from Lithium Propynethiolate and Trimethylchlorosilane

$$CH_3C{\equiv}CSLi + Me_3SiCl \xrightarrow{Et_2O\text{-hexane}} CH_3C{\equiv}CSSiMe_3 + LiCl\downarrow$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Procedure (compare [111,112])

A solution of about 0.20 mol of lithium propynethiolate is prepared from 6.4 g of dry, powdered sulfur and a suspension of 0.20 mol of propynyllithium in 140 ml of hexane and 140 ml of Et_2O (see exp. 8). The brown solution is added dropwise over 45 min to a mixture of 0.30 mol (excess) of freshly distilled trimethylchlorosilane and 100 ml of Et_2O (note 1) cooled between -30 and -40°C. The cooling bath is then removed and the temperature allowed to rise to 10 - 15°C. The solvent and other volatile components are removed in a water-pump vacuum (a tube filled with lumps of $CaCl_2$ is placed between the flask and the water aspirator). The bath temperature should not exceed 30°C during this operation. The remaining dark-brown liquid is then subjected to vacuum distillation ($p < 1$ mmHg), collecting the volatile product in a single receiver cooled below -50°C (note 2). Careful redistillation of the contents of the receiver through a 40-cm Widmer column gives the desired product, b.p. 50°C/12 mmHg, $n_D(20°)$ 1.4852, in *ca.* 55% yield (note 3).

Notes

1. If the addition is carried out in the normal sense, some dimer of the thioketene $CH_3C(SiMe_3){=}C{=}S$ (a dithiole derivative) is formed.
2. Since the silyl sulfide is very water-sensitive, all glassware should be dried carefully.

3. In the cases of higher boiling compounds a small amount of paraffin oil should be added prior to the distillation. The oil serves as a heat conductor in the last stage of the distillation, when mainly salt is present in the distillation flask.

2.11 Methyl-1-propynyl Sulfoxide from Propynyllithium and Methanesulfinyl Chloride

$$CH_3C{\equiv}CLi + CH_3S(=O)Cl \xrightarrow[-60°C]{\text{THF-hexane}} CH_3C{\equiv}CSOCH_3 + LiCl\downarrow$$

Scale: 0.30 molar.

Apparatus: fig. 1, 1 l.

Procedure

Methanesulfinyl chloride (0.30 mol [113]) is added over 15 min to a suspension of 0.30 mol of propynyllithium in 200 ml of THF and 210 ml of hexane (p. 24) with cooling between -60 and -80°C (cooling in a bath with liquid N_2 allows a quick addition). Ten min after this addition, the reaction mixture is poured into 100 ml of water. After vigorous shaking, the layers are separated and the aqueous layer is extracted *ten* times with small portions of chloroform. The combined organic solutions are dried over $MgSO_4$, after which the solvent is removed *in vacuo*. The remaining liquid is distilled at oil pump pressure to give the sulfoxide, b.p. ~70°C/0.5 mmHg, $n_D(18°)$ 1.5122, in ~75% yield.

Methyl*sulfonyl* chloride CH_3SO_2Cl and tosyl chloride give low to moderate yields of $RC{\equiv}CSO_2CH_3$ and $RC{\equiv}CSO_2$-Aryl. Part of the sulfonyl chloride reacts with the lithium alkynylide to give a chloroalkyne. A more succesful method to prepare acetylenic sulfones involves oxidation of acetylene sulfides with peracids.

2.12 Preparation of Di(1-alkynyl)sulfides and Di(1-alkynyl)sulfoxides from Alkynyllithium and Sulfur Dichloride or Thionyl Chloride

$$2\,RC{\equiv}CLi + SCl_2 \xrightarrow{Et_2O\text{-hexane}} (RC{\equiv}C)_2S + 2\,LiCl\downarrow$$

$$2\,RC{\equiv}CLi + SOCl_2 \xrightarrow[-90°C]{Et_2O\text{-hexane}} (RC{\equiv}C)_2S(=O) + 2\,LiCl\downarrow$$

Scale: 0.20 molar (SCl_2 or $SOCl_2$).

Apparatus: fig. 1, 1 l.

Procedure

Freshly distilled (b.p. 58-62°C/760 mmHg) sulfur dichloride (0.20 mol, diluted with 50 ml of Et_2O cooled to -40°C) or thionyl chloride (0.20 mol, diluted with 50 ml of Et_2O) is added dropwise over 10 to 15 min to a vigorously stirred suspension or solution of 0.40 mol of alkynyllithium (p. 24) in 280 ml of hexane and x ml (note 1) of Et_2O. During this addition, the temperature is kept between -85 and -95°C by occasional cooling in a bath with liquid N_2, care being taken that no solid layer of solvent is formed on the bottom of the flask. Ten min after the addition, the suspension is poured into y ml (note 2) of ice water. After vigorous shaking and separation of the layers, the aqueous layer is extracted three times with Et_2O (in the case of the sulfide) or three times with dichloromethane (in the case of the sulfoxides). The (unwashed) organic solutions are dried over $MgSO_4$, and then concentrated *in vacuo*. In the case of the sulfides, the remaining liquid is subjected to a high-vacuum distillation ($p < 0.5$ mmHg) and the distillate collected in a strongly cooled *single* receiver (fig. 14,note 3). Redistillation gives the following sulfides:

$(CH_3C{\equiv}C)_2S$, b.p. ~30°C/0.2 mmHg, $n_D(20°)$ 1.5335, yield ~65-80%;
$(C_2H_5C{\equiv}C)_2S$, b.p. ~45°C/0.2 mmHg, $n_D(20°)$ 1.5193, yield ~70-85%;
$(t\text{-}C_4H_9C{\equiv}C)_2S$, b.p. ~50°C/0.2 mmHg, $n_D(20°)$ 1.4881, yield ~85%;
$(Me_3SiC{\equiv}C)_2S$, b.p. ~55°C/0.2 mmHg, $n_D(20°)$ 1.4930, yield ~80%.

Notes

1. x = 400 in the cases of the sulfoxides and 800, 600 and 400, respectively in the cases of the sulfides R = CH_3, C_2H_5 and *t*-Bu (or Me_3Si). When THF is used instead of Et_2O, yields of the sulfides with R = CH_3 and C_2H_5 are only *ca.* 30%. A possible explanation is that the very base-sensitive $(CH_3C{\equiv}C)_2S$ and $(C_2H_5C{\equiv}C)_2S$ are attacked by alkynyllithium: in the more polar THF this attack is more serious than in Et_2O while the solubility of the RC≡CLi in Et_2O is also much less.
2. y = 300 in the case of the sulfides and 100 in the case of the sulfoxides.
3. The viscous, brown residue may undergo vigorous decomposition. This explains the necessity of a first "rough" distillation at very low pressure with moderate heating.

3. Other Preparative Methods

The methods based on direct introduction of the heteroatom or heteroatom-containing group discussed and exemplified in the previous sections give access to a wide variety of acetylenic sulfides, selenides and tellurides. The chapter on acetylenic sulfides in ref 6 gives a review of all synthetic methods for these classes of compounds. Some of these have been illustrated by procedures in the other chapters of our book. In our selection also the effort which has to be put in the synthesis of the precursors has been taken into account. The relevant methods are represented here by schemes only.

$$H_2C{=}CHSR \xrightarrow{Br_2} BrCH_2CH(Br)SR \xrightarrow[2.\ H_2O]{1.\ 3\ NaNH_2,\ NH_3} HC{\equiv}CSR$$

(Chap. IX, exp. 8.)

$$H_2C{=}CHCl \xrightarrow{SCl_2} (Cl_2CHCH_2)_2S \xrightarrow[CH_3OH]{KOH} (ClCH{=}CH)_2S \xrightarrow[2.\ H_2O]{1.\ 4\ NaNH_2} (HC{\equiv}C)_2S$$

(ref. 4)

$$ClCH_2C{\equiv}CCH_2Cl \xrightarrow{2\ RS^-} RSCH_2C{\equiv}CCH_2SR \xrightarrow[THF\ or\ NH_3]{t\text{-}BuOK} RSC{\equiv}CCH{=}CH_2$$

(ref. 4)

$$HC{\equiv}CCH_2Cl \xrightarrow{RS^-} HC{\equiv}CCH_2SR \xrightarrow[liq.\ NH_3]{base} CH_3C{\equiv}CSR$$

(Chap. XI, exp. 3.6)

$$RC{\equiv}CSR' \xrightarrow{NaIO_4} RC{\equiv}CSOR'$$

$$RC{\equiv}CSR' \xrightarrow[H_2O_2]{CH_3COOH} RC{\equiv}CSO_2R'$$

(Chap. XII, Section 4)

Chapter VIII
Halogenation and Cyanation

1. Methods for the Direct Introduction of Halogen and Cyano Groups

The principal methods for direct preparation of halogenoacetylenes from the corresponding 1-alkynes are represented in the following equations [6]:

$$RC{\equiv}CM + ArSO_2Cl \longrightarrow RC{\equiv}CCl + ArSO_2M$$

$$RC{\equiv}CM + X_2 \longrightarrow RC{\equiv}CX + MX \qquad (X = Cl, Br, I)$$

$$RC{\equiv}CM + X\text{-}L \longrightarrow RC{\equiv}CX + ML$$

(L = C≡N; X = Br, or L = succinyl, X = Cl or Br)

$$RC{\equiv}CH + NaOX \longrightarrow RC{\equiv}CX + NaOH \qquad (X = Cl \text{ or } Br)$$

Alkynenitriles can be obtained from metallated acetylenes and the "pseudo-halogen" ClC≡N [114,115]:

$$RC{\equiv}CM + ClC{\equiv}N \longrightarrow RC{\equiv}CC{\equiv}N$$

The preparation of the extremely unstable (explosive) monohaloacetylenes HC≡CX by these methods has no practical importance.

A general method for chloroalkynes is the reaction of a metallated acetylene with an arenesulfonyl halide in an organic solvent [116]. Sodium alkynylides have most often been used, though there are no indications that the lithium compounds give less satisfactory results. Yields of about 60% have been reported. The sodium alkynylides can be prepared by heating a suspension of (commercially available) sodamide in an organic solvent (Et_2O or THF) with the alkyne until the evolution of ammonia has stopped. The practical problem is that the conversion takes place under heterogeneous conditions: starting from a suspension of sodamide, a suspension of sodium alkynylide is obtained. Alternatively one may first prepare a suspension of RC≡CNa in liquid ammonia, after which the ammonia is gradually replaced by Et_2O or THF, though this operation is tedious. In view of the sensitivity of the sulfonyl halides towards ammonia, it must be removed completely. Working with the lithium compounds is more convenient, as their solubility is better. Solutions of lithium alkynylide in THF can be quickly prepared by warming commercially available lithium amide with the acetylene in THF until the evolution of ammonia has ceased.

A useful variant of the sulfonyl chloride method is chlorination with *N*-chloro-

succinimide in organic solvents [117]. Bromoacetylenes can be prepared in a similar way from alkynyllithium or alkynyl Grignard reagents and *N*-bromosuccinimide [118]. A disadvantage of the halosuccinimide method is the fact that the metal succinimide always forms a very thick suspension making it necessary to use relatively large volumes of solvents [2]. In this respect the bromination with cyanogen bromide is more convenient [114].

In many cases, the free halogens dissolved in a suitable solvent such as Et_2O (for Br_2 or I_2), THF (for I_2) or strongly cooled pentane (for Cl_2) can be used [6,23,120]. Generally, the iodinations give the highest yields as there is little competition of *addition* of I_2 to the unsaturated system. The introduction of iodine can even be carried out in liquid ammonia with excellent results [121].

The halogenations with Cl_2, Br_2 and I_2 are carried out most conveniently with the *lithium* alkynylides [2,119]. Subsequent addition of Cl_2 and Br_2 to the triple bond can, in many cases, be avoided by a sufficiently slow addition of the solution of the halogen to a strongly cooled solution or suspension of the lithiated alkyne in Et_2O or THF.

Halogenoalkynes are also formed from alkynes and aqueous solutions of hypohalites. In these reactions, alkynylide anions are transient intermediates. The conversions give good results only when the acetylene has a low pK (*e.g.* aryl-C≡CH and RC≡CC≡CH) or good solubility in water (*e.g.* $HC{\equiv}CC(CH_3)_2OH$) [122]. The hypohalite method of Strauss [123] has most applications in the synthesis of *bromo*acetylenes.

Finally, the peculiar formation of iodoalkynes from iodine and acetylenes with relatively low (< 25) pK values in liquid ammonia should be mentioned [121]. The most likely intermediates occurring are acetylide "anions" formed in very low concentrations from the acetylene and the base ammonia. The conversions proceed very slowly and iodination of the lithiated alkynes in the same solvent is undoubtedly a far superior method.

The formation of alkynenitriles from alkynylmagnesium halides and cyanogen chloride was described for the first time by Grignard [114]. A number of these nitriles have been prepared in our laboratory from alkynyllithium and cyanogen chloride using Et_2O as a solvent [115]. Cyanogen *bromide* is unsuitable because the alkynylide attacks on bromine [2].

2. Other Preparative Methods

The various synthetic methods for 1-halo-1-alkynes have been reviewed in 1969 by Delavarenne and Viehe [6]. Some of these methods, which have (shown) preparative importance and which are complementary to those mentioned in the previous section, are discussed briefly below.

a. Elimination of hydrogen halide

Elimination reactions are considered when simple, volatile haloacetylenes are to be prepared. Dichloroacetylene, for example, has been prepared as an ethereal solution [124] (the undiluted compound is highly explosive) by treating $Cl_2C{=}CHCl$ with KOH at ~200°C. Dibromoacetylene is formed under milder conditions, namely from $Br_2C{=}CHBr$ and ethanolic

potassium hydroxide [125] (tribromoethene may be obtained *in situ* from $Br_2CHCHBr_2$ and KOH under similar conditions). It is thus easy to obtain BrC≡CBr as an ethereal solution (which may be used for Cadiot-Chodkiewicz couplings) by successive addition of Et_2O and water to the alcoholic reaction mixture.

Dichloroacetylene, ClC≡CCl, can be prepared by treating trichloroethene with lithium diisopropylamide at low temperatures [2]:

$$Cl_2C{=}CHCl \xrightarrow[Et_2O,\ \sim -70°C]{\text{LDA}} ClC{\equiv}CCl + HN(i\text{-}C_3H_7)_2$$

It is possible to obtain an ethereal solution of ClC≡CCl by pouring the cold reaction mixture into just sufficient dilute hydrochloric acid, to neutralize the amine [2]. The conversion of trichloroethene into dichloroacetylene proceeds quantitatively. *Dibromo*acetylene might be prepared in a similar way by adding the solution of LDA to a mixture of $Br_2C{=}CHBr$ and Et_2O.

b. In situ generation of metallated haloacetylene, followed by functionalization

This method, which has not been fully explored so far, lends itself to the preparation of a wide variety of chloro- and bromoacetylenes [126,127]:

$$\underset{E \text{ or } Z}{XCH{=}CHX} + 2\,LiNH_2 \xrightarrow[< -33°C]{\text{liq. } NH_3} LiC{\equiv}CX + LiX + NH_3$$

$$LiC{\equiv}CX \xrightarrow{\text{"}E^+\text{"}} EC{\equiv}CX$$

$$XCH{=}CHX + 2\,LiN(i\text{-}C_3H_7)_2 \xrightarrow[\text{low temp.}]{Et_2O \text{ or THF}} LiC{\equiv}CX + LiX + HN(i\text{-}C_3H_7)_2$$

Procedures for the butylation and hydroxyalkylation of LiC≡CCl are presented respectively, on p. 56 and 90. Other alkyl chloroacetylenes and alkyl bromoacetylenes can also be prepared with good yields in liquid ammonia, while hydroxyalkylations may be performed in Et_2O or THF as well as in liquid ammonia. 1-Bromo-1-propyne, for example, can be prepared in a high yield by treating BrCH=CHBr with two equivalents of $LiNH_2$ in liquid NH_3 and subsequently adding methyl iodide (see p. 75). Silylations and stannylations may be carried out with solutions of metallated haloacetylenes in Et_2O or THF. For reaction conditions, the reader should consult the experiments in the previous chapters.

Alkynenitriles, RC≡CC≡N, are generally prepared by dehydration of acid amides, $RC{\equiv}CC(=O)NH_2$, with phosphorous pentoxide. For HC≡CC≡N and N≡CC≡CC≡N [130] this is the only available method: it requires the previous synthesis of the carboxylic esters and their conversion into the acid amides. In principle it should be possible to prepare these useful

compounds in a catalytic way, using transition metal compounds. We have also employed the classical way of preparing alkynenitriles by treating bromoalkynes RC≡CBr with copper(I)cyanide (p. 229) [2].

3. Choice of the Method and Reaction Conditions

The choice of the preparative method and reaction conditions (temperature, solvent, *etc.*) for the synthesis of a particular haloacetylene is determined by its chemical (*e.g.* stability) and physical (*e.g.* volatility) properties and other factors, such as the availability of the precursors. An extremely sensitive compound such as $BrC{\equiv}COC_2H_5$ cannot be prepared by the hypobromite method since this involves exposure of both the sensitive ethoxyethyne and the desired product (if formed at all!) to aggressive conditions. Bromination of the hetero-substituted acetylenes $HC{\equiv}CSiMe_3$ and $HC{\equiv}CPR_2$ by this method will not be successful, fission of the ≡CSi bond and formation of the phosphine oxide respectively, being the most likely reactions to occur. Particularly the synthesis of volatile or unstable haloalkynes may give rise to experimental problems. Suggestions for their preparation are given below:

Volatile chloroalkynes, *e.g.* $CH_3C{\equiv}CCl$, $C_2H_5C{\equiv}CCl$, $C_3H_7C{\equiv}CCl$: alkylation of $LiC{\equiv}CCl$ in liquid NH_3 with respectively, CH_3I (10% excess at -40°C), with Et_2SO_4 (10-15 % excess, introduced with the aid of a syringe, over ~15 min, at between -35 and -40°C) and with C_3H_7Br (10% short measure, added over 30 min at ~ -35°C). After 1 h at these temperatures, acetone is added to "neutralize" the remaining $LiC{\equiv}CCl$. For the experimental conditions see p. 57. For the work-up, see Chap. I-2.6 and pag 57. Redistillation at atmospheric pressure under N_2.

Heterosubstituted chloroacetylenes $Me_3SiC{\equiv}CCl$, $N{\equiv}CC{\equiv}CCl$, $N{\equiv}CC{\equiv}CBr$, $EtOC{\equiv}CI$, $EtOC{\equiv}CBr$ ($EtOC{\equiv}CCl$ is probably extremely unstable).

$Me_3SiC{\equiv}CCl$: two equivalents of EtLi.LiBr [1] in Et_2O are added dropwise to a strongly cooled solution of ClCH=CHCl (*E* + *Z*) in Et_2O at -70°C, and after allowing the temperature to rise to -30°C (over 15 min), the calculated amount of Me_3SiCl is added. The temperature is then allowed to rise to 10 or 20°C and the reaction mixture is subsequently hydrolysed. After drying the ethereal solution over $MgSO_4$, a small amount of Et_2O is evaporated under reduced pressure: any $HC{\equiv}CCl$ if present in the solution is removed in this way. The remaining solution is then carefully distilled under atmospheric pressure.

$N{\equiv}CC{\equiv}CCl$: the ethereal solution of $LiC{\equiv}CCl$ prepared as described above is cooled to -70°C and an excess (~30%) of $ClC{\equiv}N$ is added, after which the temperature is allowed to rise to 10°C. After addition of water, the product is isolated in the usual way (extraction, drying, removal of the Et_2O *in vacuo*).

$N{\equiv}CC{\equiv}CBr$: two equivalents of an ethereal solution of $CH_3Li.LiBr$ (prepared from CH_3Br and Li in Et_2O, see ref. 1) are added dropwise at -70°C to a solution of *E*- or *Z*-BrCH=CHBr in Et_2O. Subsequently, a 20-30% excess of $ClC{\equiv}N$ is added at a low

temperature, after which the temperature is allowed to rise gradually to 10°C.

$EtOC{\equiv}CBr$: this is an extremely sensitive and lachrymatory compound. It is therefore necessary to work carefully. Distillation involves a high risk of explosive decomposition. The best procedure seems to be addition at -20°C of a 10% short measure of pure *N*-bromo-succinimide or $BrC{\equiv}N$ to a solution of $EtOC{\equiv}CLi$, prepared from $HC{\equiv}COEt$ and EtLi.LiBr in Et_2O (ref. 1). After completion of the reaction (allowing the temperature to rise to 10°C), the reaction mixture is poured into ice water and the succinimide is removed by washing with water. After drying the ethereal solution over $MgSO_4$, the solvent is removed *in vacuo*, keeping the temperature as low as possible. Immediate use is recommended.

$EtOC{\equiv}CI$: this compound may also explode upon heating. A good procedure seems to be addition of a (10%) short measure of a solution of I_2 in Et_2O to a cooled (-30°C) solution of $EtOC{\equiv}CLi$ in Et_2O. After the usual work-up (addition of water, extraction with Et_2O and drying) the solvent is removed in a water-pump vacuum with a bath temperature not higher than 20°C. The remaining $EtOC{\equiv}CI$ should be used immediately for further reactions. Storage is dissuaded.

4. Experiments

All temperature are internal, unless indicated otherwise

Warning

Especially those haloalkynes with a conjugated unsaturated system or other heterosubstituents are unstable and may undergo vigorous decomposition upon heating. Even during storage at low temperatures extensive deterioration may occur. It therefore has little sense to prepare large amounts for use over a long period. Simple haloalkynes such as $CH_3C{\equiv}Cl$, C_2H_5-$C{\equiv}CBr$ and $C_4H_9C{\equiv}CCl$ have been stored for several months at -20°C without deterioration. In view of possible physiological effects, contact with the skin and inhalation of vapours should be avoided.

4.1 Preparation of 1-Chloro-2-phenylacetylene from Lithium Phenylacetylide and Benzenesulfonyl Chloride

$$PhC{\equiv}CH + LiNH_2{\downarrow} \xrightarrow[20 \rightarrow 65°C]{THF} PhC{\equiv}CLi + NH_3{\uparrow}$$

$$PhC{\equiv}CLi + PhSO_2Cl \xrightarrow[-15 \rightarrow 35°C]{} PhC{\equiv}CCl + LiSO_2Ph{\downarrow}$$

Scale: 0.50 molar.

Apparatus: fig. 1, 2 l, at a later stage the thermometer is replaced with a reflux condenser.

Introduction

The procedure for chlorophenylacetylene exemplifies a fairly general and satisfactory method for the preparation of 1-chloro-1-alkynes [116]. In the original procedure, sodium alkynylides are used. They may be prepared by treating 1-alkynes with (commercially available) sodamide in an organic solvent. We prefer to use lithium amide, since the progress of the conversion into lithium alkynylide is usually easier to follow than in the reaction with sodamide: since most lithium alkynylides (except the lower homologues, see Chap. II) have a good solubility in THF, disappearance of the suspended lithium amide is a good criterium for completion of the metallation. Although Et_2O may be a satisfactory solvent in most cases, the advantage of THF is that the attainable temperatures are higher (the commercial alkali amides may react sluggishly). The method is applicable for chloroalkynes which can easily be separated from Et_2O or THF by distillation.

Procedure

Phenylacetylene (0.50 mol) is added over a few seconds to a mixture of 0.60 mol of (commercially available) lithium amide and 350 ml of THF. Subsequently a solution of 1.5 g of *t*-BuOK in 5 ml of THF (note 1) is added and the mixture is warmed to about 40°C. The mixture is stirred for 30 min at 40-50°C (occasional cooling may be necessary). The evolution of ammonia gradually sets in, while a coarse suspension of $PhC{\equiv}CLi.NH_3$ is formed. The conversion is completed by heating the mixture at reflux for an additional 45 min, until the evolution of ammonia has ceased and the suspension has virtually disappeared (a faint turbidity due to a small amount of PhC≡CK remains). Traces of dissolved ammonia are removed by distilling off about 50 ml of THF from the solution (rotary evaporator). The solution is cooled to -20°C and a mixture of 0.60 mol of benzenesulfonyl chloride and 150 ml of THF is added over 30 min, while keeping the temperature of the mixture between -20 and -10°C. A yellowish-brown, thick suspension is formed. The temperature is subsequently allowed to rise to 15°C. When heat is no longer evolved, the temperature is raised to 35°C and maintained there for an additional 15 min. Water (1 l) is then added with vigorous stirring. After separation of the layers, four to six extractions with pentane are carried out. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated in a water pump vacuum (keeping the bath temperature below 35°C, note 2). The remaining dark liquid is subjected to a careful distillation through a 40-cm Vigreux column. After a small first fraction of phenylacetylene, the chloroalkyne comes over and a small viscous residue remains. Redistillation gives the chloroalkyne, b.p. 64°C/15 mmHg, $n_D(20°)$ 1.5783, in 76% yield.

Notes

1. This base is added to activate the amide [131].
2. When the solvent is distilled off too quickly, lower yields are obtained.

1-Cyclohexenyl-C≡CCl, b.p. 75°C/15 mmHg, $n_D(20°)$ 1.5254, is obtained in 72% yield from cyclohexenylacetylene (p. 203), $LiNH_2$ and $PhSO_2Cl$ by a similar procedure.

4.2 Preparation of 1-Bromo-1-alkynes from Alkynyllithium and Bromine

$$RC{\equiv}CLi + Br_2 \xrightarrow[<-30°C]{Et_2O(hexane)} RC{\equiv}CBr + LiBr$$

Scale: 0.50 molar.

Apparatus: fig. 1, 1 l.

Introduction

The best method to prepare bromoalkynes RC≡CBr (in which R represents an alkyl or cycloalkyl group) consists of adding bromine to a strongly cooled solution of the lithiated alkyne in Et_2O or THF. Yields are generally high. The method is less attractive for the preparation of the volatile bromopropyne (b.p. 63°C) which is difficult to separate from Et_2O. For the generation of the alkynyllithium intermediates, the most suitable basic reagent in the cases of preparation of volatile bromoalkynes is an ethereal solution of EtLi.LiBr (prepared from C_2H_5Br and Li). A solution of BuLi.LiBr may contain small amounts of octane, while butanol may be formed by oxidation during transfer of the reagent. These compounds cannot easily be separated from the volatile bromoalkynes.

The bromoalkyne can undergo a subsequent addition of bromine. This reaction can be largely avoided by adding bromine at a sufficiently low rate and low temperature. This further reaction with bromine is much more serious during the bromination of lithiated enynes RCH=CHC≡CLi, which gives yields of only some 60%.

Procedure

A solution of ethyllithium (0.50 mol in 500 ml of Et_2O) is prepared from ethyl bromide and lithium as described in refs. 1, 3, and 4. The alkyne (0.50 mol; in the case of butyne a mixture of 0.55 mol and 50 ml of Et_2O, cooled to -20°C) is added with cooling below -20°C. Subsequently 0.50 mol of bromine (dried by shaking with 96% H_2SO_4 and subsequent distillation) is added dropwise over 30 min with vigorous stirring and cooling below -40°C (if possible lower than -60°C). The reaction mixture (at low temperatures a salt suspension) is then poured into 500 ml of ice water and the flask rinsed with water and Et_2O. After shaking and separation of the layers, two extractions with Et_2O are carried out. The combined organic solutions are dried over $MgSO_4$, after which most of the Et_2O is distilled off at atmospheric pressure (note 1) in a slow stream of N_2. The remaining liquid is distilled *in vacuo*. $C_2H_5C{\equiv}CBr$, b.p. ~50°C/200 mmHg, $n_D(20°)$ 1.4695, *t*-BuC≡CBr, b.p. 70°C/150 mmHg, $n_D(20°)$ 1.4610, and BuC≡CBr, b.p. 66°C/50 mmHg, $n_D(20°)$ 1.4657, are obtained in greater than 75% yields (note 2).

Notes

1. In the case of $C_2H_5C{\equiv}CBr$, the Et_2O is slowly distilled off through a 50-cm Widmer

column. The temperature of the heating bath is raised to ~110°C in the last stage of the distillation.

2. A small, high-boiling residue, presumably the adduct of Br_2 and the bromoalkyne is left behind.

Enynes, RCH=CHC≡CH, may be brominated by a similar procedure. The lithiated enyne is prepared by addition of EtLi.LiBr to a strongly cooled (< -40°C) mixture of the enyne RCH=CHC≡CH (5% excess) and Et_2O. C_2H_5CH=CHC≡CBr (b.p.~30°C/10 mmHg) was obtained in a ~65% yield from a mixture of *E*- and *Z*-HC≡CCH=CHC_2H_5. There was a considerable residue. In general, bromination with hypobromite is the preferred method in the case of preparation of RCH=CHC≡CBr and RC≡CC≡CBr. For the bromination of enynes and diynes of the types RCH=CHCH_2C≡CH and RC≡CCH_2C≡CH, the reaction of the *Grignard* derivative with *N*-bromosuccinimide or BrC≡Nseems the best method since these conditions involve the least risk of an isomerization of the skipped system. This method is also recommended for the bromination of hydrocarbons with systems C=C$(CH_2)_n$C≡CH, having n > 1. For the bromination of (hydrocarbon) diynes RC≡C$(CH_2)_n$C≡CH with n > 1, we recommend a procedure similar to the ones of exps. 2 and 8.

4.3 Bromination of Acetylenes with Hypobromite

$$RC{\equiv}CH + KOBr \xrightarrow{H_2O} RC{\equiv}CBr + KOH$$

Scale: 0.25-0.30 molar.

Apparatus: fig. 1, 1 l (no dropping funnel is used).

Introduction

The bromination with alkali hypobromite in aqueous solution gives good results with (hetero)arylacetylenes, enynes (RCH=CHC≡CH) and diynes (RC≡CC≡CH); all acetylenes that are more acidic than those acetylenes in the aliphatic or cycloaliphatic series with an isolated triple bond. For the conjugated systems the hypobromite method is superior to the reaction of metallated acetylenes with bromine. Various acetylenic alcohols are also brominated smoothly, which can be explained in part by their better solubility in water. Since in the case of primary and secondary ethynyl alcohols, oxidation of the alcohol can occur, the use of an excess of hypobromite should be avoided. The best procedure is dropwise additon of a small short measure of hypobromite to a mixture of alcohol and water. If the bromoalkynes to be prepared are not too volatile, small amounts of *THF* or dioxane may be added to effect a better solubility of the alkyne in the aqueous phase. Addition of a co-solvent may also be desired when the starting compound is a solid (*e.g.* ethynylcyclohexanol).

Procedure

Bromine (80 g) is added to a vigorously stirred solution of 75 g (excess) of potassium hydroxide in 200 ml of water with cooling between -5 and 0°C. A pale yellow solution is formed. This solution of KOBr should be used without delay.

BrC≡C$C(CH_3)_2$OH, b.p. 70°C/15 mmHg, $n_D(20°)$ 1.4899, is obtained in greater than 90% yield by adding HC≡C$C(CH_3)_2$OH (0.30 mol) over 15 min to the solution of KOBr, while keeping the temperature between 10 and 20°C (occasional cooling). After an additional 15 min at 20°C the mixture (turbid aqueous phase and lower layer) is extracted four times with Et_2O. The unwashed organic solutions are dried over $MgSO_4$, the Et_2O is removed under reduced pressure, and the remaining liquid distilled off through a 20-cm Vigreux column.

BrC≡C$CH(CH_3)$OH, $n_D(20°)$ ~1.500 (undistilled), is obtained in *ca.* 85% yield as a viscous liquid after removal of the Et_2O from the extracts: from the solution of KOBr (~0.3 mol), 60% is added dropwise over 30 min to a mixture of 0.32 mol (slight excess) of HC≡C$CH(CH_3)$OH and 40 ml of water. During this addition, the temperature of the mixture is kept between 5 and 10°C. After an additional 15 min (at 10°C) four extractions with Et_2O are carried out. The unwashed organic solutions are dried over $MgSO_4$.

PhC≡CBr, $n_D(20°)$ 1.606 (undistilled), is obtained in almost 100% yield by vigorously agitating over a 3-h period under N_2 (compare [128]) a mixture of 0.25 mol of PhC≡CH and the KOBr solution described above. The reaction is carried out in a 500-ml flask insulated by cotton wool. The initial temperature is *ca.* 20°C. After 2.5 h, the n_D of the upper layer (temporary interruption of stirring) has become ~1.605 and the temperature 31 to 33°C. After stirring for 3 h, the product is isolated by adding 200 ml of ice water and extracting four times with Et_2O. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*.

Other ArC≡CBr and 2-thienyl-C≡CBr (b.p. ~50°C/0.06 mmHg, $n_D(20°)$ 1.6469) can be prepared in a similar way.

C_3H_7CH=CHC≡CBr (*E*/*Z*-mixture) is prepared in a way similar to that described for PhC≡CBr. After 4 to 5 h, the n_D of the upper layer reaches a maximum (~1.51). The mixture is then extracted with very small portions of pentane. The combined organic solutions are concentrated *in vacuo* (bath temperature < 25°C) after drying over $MgSO_4$. The yield of the bromoenyne (undistilled, satisfactory purity) is at least 75%. Distillation (b.p. ~58°C/15 mmHg) gives the pure bromoenyne.

In the case of bromination of 1,3-diynes RC≡CC≡CH (R = CH_3 or higher alkyl), a small amount of pentane (~50% v/v) may be added as diluent and stirring (at 25-30°C) is continued for a few hours (monitoring may be carried out by determining the n_D of the mixture of diyne and pentane). The bromination is expected to take less time than in the case of enynes. Distillation of these bromodiynes seems risky.

4.4 Reaction of Alkynyllithium with Iodine in Organic Solvents

$$RC{\equiv}CLi + I_2 \xrightarrow[< -20^\circ C]{\text{THF or } Et_2O\text{-hexane}} RC{\equiv}CI + LiI$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Procedure

Finely powdered iodine (0.20 mol, the dropping funnel is replaced with a powder funnel) or a saturated solution of 0.20 mol of iodine in Et_2O or THF is added over 15 to 30 min to a solution or suspension of the lithiated acetylene (p. 24) in a mixture of Et_2O and hexane or THF and hexane with cooling between -15 and -30°C. After this addition, the cooling bath is removed and the temperature allowed to rise to about 0°C (suspensions of RC≡CLi may react more slowly). Water (200 ml) is then added with vigorous stirring, and, after separation of the layers, the aqueous layer is extracted with Et_2O (small amounts of I_2 can be removed with an aqueous $Na_2S_2O_3$ solution). The organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*, followed by distillation of the remaining liquid. $C_4H_9C{\equiv}CI$, b.p. 60°C/10 mmHg, $n_D(20^\circ)$ 1.5166, is obtained in > 80% yield. Volatile iodo-acetylenes (b.p. < 40°C/10 mmHg) can best be prepared using Et_2O as the only solvent. The lithium alkynylide is generated from the acetylene and EtLi.LiBr [1] in Et_2O (p. 24). For another useful procedure for volatile iodoacetylenes see exp.5. Acetylenic Grignard derivatives in Et_2O or THF also give iodoalkynes upon addition of iodine at -10 to -20°C.

4.5 Preparation of Iodoacetylenes from Lithiated Acetylenes and Iodine in Liquid Ammonia

$$RC{\equiv}CLi + I_2 \xrightarrow[< -40^\circ C]{\text{liq. } NH_3} RC{\equiv}CI + LiI$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Introduction

In the presence of water, iodine reacts with ammonia to give explosive NI_3 as a black precipitate. In anhydrous liquid ammonia at -33°C (or at lower temperatures) practically no conversion takes place, however. This appears most convincingly from the fact that aryl- or heteroaryl iodoacetylenes can be prepared in excellent yields by stirring a mixture of equimolar amounts of iodine and the acetylene in liquid ammonia for several hours [121]. For the less

acidic *alkyl*acetylenes, this method has no practical importance, since very long reaction times are needed. A much quicker procedure is to add iodine as a solution in Et_2O or THF to an ammoniacal solution of the lithiated acetylene, cooled to below -33°C : this reaction is almost instantaneous and generally gives iodoacetylenes in excellent yields. The volatile iodopropyne, for example, can be prepared by adding an ethereal solution of iodine to a solution of propynyllithium in ammonia cooled to below -60°C. Under these conditions the iodination proceeds almost instantaneously.

The alternative method for volatile iodoacetylenes - RC≡CLi + I_2 in Et_2O - is more time consuming, since it requires preparation of a solution of EtLi.LiBr from ethyl bromide and lithium in Et_2O [1]).

Procedure

A solution of 0.20 mol of alkynyllithium in about 250 ml of liquid ammonia is prepared as described on p. 20. *Propynyl*lithium and *butynyl*lithium can best be prepared by dropwise addition (over 20 min) of the 1,2-dibromoalkanes (0.20 mol, see Chap.IX) to a suspension of a slight excess of $LiNH_2$ (0.70 mol) in ~600 ml of liquid ammonia (compare Chap.VII, exp.5). The solutions in ammonia are cooled to below -60°C (occasional cooling in a bath with liquid N_2), while N_2 is passed through the flask (0.5 l/min). A solution of 0.25 mol (excess) of iodine in Et_2O (~300 ml) or THF (250 ml) is then added over ~15 min with efficient stirring, while keeping the temperature between -50 and -70°C (for the volatile iodoalkynes with b.p. < 50°C/15 mmHg, Et_2O should be used). After an additional 15 min (at ~ -50°C), the reaction mixture is cautiously poured onto 500 g of finely crushed ice, contained in a 2 to 3-l wide-necked conical flask. The reaction flask is rinsed with a small amount of ice water. A solution of 20 g of $Na_2S_2O_3$ in 150 ml of water is then added to the mixture. After melting of the ice (some warming may be applied) and vigorous shaking, the layers are separated. The aqueous layer is extracted three to five times with small portions of pentane (this gives a better separation than Et_2O). The combined organic solvents are dried over $MgSO_4$, after which the greater part of the solvent is removed: in the cases of $CH_3C{\equiv}CI$, $C_2H_5C{\equiv}CI$ and $C_3H_7C{\equiv}CI$, the Et_2O is distilled off at atmospheric pressure through a 40-cm Vigreux column, keeping the bath temperature below 100°C, in the other cases the solvent can be removed using a rotary evaporator. The remaining liquid is carefully distilled through a 40-cm Vigreux column under reduced pressure, appropriate for the volatility of the product: $CH_3C{\equiv}CI$, b.p. ~50°C/100 mmHg, $n_D(20^\circ)$ 1.5500, and $C_5H_{11}C{\equiv}CI$, b.p. 78°C/10 mmHg, $n_D(20^\circ)$ 1.5105, can be obtained in excellent yields.

4.6 Preparation of 1-Chloro-2-phenylacetylene from Lithium Phenylacetylide and Chlorine

$$PhC{\equiv}CLi + Cl_2 \xrightarrow[< -60^\circ C]{Et_2O\text{-hexane}} PhC{\equiv}CCl + LiCl$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Introduction

In analogy with the reaction of lithiated acetylenes with bromine, chloroalkynes can be prepared by chlorination of metallated acetylenes at low temperatures with free chlorine. Since the solvents Et_2O and THF are readily attacked by chlorine, introduction of gaseous chlorine seems a risky operation. In the procedure for 1-chloro-2-phenylacetylene, a solution of chlorine in dichloromethane (prepared by diluting liquified chlorine with strongly cooled dichloromethane) is added at a low temperature to a solution of lithium phenylacetylide in Et_2O and hexane. Presumably an aliphatic or alicyclic acetylene RC≡CH (R = alkyl or cycloalkyl) with a b.p. that is sufficiently higher than that of hexane, can be prepared in a similar way. For chloroalkynes containing double bonds or other chlorine-sensitive groups, the procedure of exp. 4.1 seems better. Instead of lithiated acetylenes, Grignard derivatives can be employed. Since chlorine can react with $MgBr_2$ to give free bromine, the acetylenic Grignard derivatives have to be prepared with alkylmagnesium *chlorides*.

Procedure

A solution of 0.20 mol of lithium phenylacetylide in 140 ml of hexane and 150 ml of Et_2O (p. 24) is cooled to below -60°C. A mixture of 0.20 mol of chlorine and 30 ml of dry dichloromethane (prepared just before, by adding the strongly cooled solvent to the liquified chlorine) is added by pouring from the cold trap, over about 10 min to the vigorously stirred solution which is kept below -70°C. Occasional cooling in a bath with liquid N_2 allows this quick addition. After an additional 2 min, the mixture is hydrolysed, the layers separated and the organic solution dried over $MgSO_4$. After evaporation of the solvent *in vacuo* the remaining liquid is distilled through a 30-cm Vigreux column to give the chloroacetylene in greater than 80% yield (compare exp. 4.1). Since lithium alkynylides that are more strongly basic than PhC≡CLi, react easily with CH_2Cl_2, it is better to add the chlorine portionwise as a solution in strongly cooled pentane or hexane (< -50°C) in these cases.

4.7 Preparation of Alkynenitriles by Reaction of Alkynyllithium with Cyanogen Chloride

$$RC{\equiv}CLi + ClC{\equiv}N \xrightarrow[-40 \rightarrow +20^\circ C]{Et_2O\ (hexane)} RC{\equiv}CC{\equiv}N + LiCl\downarrow$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Introduction

In 1926, Grignard [114] published the synthesis of alkynenitriles from acetylenemagnesium halides and cyanogen chloride. We found [115] that good results can also be obtained by using lithiated acetylenes, which can be prepared more quickly from acetylenes and alkyllithium (see p. 24). Acetylenic nitriles are extremely base-sensitive. Therefore, the inversed addition procedure, *i.e.* adding the lithiated acetylene to a small excess of cyanogen chloride, is preferred to the usual way of addition. For the same reason, Et_2O seems to be a better solvent than the more polar THF. Cyanogen *bromide* is attacked on bromine to give bromoalkynes in good yields (see exp. 8).

The cyanation with cyanogen chloride is not a general reaction. 2-Thienyllithium, for example, reacts with ClC≡N to give mainly 2-chlorothiophene [2].

Warning

Cyanogen chloride is extremely poisonous. The experiments should be carried out in a well-ventilated hood.

Procedure

A solution of the lithiated acetylene (0.20 mol in 180 ml of Et_2O and 140 ml of hexane, (p. 24) is added over 30 min to a solution of 0.25 mol of cyanogen chloride (note 1) in 100 ml of Et_2O. During this addition, the temperature of the reaction mixture is kept between -20 and -10°C. In the case of $CH_3C{\equiv}CLi$ and $C_2H_5C{\equiv}CLi$, no hexane co-solvent is used and the suspensions (prepared from the alkynes and EtLi.LiBr in Et_2O [1]), are added portionwise to the ethereal solution of ClC≡N with cooling between -5 and + 5°C. The conversions are completed by stirring for an additional 30 min at 10-20°C, and in the cases of $CH_3C{\equiv}CLi$ and $C_2H_5C{\equiv}CLi$, for 2-3 h at this temperature. The brown suspensions are then poured into 500 ml of ice water. After vigorous shaking, the layers are separated. The dark-brown aqueous layers are extracted four times with small portions of pentane. The (unwashed) organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. In the cases of $CH_3C{\equiv}CC{\equiv}N$ and $C_2H_5C{\equiv}CC{\equiv}N$, however, the greater part of the solvent is slowly distilled off at normal pressure through a 40-cm Widmer column.

In all cases, the remaining brown liquids are subjected to a "flash"-distillation in vacuum and the distillate collected in a strongly cooled receiver (fig.14). For volatile nitriles a water-pump vacuum is applied, for less volatile nitriles an oil-pump vacuum. Redistillation affords the pure nitriles. The compound $CH_3C{\equiv}CC{\equiv}CC{\equiv}N$ is not distilled: the solid, light-brown residue remaining after removal of the solvent, is recrystallized from pentane at low temperature (< -20°C).

The following compounds have been prepared in greater than 75% yields:

$CH_3C{\equiv}CC{\equiv}N$, b.p. 109°C/760 mmHg, $n_D(20^\circ)$ 1.4340;

$C_2H_5C{\equiv}CC{\equiv}N$, b.p. 125°C/760 mmHg, $n_D(20^\circ)$ 1.4387;

$C_4H_9C{\equiv}CC{\equiv}N$, b.p. 56°C/15 mmHg, $n_D(20^\circ)$ 1.4501;

1-cyclohexenyl-C≡CC≡N, b.p. 95°C/15 mmHg, $n_D(20^\circ)$ 1.5421;

$CH_3C{\equiv}CC{\equiv}CC{\equiv}N$, m.p. 95-96°C;
$C_6H_{13}C{\equiv}CC{\equiv}N$, b.p. 85°C/15 mmHg, $n_D(20°)$ 1.4531.

Notes

1. Cyanogen chloride is commercially available (expensive lecture bottles) but can also be prepared from chlorine and sodium cyanide. Since we experienced the procedure in Inorganic Syntheses [109] as rather tedious, we developed a simpler procedure. Chlorine (1.0 mol, liquified in a cold trap) is introduced over 1 h into a suspension of 2 mol of finely powdered $NaC{\equiv}N$ in 300 ml of CCl_4, to which 4 ml of acetic acid has been added. The temperature of the suspension is maintained between -5 and -10°C. After an additional 5-h period of stirring (at -5°C) the suspension is filtered through a large plug of glass wool, placed in a funnel, and the solid rinsed with four 25-ml portions of CCl_4. If the filtrate still contains chlorine (yellow solution) it is stirred for 1-2 h at -5°C with an additional amount of 25 g of powdered $NaC{\equiv}N$ (after addition of 2 ml of acetic acid) and the filtration procedure repeated. The filtrate is then heated in a normal distillation apparatus (30-cm Vigreux column, condenser cooled in ice water) and the $ClC{\equiv}N$ collected in a receiver cooled between 0 and -5°C (fig.14)). The contents of the receiver are then redistilled and the distillate (yield ~35%) dissolved in a *weighed* amount of dry Et_2O. The solution can be stored for several months at -20°C without deterioration.

4.8 Preparation of 1-Bromo-1-alkynes from Alkynyllithium and Cyanogen Bromide

$$RC{\equiv}CLi + BrC{\equiv}N \xrightarrow[-70 \rightarrow -30°C]{\text{THF-hexane}} RC{\equiv}CBr + LiC{\equiv}N\downarrow$$

Warning

This experiment should be carried out in a well-ventilated hood.

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

A convenient and quick way to prepare 1-bromoalkynes consists of adding an ethereal solution of cyanogen bromide to a strongly cooled solution of a metallated (Li or MgX) [119] acetylene in an organic solvent (Et_2O or THF). The method seems very general and excellent yields can be obtained provided that the ethereal solution of $BrC{\equiv}N$ (which is prepared from an aqueous solution) is dried well. The advantage of this method over the introduction with elemental bromine is that CC double bonds in the acetylenic compounds do not react.

Procedure

A solution of cyanogen bromide in about 150 ml of Et_2O (note 1), prepared from 0.25 mol (large excess) of bromine and potassium cyanide is added over 15 min to a solution of 0.10 mol of the lithiated acetylene (pag. 24) in 70 ml of hexane and 80 ml of THF (note 2). During this addition the temperature is maintained between -70 and -50°C. After an additional period of 10-15 min (at -30 to -40°C) water (200 ml) is added with vigorous stirring to the white suspension. After separation of the layers, three extractions with Et_2O are carried out. The combined organic solutions are dried over $MgSO_4$, after which the solvent is removed *in vacuo* (if the volatility of the product allows it). The remaining liquid is carefully distilled through a 30-cm Vigreux column.

1-Bromo-1-octyne, b.p. 90°C/15 mmHg, $n_D(20°)$ 1.4663, and 1-cyclohexenyl-$C{\equiv}CBr$, b.p. 50°C/0.5 mmHg, $n_D(20°)$ 1.5498, are obtained in ~80% yields. Distillation should not be carried out in the case of thermally unstable bromoalkynes, e.g. $RC{\equiv}CC{\equiv}CBr$.

Notes

1. The procedure from Organic Synthesis, [132]), in which the $KC{\equiv}N$ is added over 2 h and the BrCN is isolated by steam distillation, is modified. To a vigorously stirred mixture of 0.25 mol of bromine and 40 ml of water is added over 10 min a solution of 0.25 mol of potassium cyanide in 50 ml of water. During this addition the reaction mixture is cooled between 0 and 10°C. The white suspension of cyanogen bromide is subsequently extracted three times with small portions (total amount ~120 ml) of Et_2O. The (unwashed) colourless extract is first shaken at 0°C with a relatively small amount of potassium carbonate, then decanted and subsequently vigorously shaken (with cooling at 0 to -10°C) with a small portion of P_2O_5. The solution is decanted from the syrupy mass and shaken with a second small portion of P_2O_5 (which now remains suspended; if not, the procedure is repeated).
2. The reaction with cyanogen bromide presumably can also be carried out succesfully with $RC{\equiv}CLi$ in Et_2O-hexane mixtures or with acetylenic Grignard derivatives (at higher temperatures) in Et_2O or THF.

Chapter IX
Introduction of the Triple Bond by Elimination and Addition-Elimination Reactions

1. Survey of Methods

Methods based upon elimination can be used to synthesise a wide variety of acetylenic compounds. For compounds such as HC≡C-*t*-Bu, HC≡COC_2H_5 and *t*-BuC≡CNO_2 no alternative preparative method is available.

In this chapter we give a brief survey of the most important elimination methods and some special ones. For extensive reviews the reader is referred to the chapters of Köbrich and Buck in ref. 6 and Jäger and Viehe in ref. 10a.

1.1 Double Dehydrohalogenation from Geminal and Vicinal Dihalogeno Compounds

$RCCl_2CH_3$; RCH_2CHCl_2 (or Br_2); $RCHBrCH_2Br$ (or Cl); $RCHBrCHBrR$ (or Cl).

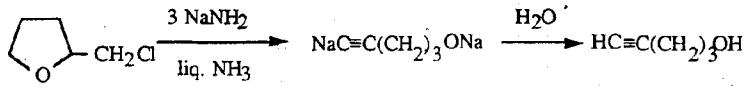
Sodamide in liquid ammonia generally gives good results, except in the cases where R = CH_3O or C_2H_5O. Since sodium alkynylide is formed, at least three equivalents of sodamide are required for the complete conversion of the halogen compound. Other bases, *e.g.* potassium hydroxide or sodium ethoxide in ethanol, are in most cases not reactive enough and the elimination stops at the stage of the vinylic halide. Phenylacetylene, however, can be successfully prepared by heating $PhCHBrCH_2Br$ with ethanolic sodium ethoxide. A recent paper from Dehmlow [133] reports the preparation of a number of 1-alkynes by heating a 1,2-dibromoalkane with powdered KOH in the presence of a phase-transfer catalyst [$(Oct)_4N^+Cl^-$] and pinacol. It may be expected (see also exps. 1 and 2) that several acetylenic compounds can be successfully prepared by this method, and many chemists will probably prefer this method to existing routes such as the elimination with alkali amides in liquid ammonia or other basic systems like butyllithium [134], lithium dialkylamides [135], and potassium *tert*-butoxide (in DMSO [136] or in organic solvents in the presence of crown ethers [137]).

1.2 1,2-Elimination of Hydrogen Halides and Alcohol

Methoxyethyne and ethoxyethyne are obtained in good yields by treating the (commercially available) chloroacetaldehyde acetals with three equivalents of sodamide in liquid ammonia (compare [138]):

$$ClCH_2CH(OR)_2 \xrightarrow[\text{liq. } NH_3]{3\ NaNH_2} [ClCH{=}CHOR] \rightarrow NaC{\equiv}COR \xrightarrow{H_2O} HC{\equiv}COR$$

A related elimination is the formation of 4-pentyn-1-ol from tetrahydrofurfuryl chloride and sodamide [139]:



1.3 Elimination of Hydrogen Halide from Halo-olefinic Compounds

In a few cases, either double elimination from dihalogeno compounds is not feasible, or the dihalo compound is not available. 1,2-Dibromoethyl ethyl ether $BrCH_2CH(Br)OC_2H_5$, for example, does not give ethoxyethyne upon treatment with alkali amide (or other bases) probably as a consequence of the fact that the α-halogen atom is very prone to nucleophilic displacement [2]. In order to convert the dibromoether into ethoxyethyne, one molecule of HBr has to be eliminated first by heating with diethylaniline. The resulting *E/Z* mixture of the bromo ether $BrCH{=}CHOC_2H_5$ is treated with two equivalents of sodamide in liquid ammonia to give $NaC{\equiv}COC_2H_5$ (both isomers are converted) or with powdered KOH [24,140] (only the *Z*-isomer reacts).

Another useful example is the elimination of hydrogen iodide with KOH from the compounds $RC(I){=}CHNO_2$, accessible by addition of NO_2I (formed in situ from N_2O_4 and I_2) to acetylenes [141]:

$$RC{\equiv}CH \xrightarrow{N_2O_4 + I_2} RC(I){=}CHNO_2 \xrightarrow[\Delta]{KOH} RC{\equiv}CNO_2$$

1.4 1,4-Elimination of Hydrogen Chloride

The readily available 1,4-dichloro-2-butene and 1,4-dichloro-2-butyne undergo 1,4-elimination upon heating with powdered and aqueous potassium hydroxide, respectively, giving vinylacetylene and butadiyne in excellent yields [142]. In the case of dichlorobutyne, chlorobutatriene is formed as a short-lived intermediate. It can be isolated (together with some butadiyne) by treating dichlorobutyne with powdered KOH in a vacuum of 1 mmHg or better, collecting the reaction products in a strongly cooled receiver [2]. The 1,4-eliminations also take place with alkali amides in liquid ammonia. The alkali compounds of vinylacetylene and diacetylene so obtained can be converted into a number of derivatives (see Chap. III and IV).

$$ClCH_2CH{=}CHCH_2Cl \xrightarrow[\text{liq. } NH_3]{3\ NaNH_2} NaC{\equiv}CCH{=}CH_2$$

$$ClCH_2CH{=}CHCH_2Cl \xrightarrow{KOH} ClCH{=}CHCH{=}CH_2 \longrightarrow HC{\equiv}CCH{=}CH_2$$

$$ClCH_2C{\equiv}CCH_2Cl \xrightarrow{3 \text{ or } 4\ NaNH_2} NaC{\equiv}CC{\equiv}CH \text{ or } NaC{\equiv}CC{\equiv}CNa$$

$$ClCH_2C{\equiv}CCH_2Cl \xrightarrow{KOH} ClCH{=}C{=}C{=}CH_2 \longrightarrow HC{\equiv}CC{\equiv}CH$$

1.5 1,4-Elimination of Alcohol from 2-Alkynyl Ethers

2-Alkynyl ethers, $RCH_2C{\equiv}CCH_2OR'$ and $CH_3C{\equiv}CCH(R)OR'$, are converted into 3,1-enynes by treatment with sodamide in liquid ammonia. The reactions may be visualized as 1,4-eliminations of ethanol and subsequent metallation of the intermediary cumulenes [143]:

$$RCH_2C{\equiv}CCH_2OR' \xrightarrow{^-NH_2} RCH{=}C{=}C{=}CH_2 \xrightarrow{^-NH_2} RCH{=}CHC{\equiv}C^- \xrightarrow{H_2O} RCH{=}CHC{\equiv}CH$$

R = alkyl or O-alkyl

$$CH_3C{\equiv}CCH(R)OR' \xrightarrow{^-NH_2} H_2C{=}C{=}C{=}CHR \longrightarrow {}^-C{\equiv}C\text{-}CH{=}CHR$$

R = alkyl or O-alkyl

$$CH_3C{\equiv}CC(R)(R')OR'' \longrightarrow H_2C{=}C{=}C{=}CRR' \longrightarrow {}^-C{\equiv}CCH{=}CRR'$$

R and R' = alkyl or CRR' = cycloalkyl

In general, this synthesis of enynes has no special advantages over the alternative method which starts with allenylmagnesium bromide [144]:

$$HC{\equiv}CCH_2Br \xrightarrow[Et_2O]{Mg(HgCl_2)} H_2C{=}C{=}CHMgBr \xrightarrow{RR'C=O} HC{\equiv}CCH_2C(OH)RR' \xrightarrow{\text{Tosyl chloride}} HC{\equiv}CCH_2C(OTs)RR' \xrightarrow{KOH} HC{\equiv}CCH{=}CRR'$$

If both R and R' are alkyl, however, the tosylate $HC{\equiv}CCH_2C(OTs)RR'$ cannot be prepared. Thus, for enynes $HC{\equiv}CCH{=}CRR'$ in which R and R' are alkyl or CRR' is cycloalkyl, the elimination of R'OH from $CH_3C{\equiv}CC(R)(R')OR''$ with sodamide in liquid ammonia is the method of choice.

For enyne ethers $HC{\equiv}CCH{=}CHOR$, the 1,4-elimination with alkali amides is a very attractive method because the starting compounds $ROCH_2C{\equiv}CCH_2OR$ can be readily prepared from the commercially available butynediol.

1.6 1,4-Elimination from $R_2NCH_2C{\equiv}CCH_2OR$ and $RSCH_2C{\equiv}CCH_2SR$

Treatment of the readily accessible compounds $R_2NCH_2C{\equiv}CCH_2OR$ and $RSCH_2C{\equiv}C$-$-CH_2SR$ with *t*-BuOK in THF or liquid NH_3 (in the case of the bis-thioethers) affords enyne amines $R_2NC{\equiv}CCH{=}CH_2$ [145] and the analogous sulfides $RSC{\equiv}CCH{=}CH_2$ [146] in good to excellent yields. The schemes below represent the two possible reaction paths (analogous for $RSCH_2C{\equiv}CCH_2SR$):

$$R_2NCH{=}C{=}CHCH_2OR \xleftarrow{\text{isom.}} R_2NCH_2C{\equiv}CCH_2OR \xrightarrow{\text{1,4-elim.}} R_2NCH{=}C{=}C{=}CH_2$$

$$\downarrow \text{1,4-elimination} \qquad\qquad \downarrow \text{isomerisation}$$

$$R_2NC{\equiv}CCH{=}CH_2 \qquad\qquad R_2NC{\equiv}CCH{=}CH_2$$

Representative procedures have been described in ref. 4.

1.7 1,6-Eliminations

Double 1,6-dehydrochlorination of 1,6-dichloro-2,4-hexadiyne, analogous to the formation of butadiyne from 1,4-dichloro-2-butyne and strongly basic reagents, was described for the first time by Bohlmann and Jones *et al.* [147]. The extremely unstable 1,3,5-hexatriyne was obtained in a moderate yield as a dilute solution in an organic solvent.

$$ClCH_2C{\equiv}CC{\equiv}CCH_2Cl \xrightarrow[\text{liq. } NH_3]{NaNH_2} NaC{\equiv}CC{\equiv}CC{\equiv}CH \xrightarrow{H_2O} HC{\equiv}CC{\equiv}CC{\equiv}CH$$

Meijer [2] in our laboratory prepared hexatriyne in an excellent yield (as a solution in an organic solvent) by carrying out the elimination with *t*-BuOK in THF at low temperatures.

1.8 1,2-Elimination of Thiol from Vinylic Sulfides

Strong bases readily eliminate thiol from vinylic sulfides. 1,2-Bis(alkyl- or arylthio)ethynes for example, react with two equivalents of BuLi or alkali amide to give metallated alkyl- or arylthioacetylenes and thiolates [24]:

$$RSCH{=}CHSR \xrightarrow{B^-} {}^-C{\equiv}CSR + RS^-$$

In most cases, this reaction has no preparative importance, but analogous eliminations have been applied to synthesise special acetylenes [2,149,150]:

$$H_2C{=}C(SR)NMe_2 \xrightarrow[\text{HMPT}]{KNH_2} KC{\equiv}CNMe_2 + KSR$$

$$RC{\equiv}CCH{=}CHSR' \xrightarrow[\text{liq. } NH_3]{KNH_2} RC{\equiv}CC{\equiv}CK + KSR' \qquad R = (Alkyl)_2NCH_2,\ R''C{\equiv}C,\ etc.$$

Z-Methoxybutenyne has been converted into dimetallated butadiyne by using an excess of alkyllithium [151]:

$$HC{\equiv}CCH{=}CHOCH_3 \xrightarrow{RLi} LiC{\equiv}CC{\equiv}CLi + CH_3OLi$$

1.9 1,1-Elimination of Hydrogen Halide with Simultaneous Migration

Fritsch, Wiechell and Buttenberg [152] discovered a peculiar rearrangement to $PhC{\equiv}CPh$ during treatment of $Ph_2C{=}CHCl$ with strong bases. Mechanistic investigations [153] showed that halide is eliminated from the initial carbenoid $Ph_2C{=}C^-Cl$, with simultaneous migration of the group that is in the *trans*-position of the leaving halide. The reaction has little significance as a preparative method for disubstituted acetylenes, except in the case of bis(dialkylamino)acetylenes) [154,155].

$$(R_2N)_2C{=}CHCl \xrightarrow[KNH_2]{\text{LDA or}} [(R_2N)_2C{=}C^-Cl] \longrightarrow R_2NC{\equiv}CNR_2$$

1.10 1,2-Elimination of Chlorine from Vicinal Dichlorides

Ficini *et al.* [156] prepared a number of yneamines by treating the readily accessible trichloroenamines [157] with alkyllithium:

$$Cl_2C{=}C(Cl)NR_2 \xrightarrow[Et_2O]{R'Li} ClC{\equiv}CNR_2 \xrightarrow{R'Li} LiC{\equiv}C\text{-}NR_2 + R'Cl$$

A rather difficult experimental problem is the liberation and isolation of the extremely water-sensitive ethynylamines $HC{\equiv}CNR_2$.

1.11 Addition-Elimination Procedures

Treatment of 1-alkynylethers and 1-chloroalkynes with lithium dialkyl amide gives rise to a displacement of the heteroatom by the amino function [158,159]. The reactions are assumed to proceed *via* an adduct:

$$R'C{\equiv}CX + LiNR_2 \longrightarrow R'C(Li){=}C(X)NR_2 \xrightarrow{-LiCl} R'C{\equiv}CNR_2$$

In the case of chloroalkynes a second mechanism has to be seriously considered [160]:

$$R'C{\equiv}CCl + LiNR_2 \longrightarrow R'C(NR_2){=}C(Li)Cl \xrightarrow[\text{migration}]{-LiCl} R'C{\equiv}CNR_2$$

Analogous *1,3*-substitutions take place when cumulenic ethers and Grignard compounds are allowed to interact in the presence of catalytic quantities of copper(I) salts. Organocopper compounds are the presumed intermediates [163,164].

$$H_2C{=}C{=}CHOCH_3 + RMgBr \xrightarrow{Et_2O,\ CuBr} RCH_2C{\equiv}CH + CH_3OMgBr$$

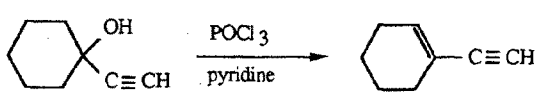
$$H_2C{=}C{=}C{=}CHOC_2H_5 + RMgBr \xrightarrow{idem} H_2{=}\underset{\displaystyle R}{\underset{|}{C}}C{\equiv}CH + C_2H_5OMgBr$$

Experimental procedures for $PhCH_2C{\equiv}CH$, cycloalkyl-$CH_2C{\equiv}CH$ and enynes, $HC{\equiv}C$-$C(R){=}CH_2$, have been described in ref. 4.

1.12 Methods for the Generation of Additional Unsaturation in Acetylenic Systems

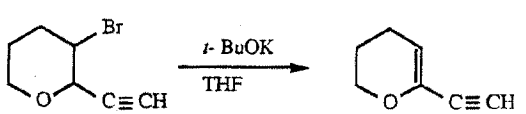
The schemes below illustrate useful methods for the generation of a double bond in conjugation with a triple bond, which is already present in the starting compound.

$$HC{\equiv}CC(CH_3)_2OH \xrightarrow[Ac_2O]{p\text{-tol. sulf. acid}} HC{\equiv}CC(CH_3){=}CH_2 \qquad [161]$$



[162]

$$HC{\equiv}CCH_2CH(OTs)CH_3 \xrightarrow{KOH} HC{\equiv}CCH{=}CHCH_3 \qquad [144]$$



[2]

2. Experiments

All temperatures are internal, unless indicated otherwise.

2.1 1-Butyne (phase-transfer method)

$$C_2H_5CHBrCH_2Br + 2\ KOH \xrightarrow[\text{petr. ether, } 90 \rightarrow 145°C]{\text{Aliquat, pinacol}} C_2H_5C{\equiv}CH\uparrow + 2\ KBr + 2\ H_2O$$

Scale: 0.50 molar.

Apparatus: 2-l round-bottomed, three-necked flask, equipped with a dropping funnel (combined with a gas inlet), a mechanical stirrer and a reflux condenser connected to a cold trap (-78°C; all connections are made gas-tight; a stirrer of the type displayed in fig. 3, is used.

Introduction

Many 1-alkynes can be prepared in high yields by adding bromine to 1-alkenes and subsequently treating the adduct with three equivalents of alkali amide in liquid ammonia: the 1-alkyne is liberated (after removal of the ammonia) by addition of water.

In a recent paper, Dehmlow *et al.* [133] describe a very attractive and simple method for the preparation of simple 1-alkynes: the 1,2-dibromo compound is heated with an excess of powdered potassium hydroxide at 80°C or higher temperatures in the presence of catalytic amounts of tetraoctylammonium halide and pinacol. The alkoxide of pinacol formed with KOH is extracted by the phase transfer catalyst (p.t.c.) into the organic phase where the double dehydrohalogenation occurs. The elimination can also be carried out with aqueous KOH and the p.t.c., but the rate of elimination is then much lower. In the procedures with powdered KOH, an inert solvent is used, *e.g.* petroleum ether. This has a double function in that it serves as a conductor of the heat supplied by the bath, and it ensures that the halogen compound is sufficiently mixed with the (larger excess of) KOH. For less volatile acetylenes, *e.g.* PhC≡CH (b.p. ~140°C at atmospheric pressure), a lower-boiling petroleum ether fraction (b.p. <100°C) should be used, while in the case of volatile acetylenes the halogen compound is diluted with higher boiling solvents. The choice of the solvent is also determined by the temperature required for a smooth dehydrohalogenation. For example, *t*-$BuCH_2CHCl_2$ and *t*-$BuCCl_2CH_3$ are converted only partially at temperatures below 120°C, rendering a high boiling (b.p. >150°C) solvent necessary. For the preparation of the compound *c*-C_6H_{11}-C≡CH from *c*-$C_6H_{11}CH_2CHCl_2$, the use of paraffin oil might be considered. The solid KOH-p.t.c. method cannot be applied to synthesise thermally less stable acetylenes, *e.g.* $C_2H_5OC{\equiv}CH$. Moreover, the starting compound $C_2H_5OCHBrCH_2Br$ is likely to undergo other reactions. Neither can acetylenes that easily undergo base-catalysed isomerization reactions be prepared by this method.

Procedure

Freshly and finely **machine-powdered** potassium hydroxide (85%, 6 mol) and high- boiling petroleum ether (b.p. >170°C, 250 ml) are placed in the flask. Methyl trioctylammonium chloride (75% aqueous solution, 7 g) and anhydrous pinacol (7 g) are added with vigorous stirring. The suspension is heated to about 90°C (temperature oil bath) and 1,2-dibromobutane (0.50 mol, exp. 27, thoroughly freed from solvent) is added dropwise over 20 min. A temporary vigorous reflux (presumably a mixture of $C_2H_5C(Br)=CH_2$ and $C_2H_5CH=CHBr$) is observed. The temperature of the bath is gradually raised over 30 min to 120°C. During this period the intensity of reflux decreases while butyne begins to condense in the cold trap. When the reflux has practically stopped, the temperature of the bath is raised to 140-145°C and kept at this level for an additional hour. The dropping funnel is then replaced by a gas inlet tube, reaching to the middle of the flask. Nitrogen (500 ml/min) is then passed through the flask for 10 min. Finally, the trap containing the butyne is connected to another trap cooled at -78°C and then placed in a water bath which is gradually warmed (initial temperature 15°C) to *ca.* 50°C. Pure 1-butyne is obtained in 72-85% yield.

2.2 *t*-Butylacetylene (phase-transfer method)

$$t\text{-BuCH}_2\text{CHCl}_2 + 2\ \text{KOH} \xrightarrow[\text{petr. ether, } 120 \rightarrow 150^\circ\text{C}]{\text{Oct}_3\text{N(CH}_3\text{)Cl + pinacol}} t\text{-BuC}{\equiv}\text{CH} + 2\ \text{KCl} + 2\ \text{H}_2\text{O}$$

Scale: 0.5 molar.

Apparatus: 2-l round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer (fig. 3) and a 40-cm Vigreux column, connected to a condenser and receiver, cooled in an ice-water bath.

Procedure (for Introduction see exp. 1)

Freshly machine-powdered KOH (85%, 9 mol) and high-boiling petroleum ether (200 ml, b.p. >170°C/760 mmHg) are placed in the flask. Stirring is started and the suspension is heated to 130°C (oil bath). Methyl trioctylammonium chloride or tetraoctylammonium chloride (70% aqueous solution, 10 g) and anhydrous pinacol (10 g) are added, followed by 0.5 mol of $t\text{-BuCH}_2\text{CHCl}_2$ (exp. 31, or a mixture of $t\text{-BuCCl}_2\text{CH}_3$ and $t\text{-BuC(Cl)=CH}_2$). *t*-Butylacetylene begins to distil out after some 15-30 min. The temperature of the bath is gradually raised over 1 h to 155°C and subsequently to 160°C over an additional hour. When distillation has stopped, the suspension (part of the KOH may form a liquid layer at the bottom of the flask) is allowed to cool. The distillate is redistilled through a 40-cm Vigreux column, to give *t*-butylacetylene, b.p. 38-40°C, $n_D(20^\circ)$ 1.3750, in 58-62% yield.

An additional 5-12% yield of the acetylene may be obtained by evacuating the apparatus (after cooling to below 40°C) and collecting the volatile product in a receiver cooled at -78°C.

Isopropylacetylene (b.p. ~28°C) can be prepared using a similar procedure.

2.3 *t*-Butylacetylene (Dehydrohalogenation with *t*-BuOK in DMSO)

$$t\text{-BuCH=CH}_2 + \text{Br}_2 \xrightarrow[< -30^\circ\text{C}]{\text{Et}_2\text{O}} t\text{-BuCHBrCH}_2\text{Br}$$

$$t\text{-BuCHBrCH}_2\text{Br} + 2\ t\text{-BuOK} \xrightarrow{\text{DMSO}} t\text{-BuC}{\equiv}\text{CH} + 2\ \text{KBr} + 2\ \text{HO-}t\text{-Bu}$$

Scale: 0.20 molar.

Apparatus: 1-l two-necked flask connected to a 40-cm Vigreux column, condenser and receiver; on the other neck of the flask is placed a dropping funnel.

Introduction

t-Butylacetylene can be prepared quickly by dehydrohalogenating the adduct of bromine and (commercially available) neohexene with *t*-BuOK in DMSO. Since the *t*-butyl alcohol produced in the dehydrohalogenation forms a 1:1 complex with *t*-BuOK which is less reactive, an excess of base is required for a smooth conversion. This method is unsuitable for the preparation of primary (and possibly also secondary) alkylacetylenes, since the base is likely to cause a rapid isomerization of the 1-alkyne to a 2-alkyne. For hetero- substituted acetylenes HC≡CXR (X = O or S), this method seems unsuitable (too aggressive reaction conditions), while arylacetylenes such as PhC≡CH can be prepared in a more economic way.

Procedure

The adduct of bromine and neohexene (carefully freed from traces of solvent, 0.20 mol, exp. 27) is added over 5-10 min to a solution of 0.50 mol of *t*-BuOK in 140 ml of DMSO. During this addition the flask is gently swirled to effect homogenization. A vigorous reaction takes place and part of the *t*-butylacetylene passes over into the single receiver which is cooled at -78°C. The flask is then heated for 30 min in a bath at 100°C. After cooling to 30°C, the dropping funnel is replaced with a stopper and the apparatus is evacuated. Traces of dissolved *t*-butyl- acetylene condense in the receiver. Redistillation of the contents of the receiver gives pure *t*-butylacetylene b.p. 38-40°C, $n_D(20^\circ)$ 1.3750, in greater than 80% yield.

2.4 Phenylacetylene

$$\text{PhCH=CH}_2 + \text{Br}_2 \xrightarrow[< -10^\circ\text{C}]{\text{CH}_2\text{Cl}_2,} \text{PhCHBrCH}_2\text{Br}$$

$$\text{PhCHBrCH}_2\text{Br} + 2\ \text{NaOC}_2\text{H}_5 \xrightarrow[\text{reflux}]{\text{C}_2\text{H}_5\text{OH}} \text{PhC}{\equiv}\text{CH} + 2\ \text{C}_2\text{H}_5\text{OH} + 2\ \text{NaBr}{\downarrow}$$

Scale: 0.50 molar.

Apparatus: 1-l three-necked, round-bottomed flask, equipped with a dropping funnel, a mechanical stirrer and a thermometer-outlet combination, which for the dehydrohalogenation is replaced with a reflux condenser.

Introduction

Although phenylacetylene can be prepared in excellent yields by treating the adduct of bromine and styrene with sodamide in liquid ammonia, the "classical" procedure using sodium ethoxide in ethanol is likely to be preferred by most chemists. In fact, the applicability of the latter method is very limited: 1,2-dibromoalkanes, alkyl-$CHBrCH_2Br$, and sodium ethoxide initially give a mixture of alkyl-$C(Br)=CH_2$ and alkyl-CH=CHBr. Both vinylic bromides react sluggishly with $NaOC_2H_5$ (Z-alkyl-CH=CHBr probably does not react at all). The excellent yields of alkynes obtained from 1,2-dibromoalkanes under the phase-transfer conditions suggest that also *syn*-elimination of hydrogen halide occurs (see exp. 1 and 2). In the case of $PhCHBrCH_2Br$ only $PhC(Br)=CH_2$ is formed as an intermediate (see ref. 1: Chap. III). The further conversion into PhC≡CH proceeds rather smoothly with sodium ethoxide in refluxing ethanol.

Diphenylacetylene can be prepared in an excellent yield from PhCHBrCHBrPh and ethanolic potassium hydroxide [165]. It should be possible to prepare heteroarylacetylenes, *e.g.* 2-thienyl-C≡CH, from the olefins by a procedure similar to the one described below.

Procedure

Styrene (0.50 mol, free from polymers) and dichloromethane (350 ml) are placed in the flask. Bromine (0.50 mol plus a small excess, sufficient to give a persisting brown solution at the end) is added dropwise, while keeping the temperature below -20°C. The equipment is then removed and stoppers are placed on the two outer necks. The solvent is carefully removed on a rotary evaporator. The flask is then equipped as indicated above and a solution of 1.5 mol (excess) of sodium ethoxide in 550 ml of absolute ethanol (note 1) is added over 15 min to the solid. The temperature rises to 60°C or higher. When the evolution of heat has ceased, the mixture is heated at reflux for an additional period of 3 h. The suspension is then cooled to room temperature and poured into 2.5 l of water. Six to eight extractions with small portions of pentane (if Et_2O is used, relatively large amounts are needed in the first extractions) are carried out. The combined organic solutions are washed with cold dilute hydrochloric acid and subsequently dried over $MgSO_4$. The greater part of the solvent is then distilled off at atmospheric pressure. Distillation of the remaining liquid gives phenylacetylene, b.p. 40°C/15 mmHg, $n_D(20°)$ 1.5480, in 68-75% yield. The residue consists mainly of $PhC(Br)=CH_2$.

Notes

1. If 96% ethanol is used, the second elimination of HBr proceeds sluggishly and much $PhC(Br)=CH_2$ is isolated.

2.5 Cyclopentylacetylene and Cyclohexylacetylene

$$\text{Cycloalkyl-}CH_2CHCl_2 + 3\ NaNH_2 \xrightarrow[-33°C]{\text{liq. } NH_3} \text{Cycloalkyl-C}{\equiv}\text{CNa} + 2\ NaCl + 2\ NH_3$$

$$\text{Cycloalkyl-C}{\equiv}\text{CNa} \xrightarrow{H_2O} \text{Cycloalkyl-C}{\equiv}\text{CH}$$

Scale: 1.0 molar.

Apparatus: fig. 4, 5 l; stirrer, fig. 3.

Introduction

The title compounds can be prepared by the phase-transfer procedure of exp. 2 when a high-boiling (b.p. ≥ 200°C) petroleum ether fraction is used. The cycloalkylacetylenes presumably remain dissolved in the solvent (instead of the Vigreux column of exp. 2, a reflux condenser is used). After termination of the reaction (3-4 h heating at ~145°C) and cooling to room temperature, water is added and careful fractional distillation of the organic layer (water-pump vacuum, receiver cooled below -20°C) will give the desired cycloalkylacetylene.

The elimination procedure described below is merely offered as an alternative, which may be chosen when no mill is available for powdering KOH (indispensable in the phase-transfer method) or when no high-boiling petroleum ether is available.

The yields of the sodamide procedure are moderate and a considerable amount of resinous product, which may cause some difficulties during the work-up, is formed. The nature of the side reactions has not been investigated.

Procedure

A mixture of 1.0 mol of crude dichloride (exp. 31) and 150 ml of Et_2O is added dropwise over 1 h to a vigorously stirred suspension of 4.0 mol of sodamide (ref. 1) in 2.5 l of liquid ammonia. After an additional 30 min, stirring is stopped and the ammonia is allowed to evaporate overnight (fig. 11). After addition of 200 ml of pentane, ice water (~1 l) is added. Dissolution of the solid is effected by manual swirling. The layers are separated as completely as possible, the resinous material being filtered off on a sintered-glass funnel and rinsed with Et_2O or pentane. After drying the combined organic solutions over $MgSO_4$, the greater part of the solvent is distilled off at atmospheric pressure through a 40-cm Vigreux column and the remaining liquid subjected to a rough distillation, using a strongly cooled receiver (fig. 14). Redistillation of the contents of the receiver through a 30-cm Vigreux column gives cyclopentylacetylene, b.p. 105°C/760 mmHg, $n_D(20°)$ 1.4412, and cyclohexylacetylene, b.p. 131°C/760 mmHg, $n_D(20°)$ 1.4550, in ~35-40% yields.

The dehydrohalogenation of cycloalkyl-$C(Cl_2)CH_3$ (from the ketones and PCl_5) can be carried out by a similar procedure.

2.6 1,5-Hexadiyne

$$BrCH_2CH(Br)CH_2CH_2CH(Br)CH_2Br + 6\ NaNH_2 \xrightarrow[-33°C]{\text{liq. } NH_3} NaC{\equiv}CCH_2CH_2C{\equiv}CNa + 4\ NaBr{\downarrow} + 4\ NH_3$$

$$NaC{\equiv}CCH_2CH_2C{\equiv}CNa + 2\ H_2O \longrightarrow HC{\equiv}CCH_2CH_2C{\equiv}CH + 2\ NaOH$$

Scale: 0.50 molar.

Apparatus: fig. 8, 5 or 6 l; stirrer: fig. 3.

Introduction

1,5-Hexadiyne cannot be prepared by reaction of alkali acetylide with 1,2-dibromoethane because this bromo compound undergoes extensive dehydrohalogenation with most strongly basic nucleophiles. Starting from allyl bromide, the diyne can be synthesised with good overall yields: Würtz-coupling of allyl bromide under "Grignard" conditions gives 1,5-hexadiene, which can *in situ* be converted into tetrabromohexane. The dehydrobromination is carried out with sodamide in liquid ammonia. Prior to adding the bromo compound to the alkali amide, the greater part of the diethyl ether, the solvent of the bromination, is removed by evaporation under reduced pressure. When, after the removal of the ammonia, the reaction mixture is hydrolysed, only small amounts of Et_2O are still present. The actual solvent with which the diyne is extracted is high-boiling petroleum ether.

Procedure

A concentrated solution of 0.50 mol of tetrabromohexane in ~75 ml of Et_2O (prepared by concentrating the solution *in vacuo*, for the preparation of the solution see exp. 36) is added over 15-25 min (adding by means of a syringe is most convenient) to an efficiently stirred suspension of 3.5 mol of sodamide [1,3,4] in 2.5 l of liquid ammonia (original volume). The reaction is very vigorous. The stirrer is removed immediately after the addition, 250 ml of high-boiling (b.p. ≥ 180°C) petroleum ether is added, and the flask is placed in a water bath at 40°C. When the flow of escaping ammonia vapour begins to diminish, a rubber stopper having a wide hole is placed on the flask. Heating is continued until the flow has become weak. Crushed ice (1 kg) is then added very quickly (over a few seconds), after which the flask is vigorously swirled by hand. After the remaining ice has melted, the layers are separated and the aqueous phase is extracted twice with 50-ml portions of petroleum ether. The combined extracts are washed with 3N hydrochloric acid (to remove some ferric hydroxide gel) and dried over $MgSO_4$. The solution is then gradually heated in a distillation

apparatus (40-cm Vigreux column, receiver cooled at -78°C, see fig. 14) until some 5 ml of petroleum ether has passed over. Careful redistillation of the contents of the receiver gives 1,5-hexadiyne, b.p. 87°C/760 mmHg, $n_D(20°)$ 1.4387, in 66-75% yield.

2.7 Ethoxyethyne from 2-Bromovinyl Ethyl Ether and Potassium Hydroxide

$$BrCH{=}CHOC_2H_5 + KOH \xrightarrow{\Delta} HC{\equiv}COC_2H_5 + KBr + H_2O$$

Scale: 0.50 molar.

Apparatus: 1-l round-bottomed flask, which is connected to a distillation system consisting of a 30-cm Vigreux column, condenser and receiver, cooled at -78°C (fig. 14).

Introduction

The procedure below is the most convenient and quick way to prepare ethoxyethyne [24]. Yields are usually excellent provided that the Z-isomer is the major component in the mixture of isomers of the bromovinyl ether. The *E*-isomer remains unchanged under the conditions of the elimination (rule of *trans*-elimination). The bromovinyl ether can be prepared in good yields starting from ethyl vinyl ether.

Procedure

Freshly machine-powdered potassium hydroxide (85%, 3.0 mol) is placed in the flask. 2-Bromovinyl ethyl ether (rich in the Z-isomer) (0.50 mol, exp. 28) is added in one portion and the mixture is directly shaken or swirled (by hand) to a slurry which should be as homogeneous as possible. The flask is then immediately connected to the column of the distillation apparatus. The flask is heated in an oil bath at ~120°C (cautious local heating of the flask with an open flame is also effective). The reaction which is very exothermic, starts after a short time and the greater part of the ethoxyethyne passes over. Fifteen minutes after this distillation has stopped, the system is evacuated (water-aspirator pressure) without external heating. The remainder of the ethoxyethyne and some *E*-2-bromovinyl ether condense in the strongly cooled receiver. After warming the receiver to room temperature, sufficient magnesium sulfate is added in small portions, with intermediate shaking, to just form a coagulate with the water. The almost clear liquid is decanted from the drying agent and subsequently distilled at normal pressure through a 30-cm Vigreux column. Ethoxyethyne, b.p. 52°C/760 mmHg, $n_D(20°)$ 1.382, is obtained in excellent yields (calculated on the amount of Z-isomer present in the mixture of isomers).

2.8 Methylthioethyne and Ethylthioethyne

$$BrCH_2CH(Br)SR + 3\,NaNH_2 \xrightarrow[-33^\circ C]{\text{liq. } NH_3} NaC{\equiv}CSR + 2\,NaBr{\downarrow} + NH_3$$

$$\downarrow H_2O$$

$$HC{\equiv}CSR$$

Scale: 0.50 molar.

Apparatus: fig. 4, 3 l; stirrer: fig. 3.

Introduction

In contrast to 1,2-dibromoalkyl (*oxygen*) ethers, the analogous sulfides can be successfully dehydrohalogenated with sodamide in liquid ammonia [166]. This experiment gives an efficient procedure for the volatile sulfides, methylthioethyne and ethylthioethyne [24]. These compounds are not thermally stable: the use of Et_2O as extraction solvent is avoided, since distillative separation of this solvent and the thioethers involves prolonged heating. After termination of the addition of bromine to the vinylic sulfides $H_2C{=}CHSR$, which can be carried out in Et_2O or dichloromethane, the solvent is completely removed by evaporation. For the isolation, high-boiling (b.p. ≥ 170°C) petroleum ether is used as extraction solvent: separation in vacuum of the desired product from the solvent requires only moderate heating.

Sodium ethoxide in ethanol (compare the preparation of $PhC{\equiv}CH$, exp. 4) seems an unsuitable system for the dehydrohalogenation because ethynyl thioethers smoothly give adducts $ROCH{=}CHSR$ under these conditions [167].

Procedure

A solution of 0.50 mol of the dibromosulfide in dichloromethane prepared as described in exp. 27, is concentrated using a water-pump vacuum (bath temperature not higher than 45°C). The last traces of solvent are removed in a vacuum of 1 mmHg or less (bath temperature 20-25°C). The remaining liquid is added dropwise or portionwise (note 1) over 30 min to a suspension of 1.8 mol of sodamide in 2 l (original volume) of liquid ammonia. The reaction is very vigorous and it may be necessary to remove the outlet temporarily. Ten minutes after this addition, 250 ml of high-boiling (b.p. > 170°C) petroleum ether is added with stirring. The mixture is then cautiously poured onto 1 kg of finely crushed ice in a 5-l round-bottomed flask and the slurry remaining in the reaction flask is hydrolysed with 500 ml of ice water. After the ice has melted, the layers are separated and three extractions with small portions of petroleum ether are carried out. The combined organic solutions are dried over $MgSO_4$, after which the volatile acetylene sulfides are isolated by the evacuation procedure (described in Chap. I-2.6, and fig. 14). Repetition of this procedure with the contents of the receiver gives $HC{\equiv}CSCH_3$, $n_D(20^\circ)$ 1.485 and $HC{\equiv}CSC_2H_5$, $n_D(20^\circ)$ 1.478, in yields of 60 and 70% (or slightly higher), respectively. Since the compounds have a limited thermal stability, distillation at normal pressure [24] should be carried out (under N_2) with relatively small amounts.

$HC{\equiv}CSCH_3$ boils at 70°C/760 mmHg, the b.p. of $HC{\equiv}CSC_2H_5$ is 92°C.

$HC{\equiv}CSPh$ can be prepared by adding an ethereal solution of $BrCH_2CH(Br)SPh$ (obtained by adding bromine at low temperatures to a mixture of $PhSCH{=}CH_2$ and Et_2O) to sodamide.

The dehydrohalogenation of the bromosulfides can also be carried out as described in exp. 10.

Notes

1. Addition may also be carried out with a syringe.

2.9 10-Undecynoic Acid

$$H_2C{=}CH(CH_2)_8COOH + Br_2 \xrightarrow[<-20^\circ C]{Et_2O} BrCH_2CH(Br)(CH_2)_8COOH$$

$$BrCH_2CH(Br)(CH_2)_8COOH + 4\,NaNH_2 \xrightarrow[-33^\circ C]{\text{liq. } NH_3} NaC{\equiv}C(CH_2)_8COONa{\downarrow} + 2\,NaBr{\downarrow}$$

$$NaC{\equiv}C(CH_2)_8COONa \xrightarrow{H^+,\,H_2O} HC{\equiv}C(CH_2)_8COOH$$

Scale: 0.20 molar.

Apparatus: fig. 4, 2 l; stirrer: fig. 3.

Introduction

The preparation of 10-undecynoic acid from 10-undecenoic acid is described in Org. Synth. [168]. The procedure given in this exp. is essentially similar to this preparation. As in the other procedures described in this book, no reflux condenser is used during the dehydrohalogenation. The suspension of sodamide in liquid ammonia is prepared as described previously [1,3,4], using less iron salt than mentioned in the Organic Syntheses procedure. Since the dehydrohalogenation proceeds instantaneously, the ammonia can be removed by evaporation immediately after the addition of the ethereal solution of the dibromoacid. Distillation of the crude 10-undecynoic acid is not carried out. Yields in our procedure are much higher than those reported in Organic Syntheses.

Procedure

Bromine (~0.21 mol) is added over 15 min to a solution of 0.20 mol of 10-undecenoic acid in 200 ml of Et_2O, cooled below -20°C. If the solution remains colourless after the addition, a small amount of bromine is added to give a brown solution. This solution is added dropwise or portionwise over 30 min to a suspension of 1.0 mol of sodamide in liquid ammonia

(original volume 1.5 l). A thick suspension is formed. The dropping funnel and outlet are then removed and the ammonia is evaporated by placing the flask in a water bath at 40°C. When most of the ammonia has evaporated (weak stream of ammonia vapour escaping from the flask), the stirrer is removed and the flask is evacuated (water-pump vacuum). During this procedure the flask is warmed in a water bath at 30-35°C. When the pressure has dropped to below 25 mmHg, nitrogen is admitted. The solid is dissolved by addition of 500 ml of water. Concentrated hydrochloric acid is then added to bring the pH of the aqueous layer to ~3 - 4. Subsequently, four extractions with a 1:1 mixture of Et_2O and pentane or hexane are carried out. The combined organic solutions are dried over $MgSO_4$. Concentration *in vacuo* gives the crude acetylenic acid. Crystallization from hexane affords pure 10-undecynoic acid (m.p. 41-42°C) in > 85% yield.

2.10 Methoxyethyne and Ethoxyethyne (from Chloroacetaldehyde Dialkylacetals)

$$ClCH_2CH(OR)_2 + 3\,NaNH_2 \xrightarrow[-33°C]{\text{liq. } NH_3} NaC{\equiv}COR + NaOR\downarrow + NaCl\downarrow + 3\,NH_3$$

$$\downarrow H_2O$$

$$HC{\equiv}COR$$

Scale: 2.0 molar.

Apparatus: fig. 8, 10 l; stirrer: fig. 3.

Introduction (see also exp. 11)

Treatment of the commercially available chloroacetaldehyde acetals $ClCH_2CH(OR)_2$ (R = CH_3 or C_2H_5) with three equivalents of sodamide in liquid ammonia results in the elimination of ROH and HCl with formation of sodium alkoxyacetylide. Since metallated alkoxyacetylenes are very unstable at higher temperatures and very sensitive towards oxygen, special conditions are required for the liberation of the acetylenic ethers from the sodium compounds. Since the ethynyl ethers are volatile, the greater part of the ammonia has to be removed by evaporation before the hydrolysis can be carried out. Complete removal of the ammonia would be very risky, however, because addition of water to the remaining solid mass would result in the local evolution of much heat. In the procedure described below, complete evaporation of the ammonia is avoided. After addition of a sufficient amount of high-boiling petroleum ether, the remaining slurry which still contains a considerable amount of ammonia, is quenched with a large amount of crushed ice, which has to be added as quickly as possible. This quenching operation would be impossible in a normal three-necked reaction flask, therefore, the reaction is carried out in a large wide-necked (diameter of the neck ≥ 5 cm) round-bottomed flask.

Procedure (compare [138])

A suspension of 7.0 mol of sodamide (note 1) in 5 l of liquid ammonia is prepared as described in refs. 1, 2 or 4 (note 2). The chloroacetal (2.0 mol) is added (pouring) in 10-g portions over 45 min with efficient stirring (the acetal should not flow down the glass wall). After an additional 30 min, the stirrer is removed and the greater part of the ammonia is removed by placing the flask in a water bath at 40°C. When about 70% of the ammonia has evaporated, 500 ml of high-boiling (b.p. >170°C) petroleum ether is added, after which the evaporation procedure is continued. A rubber stopper with a hole of ~7 mm is placed on the flask. When the stream of ammonia escaping through the hole has become markedly less, the bath is removed. N_2 is introduced for a few min (2 l/min) and 2.5 kg of finely crushed ice is added over a few seconds. Hydrolysis of the slurry on the bottom is effected by vigorous swirling (by hand), part of the ice melts. The flask is then warmed in a bath at 40-50°C until the remaining ice has melted. After separation of the layers, the aqueous layer is extracted (as quickly as possible, note 3) seven times with 50-ml portions of petroleum ether. The unwashed organic solutions are dried over $MgSO_4$ and subsequently placed in a 3-l round-bottomed flask. In the case of methoxyethyne the flask is equipped with a reflux condenser which is connected to a trap cooled in a bath with liquid N_2. The connection is made in such a way that during the evacuation the vapour of the methoxyethyne enters the large annular space of the trap. A tube filled with KOH pellets is placed between the trap and the water aspirator. In the case of ethoxyethyne, the flask is equipped for a normal distillation *in vacuo*, using a receiver cooled at -78°C (see fig. 14). The flask is gradually heated until the petroleum ether refluxes in the condenser ($HC{\equiv}COCH_3$) or in the top of the column ($HC{\equiv}COC_2H_5$). Nitrogen is then admitted and redistillation of the contents of the trap and receiver gives $HC{\equiv}COCH_3$, b.p. ~20-25°C/760 mmHg, $n_D(20°)$ 1.368, in ~48-66% yield and $HC{\equiv}COC_2H_5$, b.p. 53°C/760 mmHg, $n_D(20°)$ 1.382, in 67-82% yield. In both cases the receiver is cooled in a bath at 0°C.

Notes

1. Part of the excess of sodamide compensates losses caused by the introduction of moisture through the wide neck.
2. Ferric nitrate (aq.), ~800 mg is first added, followed by 5 g of sodium after 10 seconds. The remainder of the sodium is added in 2-g pieces (over 10 min) as soon as the blue colour has disappeared. If after 30 min the conversion is not yet complete, stirring is interrupted and a plug of cotton wool is placed in the neck (to prevent introduction of moisture). After disappearance of the blue colour the plug is removed and the suspension is stirred very vigorously for a few seconds in order to remove the sodium mirror from the glass wall.
3. Ethynyl ethers react (slowly) with aqueous ammonia [24].

2.11 1,1-Dimethoxy-2-propyne and 1,1-Diethoxy-2-propyne

$$H_2C{=}CHCH{=}O + Br_2 \xrightarrow[< -30^\circ C]{Et_2O} BrCH_2CH(Br)CH{=}O$$

$$BrCH_2CH(Br)CH{=}O + HC(OR)_3 \xrightarrow[20 \rightarrow 45^\circ C]{ZnCl_2,\ ROH} BrCH_2CH(Br)CH(OR)_2 + HCOOR$$

$$BrCH_2CHBrCH(OR)_2 + 3\ NaNH_2 \xrightarrow[-33^\circ C]{\text{liq. } NH_3} \underset{\downarrow H_2O}{NaC{\equiv}CCH(OR)_2} + 2\ NaBr\downarrow$$

$$HC{\equiv}CCH(OR)_2$$

Scale: 1.0 molar.

Apparatus: fig. 8, ≥ 6 l; stirrer: fig. 3.

Introduction (compare [169])

The procedures for the elimination of hydrogen bromide from the bromo acetals $BrCH_2$-$CHBrCH(OR)_2$ and the hydrolysis of the reaction mixture are similar to those in exp. 10. The reason for applying the quenching procedure with crushed ice is the (presumed) limited thermostability of the sodium compounds $NaC{\equiv}CCH(OR)_2$ (vigorous decomposition was observed when nearly dry $NaC{\equiv}CCH(OCH_3)_2$ came in contact with air). In our opinion this way of carrying out the hydrolysis is safer than gradual addition of water, from a dropping funnel placed on the (conventional) three-necked round-bottomed flask, which might give rise to local evolution of heat.

Procedure

The dibromoacetal (1.0 mol, thoroughly freed from volatile components by evacuation, exp. 29) is added dropwise or in 10-g portions (note 1) over 20 to 30 min to an efficiently stirred suspension of 3.6 mol of sodamide in 2.5 to 3 l of liquid ammonia (initial volume). The reaction is very vigorous. After an additional 15 min the stirrer is removed and the flask is placed in a water bath at 40°C. When the greater part of the ammonia has evaporated (but the stream of escaping ammonia is still vigorous), a rubber stopper with a 5-7 mm wide hole is placed on the flask. When the flow from the hole has become weaker, the stopper is removed, 350 ml of high-boiling (b.p. > 180°C) petroleum ether ($HC{\equiv}CCH(OCH_3)_2$) or 350 ml of a 1:1 mixture of Et_2O and pentane ($HC{\equiv}CCH(OEt)_2$) is then quickly poured into the flask. A vigorous stream (2 to 3 l/min) of N_2 is then directly led through the flask for 2 to 3 min, after which 1.5 kg of finely crushed ice is added through the wide neck as quickly as possible (in a few seconds). The mixture is swirled vigorously by hand in order to effect dissolution of the solid material. After the remaining ice has melted, the layers are separated and the aqueous

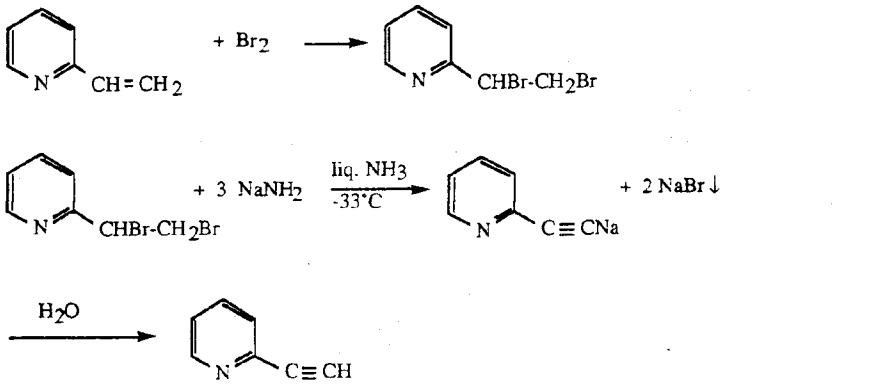
layer is extracted six times with the extraction solvent (50 to 75-ml portions). The unwashed organic solutions are dried over potassium carbonate. In the case of $HC{\equiv}CCH(OCH_3)_2$ the solution is subjected to a distillation in a water-pump vacuum, using a 40-cm Vigreux column and a receiver cooled at -78°C. The distillation is stopped as soon as the petroleum ether begins to distill (b.p. > 60°C/15 mmHg, see fig. 14). The contents of the receiver are redistilled at atmospheric pressure through a 20 to 30-cm Vigreux column to give $HC{\equiv}CCH(OCH_3)_2$, b.p. 100°C/760 mmHg, $n_D(20^\circ)$ 1.4072, in 75% yield.

$HC{\equiv}CCH(OC_2H_5)_2$, b.p. 38°C/10 mmHg, $n_D(20^\circ)$ 1.4130, is obtained in 80% yield by successive distillation of the greater part of the solvent at atmospheric pressure and the remaining liquid *in vacuo* through a 40-cm Vigreux column.

Notes

1. Addition by means of a syringe may be convenient.

2.12 2-Ethynylpyridine



Scale: 0.5 molar.

Apparatus: fig. 8, 4 l (for the dehydrohalogenation).

Introduction

The procedure for the dehydrohalogenation is similar to that for $HC{\equiv}CCH(OC_2H_5)_2$ described in exp. 11. The modest yield (~52%) of ethynylpyridine is explained by the fact that the addition of bromine to 2-vinylpyridine is not a clean reaction. We have not investigated this addition in detail but it is possible that at very low temperatures bromine first forms a complex $=N^+Br{-}{-}{-}Br_2$ instead of adding across the (electron-poor) double bond. When in the beginning bromine is added at ~ -70°C to the solution of vinylpyridine in Et_2O or dichloro-

methane, a red coloured solution is formed. This might be the complex mentioned. At a somewhat higher temperature (~ -45°C) the solution turns yellow. At a later stage a yellow precipitate is formed and this does not dissolve even when the reaction mixture is heated under reflux. When the addition of Br_2 is carried out quickly, more of the yellow precipitate is formed and the yield of 2-ethynylpyridine is lower. 4-Vinylpyridine and bromine form a thick yellow precipitate in CH_2Cl_2 or Et_2O. Dehydrohalogenation was not attempted.

Procedure

A mixture of 84 g (4 g excess) of bromine and 100 ml of dichloromethane is added dropwise over 45 min to a mixture of 0.50 mol of freshly distilled 2-vinylpyridine and 250 ml of dichloromethane. During this addition the temperature is maintained between -40 and -45°C. In the final stage of the addition a yellow suspension is formed. This is heated under reflux for 1 h and then allowed to stand at room temperature overnight (note 1). After this period the colour of the solid material has changed to grey. Water (200 ml) is added with vigorous stirring, after which the layers are separated. The organic layer is dried over $MgSO_4$ and subsequently concentrated *in vacuo*, the last traces of dichloromethane being removed thoroughly. The remaining oil is added portionwise or dropwise over 20 min to a suspension of 1.5 mol of sodamide in 2 l of liquid ammonia [1;3,4]. After an additional 10 min, powdered ammonium chloride (50 g) is added in 2 g-portions over 15 min. The ammonia is then removed by placing the flask in a water bath at 40°C. To the remaining slurry are successively added 1 l of ice water and 200 ml of Et_2O. After separation of the layers (note 2), four extractions with Et_2O are carried out. The (unwashed) dark organic solution is dried over K_2CO_3 and subsequently concentrated *in vacuo*. Distillation of the remaining liquid through a 20-cm Vigreux column gives 2-ethynylpyridine, b.p. 74°C/15 mmHg, $n_D(20°)$ 1.5595, in 53% yield (based on 2-vinylpyridine, note 3).

Notes

1. It has not been confirmed whether this treatment is actually necessary.
2. Some tarry material, insoluble in Et_2O, may be present. This can be removed from the glassware by rinsing with dilute acid.
3. Optimalisation of the reaction conditions of the bromine addition might lead to improved yields.

2.13 Vinylacetylene from 1,4-Dichloro-2-butene (phase-transfer method)

$$ClCH_2CH{=}CHCH_2Cl + 2\,KOH \xrightarrow[\text{petr. ether}]{\substack{MeN^+Oct_3Cl^-,\\ \text{pinacol}}} H_2C{=}CHCH{=}CHCl \rightarrow HC{\equiv}CCH{=}CH_2\uparrow$$

Scale: 0.50 molar (for Apparatus see exp. 1).

Introduction

Vinylacetylene can be prepared in high yields by treating *trans*-1,4-dichloro-2-butene with three equivalents of sodamide in liquid ammonia (the *cis*-isomer gives much resinous material) and slowly adding water to the solid remaining after complete removal of the ammonia by evaporation [3]. This preparation, however, is very laborious. In [1] a more convenient procedure is described involving treatment of *trans*-dichlorobutene with a mixture of powdered potassium hydroxide and calcium oxide at elevated temperatures in a high-boiling solvent. The procedure described below is a variant and is very similar to the preparation of 1-butyne (exp. 1), which uses methyl trioctylammonium chloride as phase-transfer catalyst and pinacol as additive. Although this procedure uses the commercially available *trans*-dichlorobutene, the *cis*-isomer (easily preparable from the diol and $SOCl_2$) and 1,4-dichloro-1-butene presumably also give good results.

Procedure

Freshly machine-powdered KOH (85%, 300 g) and high-boiling petroleum ether (b.p. > 150°C) are placed in the flask. Stirring is started and 5 g of methyl trioctylammonium chloride (75% aqueous solution, tetraoctylammonium chloride may also be used) and 5 g of pinacol are added (with temporary removal of the dropping funnel). The mixture is heated for 30 min in an oil bath at 120°C, then 1,4-dichloro-2-butene (*trans*-isomer, 0.50 mol) is added dropwise over 25 min. A slow stream of N_2 (~300 ml/min) is passed through the apparatus. The vinylacetylene condenses in two traps cooled at -78°C. After the addition the temperature of the bath is gradually raised over 30 min to 135°C. Stirring and introduction of N_2 are continued for another 1 h. The traps are successively connected to an empty one (cooled at -78°C) and then placed in a water bath at 15°C. The temperature is gradually raised to 50°C. A small amount of chlorobutadiene sometimes remains in one of the traps. The yield of pure (> 95%) vinylacetylene is usually higher than 75%.

Vinylacetylene can also be prepared in high yields by slow addition (over 45 min) of *trans*-dichlorobutene (0.45 mol), to a vigorously stirred mixture of 3 g $MeN^+Oct_3Cl^-$, 250 g of KOH and 250 ml of water, heated at 100°C (bath temperature). N_2 is slowly (200 ml/min) introduced both during and for 30 min after the addition of dichlorobutene. The contents of the cold traps are then "redistilled" as described above.

2.14 Diacetylene from 1,4-Dichloro-2-butyne

$$ClCH_2C{\equiv}CCH_2Cl + 2\,KOH \xrightarrow[70 \rightarrow 100°C]{H_2O,\ DMSO} ClCH{=}C{=}C{=}CH_2 \longrightarrow HC{\equiv}CC{\equiv}CH\uparrow$$

Scale: 0.50 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a combination of dropping funnel and gas inlet tube, an efficient mechanical stirrer (fig. 3) and a combination of a

thermometer and an efficient reflux condenser; the top of the condenser is, *via* two tubes (20 cm long) filled with lumps of $CaCl_2$, connected to two traps cooled at -78°C; both traps contain 50 g of dry THF (or any other solvent, *e.g.* CH_3OH, Et_2O) and the inlet tube of the traps dip 0.5 cm below the surface of the THF (note 1; all connections are made gas-tight.

Introduction

The preparation of butadiyne from 1,4-dichlorobutyne described in this experiment is quite similar to the reaction of 1,4-dichlorobutene with aqueous potassium hydroxide resulting in the formation of vinylacetylene (see exp. 13). 1,4-Dichlorobutyne reacts sluggishly with concentrated aqueous KOH at 70°C, because it is slightly soluble in the aqueous phase. If a small amount of the phase-transfer catalyst $MeN^+Oct_3Cl^-$ (Aliquat) is present, however, the double elimination of hydrogen chloride proceeds smoothly at that temperature. Addition of a sufficient amount of DMSO instead of Aliquat causes an increase of the solubility of dichlorobutyne and the effect is similar to that obtained with Aliquat. It seems useful to explain some other experimental conditions. The slow stream of nitrogen which is passed through the apparatus, serves to transport the diacetylene to the cold traps. A second function of nitrogen is to dilute the gaseous diacetylene (the estimated b.p. at 760 mmHg is between 10 and 20°C), and thus to diminish the danger of (explosive) decomposition. It seems essential to pass the nitrogen through the aqueous reaction mixture: in this manner the diacetylene is helped to escape from the aqueous phase. The first elimination product is the extremely unstable $ClCH{=}C{=}C{=}CH_2$. A too quick addition of dichlorobutyne would result in a too high concentration of this cumulene and consequently in formation of polymer. If the flow of N_2 is too rapid, the cumulene is swept out of the solution and forms a layer of brown polymer in the upper part of the flask and in the condenser. The results obtained with the DMSO-water mixture (yields up to 95%) are markedly better than those obtained with phase-transfer catalysis. In the latter case much amorphous black or brown material is formed, while diacetylene is obtained in yields up to a maximum of 65%.

Procedure (compare [170])

In the flask is dissolved 130 g of 85% KOH in 200 ml of water. DMSO (40 ml) is added. N_2 is introduced at a rate of ~500 ml/min. The solution is heated up to 72°C (internal) and 0.50 mol of 1,4-dichloro-2-butyne (p. 255) is added dropwise over 30 min, while maintaining the temperature between 70 and 75°C. The diacetylene condenses in the THF. After completion of the addition, the brown reaction mixture is brought to 95°C and held at this temperature for an additional 15 min. The total weight- increase of the traps corresponds to yields up to 95% (notes 2 and 3).

Notes

1. If the tube ends above the level of the THF, some diacetylene may condense as white leaves in the upper, cooled part of the first trap.
2. Lower yields are obtained when dichlorobutyne is added too quickly.

3. The solution can be stored for at least 3 days at -20°C in a well-sealed bottle without deterioration.

2.15 Hexatriyne from 1,6-Dichloro-2,4-hexadiyne

$$ClCH_2C{\equiv}CC{\equiv}CCH_2Cl + 4\ t\text{-BuOK} \xrightarrow[-90\rightarrow -60°C]{\text{THF}} HC{\equiv}CC{\equiv}CC{\equiv}CH + 2\ KCl\downarrow + 2\ t\text{-BuOK}.t\text{-BuOH}$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l; stirrer: fig. 3.

Introduction

Hexatriyne has been obtained in a moderate yield from the reaction of 2,6-dichloro--2,4-hexadiyne with alkali amide in liquid ammonia [147]. The compound is extremely unstable and the crystalline substance, isolated from the organic solution readily explodes. Generation under conditions similar to those applied for the preparation of butadiyne (exp. 14) is likely to give decomposition products. In the procedure described below [2] hexatriyne is obtained in surprisingly high yields. In analogy with the elimination of hydrogen chloride from 1,4-dichloro-2-butyne it might be assumed that the first elimination gives the chlorohexapentaene $ClCH{=}C{=}C{=}C{=}CH_2$. This compound probably does not accumulate but undergoes a rapid tele-elimination of HCl to give hexatriyne. Since the elimination reactions are strongly exothermic it is easy to follow the progress of the reaction. The *t*-butylalcohol formed in the elimination forms a much less effective 1:1 complex with *t*-BuOK, therefore a large excess of base is used. Hexatriyne is expected to be much more "acidic" than acetylene (pK ~25) and part of the compound may remain in solution (as a "complex" with KOH) when, after addition of water to the reaction mixture, the base is not neutralised. As extraction solvent high-boiling petroleum ether is used and the THF and *t*-butylalcohol are removed by repeated washing of the solution with cold dilute hydrochloric acid. Hexatriyne is subsequently isolated by gradually heating the petroleum ether solution *in vacuo*. Although it is not difficult to collect the compound as a solid in the strongly cooled receiver, it seems safer to put a (weighed) amount of an inert organic solvent with a comparable volatility (*e.g.* heptane) in the receiver prior to carrying out the vacuum "distillation".

Procedure

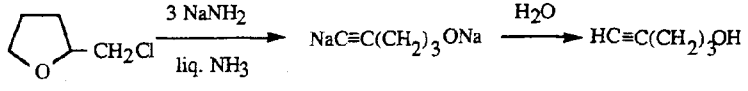
A mixture of 0.10 mol of 1,6-dichloro-2,4-hexadiyne (p. 255) and 150 ml of THF is cooled to -90°C and a solution of 0.40 mol of *t*-BuOK in 150 ml of THF is added dropwise over 25 min with vigorous stirring. Occasional cooling in a bath with liquid N_2 is applied to maintain this low temperature. Care should be taken that the THF does not solidify on the bottom of the

flask: should it do so, the addition should be interrupted until the THF has melted. After completion of the addition the mixture is stirred for an additional 30 min at -65 to -70°C. High-boiling petroleum ether (b.p. ≥ 190°C, 150 ml) is then added to the dark reaction mixture, followed by 200 ml of 2N hydrochloric acid. The layers are separated as soon as possible (note 1) and the aqueous layer extracted twice with 30-ml portions of petroleum ether. The combined organic solutions are washed ten to fifteen times with cold (-10°C) 2N HCl (150-ml portions) in order to remove the THF and *t*-BuOH thoroughly. After drying for a few minutes over $MgSO_4$, the brown solution is transferred into a 1-l round-bottomed flask which is equipped for a vacuum distillation (fig. 14). The receiver (500-ml round-bottomed flask) is filled with 50 g of cold (< -50°C) heptane (note 2), after which this system is evacuated by means of the water aspirator. The extract is gradually warmed until the solvent (b.p. ≥ 70°C/15 mmHg) begins to reflux in the top of the column (40-cm Vigreux). During this operation a small amount of petroleum ether co-distills. The evacuation operation is therefore repeated with the contents of the receiver. In the beginning no heating is applied, at a later stage the flask is placed in a bath at 10-15°C. A mixture of hexatriyne and heptane is collected in the pre-weighed receiver (cooled at -78°C). This contains up to 56.4 g of heptane solution, corresponding to a yield of ~85% of hexatriyne.

Notes

1. All operations should be carried out under N_2, without delay.
2. If no heptane or other diluent is used, the triyne is collected as a white solid in the receiver, turning violet under the influence of (traces of) oxygen. In view of the explosive character of the triyne, we do not recommend isolation in an undiluted state.

2.16 4-Pentyn-1-ol from Tetrahydrofurfuryl Chloride



Scale: 1.0 molar.

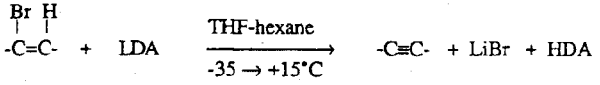
Apparatus: fig. 4, 3 l.

Procedure (compare [139])

A suspension of 3.5 mol of sodamide in about 2 l of liquid ammonia is prepared [1,3,4]. Tetrahydrofurfuryl chloride (1.0 mol, see exp. 33), dissolved in 200 ml of Et_2O is added dropwise over 40 min. After an additional 30 min, 120 g of powdered ammonium chloride is added in 1 to 2-g portions over 15 min, after which the ammonia is allowed to evaporate (fig. 11). Water (500 ml) is then added and the obtained solution is subjected to continuous extraction for a few hours with diethyl ether. To decide when the extraction procedure can be

stopped, after each hour a sample of a few ml of the supernatant ethereal layer in the extraction apparatus is taken and sprayed over a piece of ground glass. The extract is dried over potassium carbonate and subsequently concentrated *in vacuo*. Distillation of the remaining liquid through a 40-cm Vigreux column gives 4-pentyn-1-ol, b.p. 53°C/15 mmHg, $n_D(20°)$ 1.4452 (~3% of water), in greater than 80% yield.

2.17 Cyclooctyne from 1-Bromocyclooctene



Scale: 0.50 molar (bromocyclooctene).

Apparatus: fig. 1, 1 l.

Introduction

Cyclooctyne has been prepared in low yield by dehydrohalogenation of bromocyclooctene with sodamide in an organic solvent [171]. We have carried out the reaction with sodamide in liquid ammonia [2] and also obtained low yields. A serious subsequent reaction is probably the isomerization into 1,2-cyclooctadiene under the influence of the base. This allene has a very short life time and dimerizes, giving rise to a considerable amount of high-boiling residue. Butyllithium is also not suitable as dehydrohalogenating agent, since it adds very smoothly to cyclooctyne. Interaction between bromocyclooctene and butyllithium gives rise to bromine-lithium exchange. Lithium diisopropylamide generally shows little tendency to attack at bromine or to add across multiple bond systems, but is a potent proton-abstractor. In our procedure for cyclooctyne (see also ref. 172) a solution of LDA in THF and hexane is successfully used to convert the readily available 1-bromocyclooctene into cyclooctyne. The subsequent base-induced isomerization to 1,2-cyclooctadiene can be largely suppressed by using a large excess of 1-bromocyclooctene: this can easily be separated from cyclooctyne by fractional distillation.

Cyclooctyne has a reasonable thermostability. It can be stored for at least one month at -20°C with only slight polymerization.

Procedure

THF (100 ml) is added to a solution of 0.25 mol of butyllithium in 170 ml of hexane, cooled below -35°C. Subsequently 0.25 mol of diisopropylamine is added with cooling below 0°C. The solution is cooled to -40°C and 0.50 mol of bromocyclooctene (exp. 30) is added over a few minutes. The temperature of the mixture is allowed to rise over 1.5 h to +15°C and maintained at this level for an additional 1.5 h. The brown solution is then poured into a mixture of 1 l of ice water and 30 g of 36% hydrochloric acid. After vigorous shaking, the layers are separated (note 1). The organic layer is subsequently washed five times with cold

(0°C) 2N HCl in order to remove the THF. The original aqueous layer and the washings are combined and then extracted twice with small portions of pentane. The combined organic solutions are washed with water, dried over $MgSO_4$ and subsequently concentrated in a water-pump vacuum (bath temperature not higher than 25°C). Careful distillation of the remaining liquid through a 40-cm Widmer column gives cyclooctyne, b.p. 48°C/16 mmHg, $n_D(20°)$ 1.4876, in at least 70% yield (based on 0.25 mol) Most of the excess of bromocyclooctene (b.p. 85°C/15 mmHg) is recovered. There is only a small high-boiling residue.

Notes

1. Cyclooctyne has a very strong, unpleasant odour. The odour of the aqueous layers disappears upon shaking with a small amount of bromine.

2.18 *t*-Butylnitroacetylene

$$t\text{-BuC(I)=CHNO}_2 + \text{KOH} \xrightarrow[< 0.5\ \text{mmHg}]{100 - 120°\text{C}} t\text{-BuC}{\equiv}\text{CNO}_2 + \text{KI} + \text{H}_2\text{O}$$

Scale: 0.05 molar.

Apparatus: 250-ml two-necked (vertical necks!), round-bottomed flask, equipped with a evacuable dropping funnel and a very short (~5 cm) Vigreux column, connected to a short condenser and a single receiver cooled in a bath at -50°C or lower. B24 or B29 glass joints should be used.

Introduction

Jäger and Viehe [141] describe the preparation of the unstable nitroacetylenes $RC{\equiv}CNO_2$ from the readily available 2-iodonitroalkenes and solid potassium hydroxide. The compounds are extremely base-sensitive. t-$BuC(I)=CHNO_2$ reacts smoothly with powdered KOH in Et_2O at 20-30°C, but no trace of the nitroalkyne can be isolated. In the procedure published by Jäger and Viehe, the vapour of the iodo compound is led over KOH pellets in a tube heated at about 100°C. The reaction is carried out at low pressure and the vapour of the nitroalkyne is condensed in a strongly cooled receiver. In this way, the contact time of the nitroalkyne with the base is extremely short. The best results are obtained with the *t*-butyl derivative, which in fact is the only representative which can be prepared in reasonable yield. The best way to store the compound is at -20°C or lower as a dilute solution in a (volatile) organic solvent. Distillation of a sample (~5 g) which had been allowed to stand for 24 h at room temperature, gave only some 70% recovery [2].

Our procedure is a variant of the one published. Although our yields are somewhat lower that those reported by Jäger and Viehe, the actual procedure can be carried out within 1 hour (Jäger adds the iodo compound over several hours).

Procedure

In the flask are placed 50 g of KOH pellets and 20 ml of dry paraffin oil (this is added for better conduction of the heat from the bath) and in the dropping funnel 0.05 mol of the iodonitroalkene (exp. 34). The apparatus is evacuated by means of a mercury diffusion pump (pressure preferably ≤ 0.01 mmHg) and the contents of the flask are heated in a bath at 100-120°C (at higher bath temperatures the KOH "melts" during the additon of the iodo compound). After heating for 15 min at the temperature indicated, the addition of the iodo compound is started. The reaction is very fast and is accompanied by rather vigorous foaming. After completion of the addition (over 15 to 20 min), heating and evacuation are continued for an additional 10 min, then nitrogen is admitted. Pentane (50 ml) is added to the contents of the receiver. After warming to room temperature, the yellow organic solution is separated from the small amount of water and subsequently dried over a small amount of $MgSO_4$. The clear organic solution is decanted from the $MgSO_4$ (which is rinsed with some pentane). The liquid remaining after concentration of the combined pentane solutions *in vacuo*, is distilled as quickly as possible through a 20-cm Vigreux column. The nitroacetylene, b.p. ~50°C/10 mmHg, $n_D(20°)$ 1.4510, is obtained in yields varying between 50 and 75%.

2.19 Bis(dialkylamino)acetylenes from 1-Chloro-bis(dialkylamino)ethenes

$$\text{ClCH=C(NR}_2)_2 + \text{KNH}_2 \xrightarrow[-33°\text{C}]{\text{liq. NH}_3} \text{R}_2\text{NC}{\equiv}\text{CNR}_2 + \text{KCl}{\downarrow} + \text{NH}_3$$

Scale: 0.30 molar.

Apparatus: fig. 4, 1 l.

Introduction

Viehe *et al.* [154,155] described the preparation of ynediamines $R_2NC{\equiv}CNR_2$ (R = CH_3 or C_2H_5) from chloroketene aminals $ClCH=C(NR_2)_2$ with sodamide in an organic solvent. The ynediamine $Me_2NC{\equiv}CNMe_2$ was obtained by treating $Cl_2C=CHCl$ with sodamide in liquified dimethylamine [155]. In our procedure for the ynediamines, which is based on those published by Viehe *et al.*, the chloroketene aminals are dehydrochlorinated by potassium amide in liquid ammonia. Under these conditions (polar medium, good solubility of the base) the conversions into the ynediamines proceed very smoothly and the work up is simple: after evaporation of the ammonia the products are isolated by extraction of the remaining salt mass with dry Et_2O. Contact with water must be avoided, since the ynediamines are extremely water-sensitive.

Procedure (note 1)

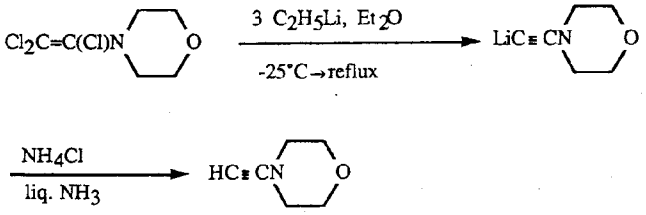
A solution of 0.35 mol of potassium amide in 350 ml of liquid ammonia is prepared as

described in refs. 1, 3, and 4 (it is not necessary to filter the solution of KNH_2, provided that good quality potassium is used). The chloroketene aminal (0.30 mol, [1]) is added over 20 minutes with efficient stirring. The reaction with the methyl derivative is faster than that of the ethyl derivative (difference in solubility). After an additional 10 minutes the ammonia is removed by placing the flask in a water bath at 30°C. In the last stage of this operation 150 ml of a 1:1 mixture of Et_2O and pentane is added to the salt slurry (note 2). Warming is continued until the flow of ammonia vapour has become scarcely perceptible. After cooling to room temperature, the supernatant organic solution is carefully decanted from the salt, which is rinsed four times with small portions of the Et_2O-pentane mixture. The combined organic solutions are concentrated in a water-pump vacuum (in the case of R = CH_3, the bath temperature should not exceed 20°C). The remaining liquid is distilled through a 30-cm Vigreux column. The ynediamine R = CH_3, b.p. ~40°C/20 mmHg (collected in a *single* receiver, cooled in ice water), $n_D(20°)$ 1.4610, and the compound with R = C_2H_5, b.p. 78°C/15 mmHg, $n_D(20°)$ 1.4582, are obtained in greater than 80% yields.

Notes

1. The ynediamines are extremely water-sensitive and anhydrous conditions must be maintained throughout the experiments.
2. The salt may contain minute particles of potassium. Cleaning of the flask with water should only be carried out when all organic solvent has evaporated!

2.20 Morpholinoacetylene



Scale: 0.05 molar.

Apparatus: fig. 1, 11.

Introduction

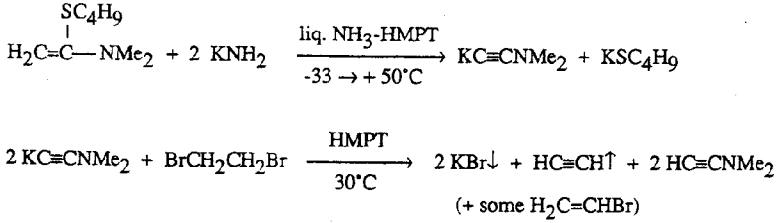
The method of Ficini [156], involving treatment of the readily available trichlorovinylamines [157] with three equivalents of alkyllithium, gives access to yneamines with a terminal triple bond. At low temperatures the trichlorovinylamine is dechlorinated with one equivalent of alkyllithium. The subsequent displacement of chlorine by lithium in the intermediary $ClC{\equiv}CNR_2$ takes place when the reaction mixture is heated under reflux. Since part of the

alkyllithium may be consumed under these conditions by a competitive "Würtz"-coupling with the alkyl chloride, more than two equivalents of alkyllithium are used. The chance of an alkylation of $LiC{\equiv}CNR_2$ by the alkyl chloride is very small. If, instead of ethyllithium, butyllithium is used, some octane may be formed in the Würtz-coupling. This is difficult to separate from the more volatile yneamines. The less strongly basic methyllithium probably would not be capable of replacing chlorine in the intermediary $ClC{\equiv}CNR_2$. Although Ficini and coworkers carry out the protolysis of the lithiated yneamines with water containing alkali hydroxide, this work-up involves the risk of water addition to the triple bond, especially in the cases of the representatives with small alkyl groups, *e.g.* $HC{\equiv}CN(C_2H_5)_2$. In our procedure for morpholinoacetylene, the yneamine is liberated by successive addition of anhydrous liquid ammonia and ammonium chloride.

Procedure

A solution of 0.15 mol (excess!) of ethyllithium in ~130 ml of Et_2O [1,3,4] is added over 15-30 minutes to a mixture of 0.05 mol of the trichlorovinylamine (b.p. ~100°C/1 mmHg, $n_D(22°)$ 1.5224, prepared as described in ref. 157) and 100 ml of dry Et_2O with cooling between -20 and -25°C. A white suspension is formed. After the addition, the thermometer-outlet combination is replaced with a reflux condenser and the mixture is heated under reflux for 15 minutes. Subsequently, it is cooled to below -30°C (the condenser is removed and nitrogen is introduced at a rate of 500 ml/min) and 200 ml of anhydrous liquid ammonia (water content < 0.1%) is cautiously introduced from the cylinder (*via* a dry plastic tube). Powdered dry ammonium chloride (6.0 g) is then added (through a powder funnel) in small (0.5 g) portions over 10 min to the stirred solution, the introduction of N_2 being continued. The gas inlet and powder funnel are then replaced with two stoppers each perforated by a hole of ~ 7 mm and the flask is placed in a water bath of 30°C. When most of the ammonia has evaporated (faint flow from the holes), 150 ml of warm (30°C) Et_2O is cautiously added. The mixture is stirred and heated for an additional 15 min in a bath at 30°C. The salt suspension is subsequently filtered on a sintered-glass funnel (G-2), the salt residue in the flask being rinsed with small portions of Et_2O. The filtrate is concentrated in a water-pump vacuum and the remaining liquid distilled in a small apparatus, affording the yneamine, b.p. 60°C/10 mmHg, $n_D(22°)$ 1.4776, in 50-58% yield.

2.21 Dimethylaminoacetylene



$$2\,KSC_4H_9 + BrCH_2CH_2Br \xrightarrow[30°C]{HMPT} C_4H_9SCH_2CH_2SC_4H_9 + 2\,KBr\downarrow$$

Scale: 0.30 molar.

Apparatus: fig. 6, 2 l; see further below.

Introduction

Dimethylaminoacetylene, a volatile (b.p. ~53°C) and extremely water-sensitive compound which has an almost explosive reaction with water, was prepared for the first time by us [149] following an indication reported by Viehe [150]. Treatment of the ketene-S,N-acetal $H_2C{=}C(SC_4H_9)NMe_2$ with potassium amide in liquid ammonia gives rise to a 1,2-elimination of butanethiol. Since this reaction seems to proceed sluggishly in liquid ammonia, this solvent first has to be replaced by HMPT. DMSO would be unsuitable because it is metallated by the alkali amide. In view of the possibility that part of the thiolate can react with acetylene or vinyl bromide during the protolysis to give a vinyl sulfide, alkyl groups smaller than butyl (in the S,N-acetal) would be less suitable. The choice of the protonating reagent is the result of careful consideration. It has to meet the following conditions: *a*. it should not give rise to the formation of volatile compounds which are hard to separate from the yneamine, *b*. it should not cause protolysis of the thiolate, since the resulting thiol undoubtedly would react with the yneamine to give the starting compound, *c*. it should have a b.p. that is significantly higher (or lower) than that of the yneamine. Possible candidates are *t*-butyl bromide, *c*-hexyl bromide, β-phenylethyl bromide ($PhCH_2CH_2Br$), 1,2-dichloroethane and 1,2-dibromoethane. Phenylethyl bromide and 1,2-dibromoethane seem to be the most suitable compounds; for reasons of availability we have chosen the latter one.

Procedure

Potassium amide is prepared from 25 g (0.6 mol + 1 g excess) of potassium and 300 ml of liquid ammonia [1,3,4]. The solution is then concentrated (water bath at 35-40°C) to a volume of about 100 ml. HMPT (350 ml, note 1) is cautiously poured into the flask, which is subsequently equipped with a gas inlet, a mechanical stirrer (fig. 3) and a thermometer-gas outlet combination. The flask is placed again in the water bath and nitrogen is introduced (~500 ml/min). The ketene-S,N-acetal (0.30 mol, exp. 37) is added in one portion and the brown suspension is brought to a temperature of 20°C. After stirring for 30 min at 20°C, the mixture is warmed to 45°C. The mechanical stirrer is removed and the flask is evacuated (water pump) at 10-20 mmHg, at 45-50°C (bath temperature). To prevent introduction of moisture, a tube filled with KOH pellets is placed between the flask and the water pump. After 1 h the evacuation and warming are terminated and N_2 is admitted to the flask, which is now equipped with a mechanical stirrer (fig. 3), a combination of dropping funnel and gas inlet and a thermometer-gas outlet combination (see fig. 1). Nitrogen is introduced at a rate of 100-150 ml/min and dibromoethane, (0.30 mol) is added dropwise over 45 min, while keeping the

temperature of the mixture between 10 and 15°C. During this addition of dibromoethane the suspension becomes much less viscous, while at the end the colour becomes grey. After stirring for an additional half hour at 20-25°C, the flask is equipped for a vacuum distillation (note 2): 40-cm Vigreux column, condenser and (single) receiver cooled at -78°C. A tube filled with KOH pellets is placed between the receiving flask and the water pump. Anhydrous potassium carbonate (1 g) is placed in the receiver. The system is evacuated and gradually heated to 90-100°C (bath temperature). The minimal pressure of 10 to 20 mmHg is not reached quickly, because acetylene escapes from the solution. Heating at 90-100°C is continued for 30 min, then N_2 is admitted. The contents of the receiver are warmed up to about 0°C, after which the flask is connected to a 40-cm Vigreux column, condenser and receiver containing 0.5 g of K_2CO_3 and cooled at -78°C (a KOH tube is again placed between the receiver and the water pump, see fig. 14). The volatile yneamine is evaporated in a 10 to 20 mmHg vacuum and condensed in a strongly cooled receiver. The distillation flask is placed in a water bath at 10-15°C. This second evacuation procedure gives reasonably pure $HC{\equiv}CNMe_2$ with ~5% of vinyl bromide in 77% yield. Distillation of a small amount at 760 mmHg gives $HC{\equiv}CNMe_2$ with a b.p. of ~53°C, $n_D(20°)$ 1.4205.

Notes

1. Commercially available dry HMPT is distilled from *t*-BuOK (~5 g for 500 ml) at < 0.5 mmHg (b.p. ~50°C). The distillate is redistilled *in vacuo*.
2. All glassware must be made perfectly dry. Dimethylaminoacetylene reacts very vigorously with water.

2.22 *N,N*-Dialkylaminoalkynes from 1-Alkynyl Ethers and Lithium Dialkylamides

$$R'C{\equiv}COC_2H_5 + LiNR_2 \xrightarrow{Et_2O} R'C{\equiv}CNR_2 + LiOC_2H_5\downarrow$$

Scale: 0.30 molar.

Apparatus: fig. 1, 500 ml, see further below.

Introduction

In addition reactions of 1-alkynyl ethers $R'C{\equiv}COC_2H_5$, nucleophilic species (Nu:) generally attack the α-carbon atom of the triple bond [6,24]. When the nucleophile is a very strong base, one might expect that after the initial addition across the triple bond alkoxide would eliminate with formation of the disubstituted acetylene $R'C{\equiv}CNu$. Our synthesis of yneamines from 1-alkynyl ethers and lithium dialkylamides is based on this principle, which also applies in the case of fluoroacetylenes $RC{\equiv}CF$ [173]. Unfortunately, these compounds are extremely unstable. 1-Chloroalkynes react with lithium dialkylamides in a manner which is seemingly analogous to that in the case of the acetylenic ethers. However, the products isolated from the

reaction of alkylchloroacetylenes, R'C≡CCl, and thiols in the presence of base are RS(R')C=CHCl. This regiochemistry suggests that the formation of yneamines from chloroalkynes and lithium dialkylamides may proceed through an initial β-adduct [158, 160].

$$R'C{\equiv}CCl + LiNR_2 \longrightarrow R'C(NR_2){=}C(Li)Cl \xrightarrow[\text{migration of } NR_2]{-LiCl} R'C{\equiv}CNR_2$$

Possible side reactions in the case of chloroacetylenes are attack of the lithium reagent on chlorine with formation of R'C≡CLi and R_2NCl, and metallation adjacent to the triple bond (if R' in R'C≡CCl contains an abstractable proton in the propargylic position). The low yields of *propynyl*amines $CH_3C{\equiv}CNR_2$ from $CH_3C{\equiv}COC_2H_5$ and $LiNR_2$ might be ascribed to a relatively easy metallation of $CH_3C{\equiv}COC_2H_5$ by the amide (alkali amides in liquid ammonia react with 1-propynyl ethers to give propargyl ethers $HC{\equiv}CCH_2OC_2H_5$ [174]). In the case of the homologues $R'CH_2C{\equiv}COC_2H_5$ this metallation is also possible, but the chance of this side reaction is diminished by using solutions of lithium dialkylamides containing lithium bromide (prepared from C_2H_5Li.LiBr and the secondary amine).

The yneamines with R and R' = alkyl have a reasonable thermostability but are very water sensitive.

Procedure

The dialkylamine (0.31 mol) is added to a solution of 0.30 mol of ethyllithium or butyllithium in ~270 ml of Et_2O (prepared from the alkyl bromide and lithium [1,3,4], with cooling below 0°C. The 1-alkynyl ether (0.30 mol, p. 50, 54) is subsequently added in one portion at 0°C. The mechanical stirrer is then replaced with a magnetic stirring bar and the flask is equipped for a distillation, using a 40-cm Vigreux column. The Et_2O is slowly distilled off over ~2 h while a slow stream of N_2 is passed through the apparatus. The temperature of the heating bath is gradually raised to 100-110°C, when most of the ether has been distilled off. After heating for an additional half hour at this temperature, the reaction mixture is allowed to cool to room temperature. The Vigreux column is replaced with a much shorter (~10 cm) one and two stoppers are placed on the flask (note 1). The receiving flask is placed in a bath at -78°C and a tube filled with KOH pellets is placed between the receiver and the water aspirator. The system is evacuated and the temperature of the heating bath gradually raised to 200°C (note 2). When the distillation has stopped completely, nitrogen is admitted. The contents of the receiver are carefully redistilled through a 30 to 40-cm Widmer column. The following compounds have been obtained in yields between 60 and 70%:

$C_2H_5C{\equiv}CN(C_3H_7)_2$, b.p. 65°C/10 mmHg, $n_D(20°)$ 1.4442;
$C_2H_5C{\equiv}CN(C_2H_5)_2$, b.p. 42°C/10 mmHg, $n_D(20°)$ 1.4421;
$C_2H_5C{\equiv}C$-piperidine, b.p. 73°C/10 mmHg, $n_D(20°)$ 1.4827;
$C_3H_7C{\equiv}CN(C_2H_5)_2$, b.p. 56°C/10 mmHg, $n_D(20°)$ 1.4448;
$C_4H_9C{\equiv}CN(C_2H_5)_2$, b.p. 71°C/10 mmHg, $n_D(20°)$ 1.4473.

Notes

1. Distillation at oil-pump pressure may be more effective.
2. In the final stage of the distillation, hot oil may be poured on the column by means of a spoon. In this way as much as possible of the product is forced to pass over.

2.23 1-(*N,N*-Dimethylamino)-2-phenylacetylene from 1-Chloro-2-phenylacetylene

$$PhC{\equiv}CCl + LiNMe_2 \xrightarrow[-20°C \rightarrow \text{reflux}]{Et_2O} PhC{\equiv}CNMe_2 + LiCl\downarrow$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l; at a later stage the thermometer-outlet combination is replaced with a reflux condenser.

Introduction: see exp. 22 and Section 2.

Procedure (see also ref. 6, p. 906; for Introduction see exp. 22 and Section 2)
Liquified dimethylamine (0.12 mol) is dissolved in 50 ml of dry Et_2O, cooled to -40°C. The solution is added to a solution of 0.10 mol of ethyllithium or butyllithium [1,3,5] in *ca.* 120 ml of Et_2O with cooling between -20 and -40°C. Subsequently 0.10 mol of 1-chloro-2-phenylacetylene (p. 148) is added dropwise over 15 min with cooling between -15 and -20°C. After the addition, the cooling bath is removed and the temperature allowed to rise. At about 20°C a weakly exothermic reaction starts. The dark brown mixture is then heated for 1 h under reflux. After cooling to room temperature, the salt is filtered off on a (dry) sintered-glass funnel and rinsed well with dry Et_2O. The solution is concentrated *in vacuo*, 5 ml of paraffin oil is added (to conduct the heat supplied by the oil bath during the distillation) and the product is distilled in a high-vacuum (mercury diffusion pump) through a 5 to 10-cm Vigreux column. The product is collected in a (single) receiver, cooled in a bath at a temperature of -20°C or lower. During the distillation the temperature of the heating bath is gradually raised to about 150°C. Redistillation of the contents of the receiver gives the yneamine, b.p. 107°C/10 mmHg, $n_D(20°)$ 1.5872, in at least 60% yield.

1-Cyclohexenyl$C{\equiv}CN(C_2H_5)_2$ was obtained in only 40% yield from the corresponding chloroenyne (p.148) and $LiNEt_2$ by a similar procedure.

2.24 1-Ethoxy-1-buten-3-yne by 1,4-Elimination from 1,4-Diethoxy-2-butyne with Sodamide

$$C_2H_5OCH_2C{\equiv}CCH_2OC_2H_5 + 2\ NaNH_2 \xrightarrow[-33^\circ C]{\text{liq. } NH_3} NaC{\equiv}CCH{=}CHOC_2H_5 + NaOC_2H_5\downarrow$$

$$\downarrow\ H_2O$$

$$HC{\equiv}CCH{=}CHOC_2H_5$$

Scale: 0.50 molar.

Apparatus: fig. 4, 2 l.

Introduction

Enyne ethers HC≡CCH=CHOR are useful synthetic intermediates. They can be prepared by base-catalysed addition of alcohols to diacetylene. The required conditions are rather forcing and not very attractive for laboratory scale preparations. A much more convenient way to prepare the enyne ethers (in these cases more than 80 rel.% of the *E*-isomer is obtained) consists in treatment of the easily accessible 1,4-dialkoxy-2-alkynes with two equivalents of alkali amide in liquid ammonia. The first step in this elimination is the (transient) formation of an "anion" RO-$\underline{C}$H-C≡CCH_2OR, which eliminates ROH [143]. The resulting cumulenic ether $ROCH{=}C{=}C{=}CH_2$ is immediately converted into the metallated enyne ether.

Procedure

The dialkoxybutyne (0.50 mol, p. 260) is added dropwise over 30 min to a suspension of 1.2 mol of sodamide [1,3,5] in 1 l of liquid ammonia. After the addition the flask is placed in a water bath at 40°C. When most of the ammonia has evaporated, 250 ml of Et_2O is added. The flask is placed in a bath with ice and ice water. Ice water (500 ml) is added over about 15 min, while introducing N_2. During this hydrolysis operation, the mixture is vigorously stirred. After disappearance of all solid material, the layers are separated and the aqueous layer is extracted five times with small portions of Et_2O. The organic solutions are washed with saturated aqueous NH_4Cl and subsequently dried over $MgSO_4$, after which the greater part of the Et_2O is distilled off through a 40-cm Vigreux column, keeping the bath temperature below 80°C. After cooling to room temperature, the enyne ether is isolated by distillation *in vacuo* using a single receiver, cooled at 0°C (fig. 14). Ethoxybutenyne, b.p. 30-35°C/10mm, $n_D(20^\circ)$ 1.466 (*Z* : *E* ~15 : 85), is obtained in greater than 80% yields.

$HC{\equiv}CCH{=}CHOCH(CH_3)OC_2H_5$ (*Z* : *E* ~10 : 90), b.p. 66-68°C/10 mmHg, $n_D(20^\circ)$ 1.465, is obtained by a similar procedure in ~70% yield from $C_2H_5OCH(CH_3)OCH_2$-C≡$CCH_2OCH(CH_3)OC_2H_5$. In this elimination three (instead of two) equivalents of sodamide are required since $^-OCH(CH_3)OC_2H_5$ decomposes into $C_2H_5O^-$ and $CH_3CH{=}O$, the aldehyde consuming an extra equivalent of alkali amide for its conversion into $H_2C{=}CHONa$.

2.25 1-Methoxy-3-methyl-1,3-hexadien-5-yne

$$CH_3C{\equiv}C\text{-}\underset{\displaystyle OCH(CH_3)OC_2H_5}{\underset{|}{C}}\text{-}CH_2CH(OCH_3)_2 + 3\ KNH_2 \xrightarrow[-33^\circ C]{\text{liq. } NH_3} KC{\equiv}CCH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}\text{-}CH_2CH(OCH_3)_2 + KOC_2H_5 + H_2C{=}CH(OK)$$

$$KC{\equiv}CCH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}\text{-}CH_2CH(OCH_3)_2 + KNH_2 \longrightarrow KC{\equiv}CCH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}\text{-}CH{=}CHOCH_3 + KOCH_3$$

$$\xrightarrow{H_2O} HC{\equiv}CCH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}\text{-}CH{=}CHOCH_3$$

Scale: 0.50 molar.

Apparatus: fig. 4, 3 l.

Introduction

1-Methoxy-3-methyl-1,3-hexadien-5-yne has been used as a C-7 building block in a synthesis of vitamine A aldehyde [78]. In the procedure described below, the unsaturated ether is prepared by treatment of the protected (by addition to ethyl vinyl ether) propyne carbinol of $CH_3COCH_2CH(OCH_3)_2$ with four equivalents of potassium amide in liquid ammonia. In the first step, the protecting group is removed in a 1,4-elimination analogous to the one described in exp. 24. For this elimination three equivalents of potassium amide are required: one for the formation of the potassium acetylide, the other two for the elimination of H^+ and $^-O\text{-}CH(CH_3)OC_2H_5$. The latter group eliminates acetaldehyde which consumes an equivalent of alkali amide:

$$^-O\text{-}CH(CH_3)OC_2H_5 \longrightarrow CH_3CH{=}O + C_2H_5O^- \xrightarrow{NH_2^-} H_2C{=}CH\text{-}OK$$

In a relatively slow subsequent reaction, methanol is eliminated from the initially formed elimination product. If *sodamide* (insoluble) is used, this elimination of methanol proceeds sluggishly and a large excess of this base has to be used, while the reaction period is much longer (3 to 5 h; with 6 to 7 mol of $NaNH_2$).

The dienyne ether is very oxygen-sensitive and polymerizes rapidly at room temperature. The compound can be stored for a few days at -80°C in an undiluted state.

Procedure

The starting compound (0.50 mol, note 1) is added dropwise over 30 min to a solution of 2.2 mol of potassium amide [1,3,4] in 1.5 l of liquid ammonia. After an additional 2 h the dropping funnel is replaced by a powder funnel and 100 g of powdered ammonium chloride is

added in 2-g portions over 15 minutes. The greater part of the ammonia is then removed by placing the flask in a water bath at 35°C. Dichloromethane (200 ml) is added to the remaining slurry, followed by ice water (500 ml over 5-10 min). After separation of the layers, the aqueous layer is extracted four times with 30-ml portions of dichloromethane. The combined organic solutions are washed with saturated aqueous NH_4Cl and subsequently dried over potassium carbonate. The solvent is then removed in a water-pump vacuum, with the temperature of the heating bath not exceeding 35°C. The remaining liquid is distilled at oil-pump pressure, keeping the bath temperature below 90°C. The liquid collected in the single receiver (fig. 14, cooled at 0°C) is redistilled to give $HC{\equiv}CCH{=}C(CH_3)$-$CH{=}CHOCH_3$, b.p. 50°C/1 mmHg, $n_D(20°)$ 1.548-1.551 as a mixture of comparable amounts of the *E*- and *Z*-isomer. Yields are greater than 80%. In both isomers the configuration of the Δ 1,2 double bond is *E*.

Notes

1. Prepared by addition of $CH_3C{\equiv}CC(CH_3)(OH)CH_2CH(OCH_3)_2$ (p. 86) to ethyl vinyl ether (for this procedure see p. 265).

2.26 1-*N*,*N*-Diethylamino-2,4-pentadiyne

$$C_2H_5SCH{=}CHC{\equiv}CCH_2NEt_2 + 2\,KNH_2 \xrightarrow[-33°C]{\text{liq. } NH_3} KC{\equiv}CC{\equiv}CCH_2NEt_2 + KSC_2H_5$$

$$KC{\equiv}CC{\equiv}CCH_2NEt_2 \xrightarrow{H_2O} HC{\equiv}CC{\equiv}CCH_2NEt_2$$

Scale: 0.20 molar.

Apparatus: fig. 4, 1 l.

Introduction

Thiols very readily add to diacetylene in the presence of bases, such as alkoxides, with formation of enyne sulfides $HC{\equiv}CCH{=}CHSR$ [175]. In strongly basic media, thiol can be eliminated from these enyne derivatives [2]. Thus, functionalization of $HC{\equiv}CCH{=}CHSR$ followed by treatment with an excess of sodium amide results in a derivative of butadiyne. This sequence of conversions permits the synthesis of some 1,3-diyne systems that are not otherwise easily accessible.

Procedure

A mixture of 0.20 mol of the starting compound (p. 213) and 200 ml of Et_2O is added dropwise over 20 min to a vigorously stirred suspension of 0.5 mol of potassium amide [1,3,5] in 500 ml of liquid ammonia. Subsequently the ammonia is removed by placing the flask in a water bath at 40-50°C. When the stream of evaporating ammonia has become faint,

introduction of N_2 (500 ml/min) is started, 250 ml of Et_2O is added and the flask is immersed in an ice water bath. Ice water (500 ml) is added to the flask over 5 to 10 min with vigorous stirring. After separation of the layers, the aqueous layer is extracted seven times with small portions of Et_2O. The combined organic solutions are washed with saturated aqueous NH_4Cl and subsequently dried over K_2CO_3. After removal of the Et_2O in a water-pump vacuum, the remaining liquid is distilled through a short Vigreux column under oil-pump vacuum. The diyne amine, b.p. ~50°C/0.4 mmHg, $n_D(20°)$ 1.4928, is obtained in an excellent yield.

2.27 Addition of Bromine to Olefinic Compounds

$$RCH{=}CH_2 + Br_2 \xrightarrow{Et_2O \text{ or } CH_2Cl_2} RCHBrCH_2Br$$

Scale: 0.50 molar

Apparatus: fig. 1, 1 l.

Procedure

The olefinic compound (0.50 mol, freshly distilled) is mixed with 150 ml of dry Et_2O (or CH_2Cl_2, note 1). Bromine (0.50 mol, dried by shaking with 96% H_2SO_4 and subsequent distillation) is added with cooling below -40°C (occasional cooling in a bath with liquid N_2 allows a rapid addition). Usually a slight excess of Br_2 is added. In most cases the reaction is very fast. In the case of acrolein, however, addition of the first milliliters of Br_2 to the ethereal solution gives a brown colour, which persists for about 5 min. The remainder of the bromine added after disappearance of this colour reacts immediately. In the reactions with vinyl sulfides (see ref. 1 for the preparation), cyclooctene and vinylpyridine, a faint yellow or brown colour is present throughout the addition, so that the colour is no reliable indicator (one should, in any case, add a slight molar excess of bromine). In some cases, it is convenient to carry out the subsequent dehydrohalogenation with the ethereal solution of the adduct (note 2). Dibromo compounds obtained from vinylic ethers or sulfides and acrolein are unstable and must be used for the further reaction without delay.

Notes

1. Propene and 1-butene are first liquified in a trap cooled in a bath at -78°C, then 50 ml of cold (< -50°C) Et_2O or CH_2Cl_2 is added and the solution is added to 150 ml of Et_2O or CH_2Cl_2 cooled below -50°C. Generally CH_2Cl_2 can be used as solvent instead of Et_2O (see, however, note 2); the addition seems to proceed faster in the former solvent, which we recommend for the cases of acrolein, cyclooctene and vinylpyridine.
2. Since CH_2Cl_2 is attacked by strong bases, this solvent has to be removed completely if the dehydrohalogenation is carried out with alkali amides or *t*-BuOK.

2.28 2-Bromovinyl Ethyl Ether

$$BrCH_2CH(Br)OC_2H_5 + PhN(C_2H_5)_2 \xrightarrow{90\text{-}100^\circ C} BrCH{=}CHOC_2H_5 + PhN(C_2H_5)_2.HBr$$

Scale: 1.0 molar.

Apparatus: fig. 1, 2 l; stirrer: fig. 3.

Procedure

The adduct from Br_2 and $H_2C{=}CHOC_2H_5$ (1.0 mol, see exp. 27, freed from Et_2O by evacuation and warming in a bath at 40°C) is added over 15 min to 2.0 mol of *N,N*-diethylaniline heated to 98°C. During this addition the temperature is kept between 95 and 100°C (note 1). The reaction is slightly exothermic. After an additional 20 min at 95°C, the dark reaction mixture is cooled to below 60°C (part of the $PhN(C_2H_5)_2.HBr$ crystallizes out) and 500 ml of ice water is added with efficient stirring. After dissolution of the salt and cooling to below 10°C, a cold (0°C) mixture of 90 g of 36% hydrochloric acid and 200 ml of water is added over 10 min with efficient stirring (note 2). Seven extractions with a 1:1 mixture of Et_2O and pentane are then carried out. After drying the combined organic solutions over $MgSO_4$, the greater part of the solvent is distilled off through a 40-cm Vigreux column (bath temperature not higher than 90°C). The remaining liquid is distilled through the same column and the distillate collected in a single receiver, cooled at 0°C. An *E/Z* -mixture of $BrCH{=}CHOC_2H_5$ (note 3), b.p. 28-47°C/12 mmHg, is obtained in ~65% yield (note 4). The residue consists mainly of $PhN(C_2H_5)_2$ and $BrCH_2CH(OC_2H_5)_2$.

Notes

1. Above 100°C a vigorous reaction resulting in the formation of tars and a lachrymatory compound (possibly $BrCH_2CH{=}O$) may set in.
2. A short measure of HCl is used for the dissolution of the excess of $PhN(C_2H_5)_2$ to minimize the risk of acid-catalysed hydration of the bromovinyl ether.
3. The ratio may vary: usually the *Z*-isomer predominates.
4. Most of the diethylaniline can be recovered by adding a 50% aqueous solution of KOH (2 mol) to the combined aqueous layers. The organic layer is dried over K_2CO_3 and subsequently distilled *in vacuo*. Yields obtained by carrying out the dehydrohalogenation with recovered diethylaniline may be ~10% higher. Commercially available $PhN(C_2H_5)_2$ may contain some $PhNH(C_2H_5)$ which is removed during the dehydrohalogenation giving the quaternization product with the dibromo ether: this remains in the aqueous phase during treatment with KOH.

2.29 Conversion of the Adduct from Bromine and Acrolein into the Dimethyl and Diethyl Acetal

$$BrCH_2CHBrCH{=}O + HC(OR)_3 \xrightarrow[ROH]{ZnCl_2} BrCH_2CH(Br)CH(OR)_2 + HCOOR$$

Scale: 0.50 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a mechanical stirrer, a thermomether and a vent.

Procedure

An ethereal solution of $BrCH_2CHBrCH{=}O$ is prepared by adding bromine (0.50 mol + 2 ml excess) to a mixture of 0.50 mol of freshly distilled acrolein and 50 ml of Et_2O (compare exp. 27). Freshly distilled methyl- or ethyl orthoformate (0.6 mol) and methanol or ethanol (5 ml), respectively, are subsequently added at 10°C to the light-brown solution. A moderately exothermic reaction ensues and the temperature gradually rises to *ca.* 40°C (some cooling may be necessary). When the reaction has ceased (evidenced by dropping of the temperature), 6 g of powdered zinc chloride is added at 35°C, which causes a limited rise in temperature. After an additional 30 min (at ~40°C) an additional amount of 5 g of $ZnCl_2$ is added and stirring at 40°C is continued for 15 minutes. The mixture is then poured into 300 ml of an aqueous solution of 100 g of ammonium chloride. After vigorous shaking, the organic layer is separated, washed once with a small amount of aqueous NH_4Cl and subsequently dried over anhydrous K_2CO_3. After filtration and rinsing of the drying agent with Et_2O, the volatile components are removed in a water-pump vacuum, the last traces in a vacuum of 1 mmHg or less (while heating in a water bath at 35°C). The remaining liquid (yield 90% or higher) is used for the dehydrobromination reaction.

2.30 1-Bromocyclooctene

$$\text{-CH(Br)-CH(Br)-} + 2\,t\text{-BuOK} \xrightarrow[0\text{-}5^\circ C]{THF\text{-}Et_2O} \text{-C(H)=C(Br)-} + t\text{-BuOH}.t\text{-BuOK}\downarrow + KBr\downarrow$$

Scale: 1.0 molar.

Apparatus: fig. 1, 2 l; stirrer: fig. 3.

Procedure

After the dichloromethane has been thoroughly removed from the dibromo adduct (exp. 27), 400 ml of dry Et_2O is added to the remaining liquid. A solution of 2.0 mol (note 1) of

t-BuOK in 200 ml of THF is added over 30 min, while keeping the temperature at about -10°C. A rather thick suspension is gradually formed. Stirring is continued for an additional period of 2.5 h at 0 to 5°C, then ice water (500 ml) is added. The aqueous layer is extracted three times with Et_2O. The combined organic solutions are washed with a saturated solution of ammonium chloride and subsequently dried over $MgSO_4$. After removal of the solvent *in vacuo*, the remaining liquid is carefully distilled through a 40-cm Vigreux column giving 1-bromocyclooctene, b.p. 90°C/18 mmHg, $n_D(20°)$ 1.5187, in yields of at least 70%. The first fraction (b.p. 40-90°C) contains some cyclooctyne.

Notes

1. The *t*-butylalcohol formed in the reaction, complexes to *t*-BuOK. This 1:1 complex is much less reactive, hence 100% excess of *t*-BuOK is used.

2.31 Geminal 1,1-Dichloroalkanes

$$RCl + H_2C{=}CHCl \xrightarrow{AlCl_3} RCH_2CHCl_2 \qquad (R = i\text{-}C_3H_7,\ t\text{-Bu},\ c\text{-alkyl})$$

Scale: 1.0 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a mechanical stirrer, a combination of thermometer and vent and a stopper.

Procedure

The dry (note 1) alkyl- or cycloalkyl halide (1.0 mol) is placed in the flask. After cooling to -40°C (note 2), 5 g of powdered sublimed anhydrous $AlCl_3$ and 10 ml of vinyl chloride are successively added (note 3). After an initiation period of a few minutes, the temperature rises to about -30°C within about one minute and the mixture turns orange. After the exothermic reaction has subsided, the remainder of the vinyl chloride (total amount 1.3 mol) is added over 45 minutes in 10-g portions. The temperature of the mixture is kept between -35 and -45°C. After completion of the addition, the temperature is allowed to rise to -15°C over 30 min, then 75 ml of 2 N hydrochloric acid is added with vigorous stirring. After careful separation (note 4) the organic layer is dried over $MgSO_4$. The excess of vinyl chloride is removed by evacuation. The residue (~100% yield) is used for the conversion into the acetylenes. The purity as judged from ^1H NMR spectra, is satisfactory.

Notes

1. It is essential to use pure and dry alkyl- and cycloalkyl chlorides. If water or ROH is present, the reaction starts at considerably higher temperatures and less pure products are obtained.
2. *t*-Butyl chloride is solid at this temperature: in this case, the first portion of vinyl chloride is added at *ca.* -25°C and the temperature is gradually lowered during the addition period.
3. The vinyl chloride is cooled to -60°C (cold trap). During the portionwise addition, the stopper is temporarily removed.
4. In the case of $i\text{-}C_3H_7CH_2CHCl_2$ some ammonium chloride should be added in order to effect a satisfactory separation of the layers.

2.32 Z-1,4-Dichloro-2-butene

$$HOCH_2CH{=}CHCH_2OH + 2\,SOCl_2 \longrightarrow ClOSOCH_2CH{=}CHCH_2OSOCl + 2\,HCl\uparrow$$
$$\downarrow$$
$$ClCH_2CH{=}CHCH_2Cl + 2\,SO_2\uparrow$$

Scale: 1.0 molar.

Apparatus: fig. 1, 2 l: the outlet is connected with a drying tube filled with lumps of calcium chloride.

Procedure

Z-Butenediol (1.0 mol, commercially available) and pyridine (5 ml) are placed in the flask. Thionyl chloride (2.25 mol) is added over 1 h, while cooling the mixture between 0 and 5°C (ice bath). The net heating effect is moderate, due to the evolution of gasses. After completion of the addition, the flask is placed in a large ice bath and left overnight. The mixture is then subjected to a careful distillation (water-pump) using a 40-cm Widmer column, and a single receiver, cooled in an ice bath. It may take a rather long time before the minimal pressure (10 to 20 mmHg) is reached, presumably because the decomposition of the intermediates is still incomplete. *Z*-Dichlorobutene, b.p. 45°C/10 mmHg, $n_D(20°C)$ 1.4883, is obtained in >80% yield.

2.33 Tetrahydrofurfuryl Chloride

$$THF\text{-}CH_2OH + SOCl_2 \xrightarrow{pyridine} THF\text{-}CH_2Cl + SO_2\uparrow \quad (+ \text{pyridine.HCl}\downarrow)$$

Scale: 1.0 molar.

Apparatus: see exp. 32; stirrer: fig. 3.

Procedure

Tetrahydrofurfuryl alcohol (1.0 mol) and dry pyridine (250 ml, note 1) are placed in the flask. Thionyl chloride (1.1 mol) is added dropwise over 30 min. The temperature is kept between 70 and 80°C by occasional cooling. The thick suspension formed in the beginning, disappears gradually and the reaction mixture turns very dark. After completion of the addition, stirring is

continued for 1.5 h. The mixture is then cooled to 20°C and 1 l of ice water is added as quickly as possible with vigorous stirring. Fifteen extractions with Et_2O are carried out. The combined extracts are washed with a cold 2 N solution of hydrochloric acid saturated with ammonium chloride in order to remove dissolved pyridine. After drying the extract over $MgSO_4$, the greater part of the Et_2O is distilled off at normal pressure through a 40-cm Vigreux column. Distillation of the remaining liquid *in vacuo* gives tetrahydrofurfuryl chloride, b.p. 45°C/10 mmHg, $n_D(20°)$ 1.4557, in 70% or somewhat higher yield.

Notes

1. When no or only a catalytic amount of pyridine is used (compare previous exp.) only tars are obtained.

2.34 2-Iodo-1-nitro-2-*t*-butylethene

$$2\ t\text{-BuC}{\equiv}\text{CH} + I_2 + N_2O_4 \longrightarrow 2\ t\text{-BuC(I)}{=}\text{CHNO}_2$$

Scale: 0.30 molar.

Apparatus: fig. 1, 500 ml.

Procedure

t-Butylacetylene (0.30 mol, see exps. 2 and 3), dichloromethane (75 ml) and iodine (0.20 mol, 52 g) are placed in the flask. A solution of 0.20 mol (18.4 g) of dinitrogen tetroxide (note 1) in 50 ml of dichloromethane is added in 20 equal portions over 1.5 h, while keeping the temperature between 25 and 30°C. The reaction is weakly exothermic. The brown mixture is allowed to stand for ~30 h at room temperature, after which the excess of N_2O_4 is removed by evacuation (water aspirator). The remaining brown solution is then shaken with 100 ml of an aqueous solution of 20 g of $Na_2S_2O_3$. The product is extracted with Et_2O. After drying the ethereal solution over $MgSO_4$, the solvent is thoroughly removed *in vacuo*. The remaining yellow liquid is distilled through a short Vigreux column giving the adduct, b.p. 75-80°C/0.5 mmHg, $n_D(20°)$ 1.5445, in ~80% yield. The product consists of the *E* and *Z*-isomer: both isomers seem to undergo elimination of HI with KOH to give *t*-butyl nitroacetylene (see exp. 18).

Notes

1. N_2O_4 is commercially available in lecture bottles: it should be possible, however, to prepare it by controlled addition of concentrated nitric acid to copper with simultaneous introduction of air to convert the NO into N_2O_4.

2.35 *N,N*-Dimethylthioacetamide and 1-Dimethylamino-1-butylthioethene

$$5\ CH_3\overset{\overset{O}{\|}}{C}NMe_2 + P_2S_5 \xrightarrow{\text{toluene}} 5\ CH_3\overset{\overset{S}{\|}}{C}NMe_2 + P_2O_5\downarrow$$

$$CH_3\overset{\overset{S}{\|}}{C}NMe_2 + KNH_2 \xrightarrow{\text{liq.}NH_3} H_2C{=}\overset{\overset{SK}{|}}{C}{-}NMe_2$$

$$H_2C{=}\overset{\overset{SK}{|}}{C}{-}NMe_2 + BuBr \xrightarrow{\text{liq.}NH_3} H_2C{=}\overset{\overset{SBu}{|}}{C}{-}NMe_2 + KBr$$

Scale: 1.0 molar.

Apparatus: for the reaction with P_2S_5: 2-l round-bottomed, three-necked flask, equipped with a powder funnel, a mechanical stirrer and a thermometer with a vent; for the S-alkylation: fig. 4, 3 l.

Procedure

Toluene (160 g) and *N,N*-dimethylacetamide (1.0 mol) are placed in the flask. Finely powdered phosphorous pentasulfide (50 g, excess) is added in one portion with vigorous stirring (after the addition, the powder funnel is replaced by a stopper). The temperature rises within 20 min to about 60°C. A resinous lump or slurry ($P_2O_5 + P_2S_5$) is formed on the bottom of the flask. The warm, yellow or orange solution is then poured into another flask. P_2S_5 (25 g) is added and stirring at *ca.* 60°C is continued for an additional half hour. The solution is then decanted from the solid. The solid material in the flasks is covered with 100 ml of water. After about 2 h the solid has dissolved completely. The combined aqueous layers are extracted fifteen times with dichloromethane (25-ml portions) and the unwashed solutions are dried over $MgSO_4$. The greater part of the dichloromethane is distilled off at atmospheric pressure. To the remaining volume of ~50 ml, 250 ml of dry Et_2O is added with swirling, followed by the decanted toluene solution. The combined solutions are cooled to -50°C for 1-2 h. The solid material then is collected on a sintered glass funnel and rinsed well with a cold (~ -60°C) 1:1 mixture of Et_2O and pentane. Concentration of the mother liquors and subsequent recooling gives an additional amount of solid material. After drying in a vacuum, reasonably pure (~95%) thioamide is obtained in excellent yield. This product is used for the next reaction. The thioamide (1.0 mol) is added in 2-g portions over 15 min to a solution of 1.1 mol of potassium amide [1,3,4] in 1.5 l of liquid ammonia (the dropping funnel is temporarily replaced by a powder funnel). After an additional 10 min, butyl bromide (1.2 mol) is added dropwise over 30 min. Stirring is continued for another half hour, then the ammonia is allowed to evaporate overnight (fig. 11). Dichloromethane (200 ml) and water (500 ml) are then added at room temperature with stirring. After separation of the layers, five

extractions with small portions of CH_2Cl_2 are carried out. The unwashed organic solutions are dried over $MgSO_4$ and subsequently concentrated in a water-pump vacuum. Distillation of the remaining liquid through a 40-cm Vigreux column gives the ketene-S,N-acetal, b.p. 80°C/10 mmHg, $n_D(20°)$ 1.4896, in 84% yield.

Notes

1. All operations should be carried out in a well-ventilated hood, because of the stench evolved during working with P_2S_5 and the ketene-S,N- acetal.

2.36 1,2,5,6-Tetrabromohexane

$$2\ H_2C{=}CHCH_2Br + Mg \xrightarrow[\text{reflux}]{Et_2O} H_2C{=}CHCH_2CH_2CH{=}CH_2 + MgBr_2\downarrow$$

$$H_2C{=}CHCH_2CH_2CH{=}CH_2 + Br_2 \xrightarrow[<\,-20°C]{Et_2O} BrCH_2CH(Br)CH(Br)CH_2Br$$

Scale: 1.0 molar (allyl bromide).

Apparatus: 2-l round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer and a reflux condenser; for the addition of bromine, the reflux condenser is replaced with a thermometer-outlet combination.

Procedure

Dry magnesium turnings (0.50 mol, 12 g) and dry Et_2O (500 ml) are placed in the flask. Iodine (~0.2 g) is added. When the brown colour has disappeared, the addition of allyl bromide (1.0 mol) is started and the mixture allowed to reflux. After the addition, which is carried out over 45 min, ether reflux is continued for an additional hour. The mixture is then cooled to ~+20°C (the reflux condenser is replaced with the thermometer) and 0.5 g of copper(I) bromide is added (note 1) with vigorous stirring. After 15 min the stirred mixture is cooled to below -30°C (the two-layer system forms a suspension), and bromine (dried by shaking with 96% H_2SO_4 and subsequent distillation, about 1 mol) is placed in the dropping funnel and added dropwise. Towards the end of the addition, the temperature of the mixture is raised to about -10°C. The addition of Br_2 is stopped as soon as the solution has turned uniformly brown. The thick brown suspension is then transferred (note 2) into a 3-l wide-necked conical flask, containing 500 ml of an aqueous solution of 50 g of NH_4Cl. The small amount of suspension remaining in the flask is hydrolysed by addition of NH_4Cl solution. After shaking and separation of the layers, the aqueous layer is extracted twice with Et_2O. The organic solution is dried over $MgSO_4$, after which it is concentrated *in vacuo* to a volume of about 150 ml. This solution (note 3) is used for the conversion into 1,5-hexadiyne.

Notes

1. When more than 0.50 mol of Mg is used and the allyl bromide is added too quickly, the solution may contain some $H_2C{=}CHCH_2MgBr$. The copper bromide is added to complete the reaction between allyl bromide and $H_2C{=}CHCH_2MgBr$.
2. One should never carry out the hydrolysis in the inverse sense, as this may result in the evolution of much heat and loss of part of the reaction mixture.
3. Concentration may lead to (partial) crystallization of the tetrabromo compound.

2.37 Isopropenylacetylene

$$HC{\equiv}CC(CH_3)_2OH + (CH_3CO)_2O \xrightarrow[\text{heat}]{p\text{-tol.sulf.acid}} HC{\equiv}CC(CH_3){=}CH_2 + 2\ CH_3COOH$$

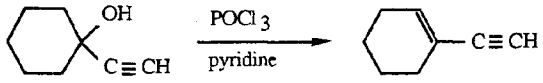
Scale: 1.0 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer and a 40-cm Vigreux column, connected to a condenser and a receiver, cooled at -20°C; stirring is carried out at a moderate rate; all connections should be made gas-tight.

Procedure

The flask is charged with 1.3 mol of acetic anhydride and 7 g of *p*-toluenesulfonic acid monohydrate (or, if available, the anhydrous acid). The acetylenic carbinol (1.0 mol, commercially available, see also p. 88) is added over 10 min with some cooling. The flask is then quickly heated until the enyne begins to distill out. Further heating is carried out in a controlled way, so that the enyne does not distil too fast: the greater part should pass over below 60°C. As the bath temperature is increased the reaction mixture turns very dark. When, after 45-60 min, the temperature in the head of the column has reached 100°C, heating is stopped. The distillate is washed twice in a small separatory funnel with 10-15 ml of cold 3 N KOH solution, in order to remove traces of acetic acid. Redistillation from 5 g of anhydrous $MgSO_4$ gives pure isopropenylacetylene, b.p. ~35°C/760 mmHg, $n_D(20°)$ 1.4173, in 62-70% yield. The compound should be stored in a refrigerator (-20 to -30°C): under these conditions polymerization is slow.

2.38 1-Ethynylcyclohexene



[162]

Scale: 0.5 molar.

Apparatus: fig. 1, 1 l.

Procedure

A mixture of 0.5 mol of ethynylcyclohexanol (commercially available, see also p. 92) and 90 ml of pyridine (note 1) is heated to 100°C. A mixture of 33 ml of phosphorylchloride and 40 ml of pyridine is then added over 15 min, while stirring at a moderate rate. The temperature of the reaction mixture is kept between 105 and 110°C by occasional cooling or temporarily increasing the rate of stirring. After the addition, heating at 105-110°C is continued for 15 min. The mixture is cooled to below 75°C (partial solidification), and 400 ml of ice water is poured into the flask. After vigorous stirring, the layers are separated and five to seven extractions with small portions of a 1:1 mixture of Et_2O and pentane are carried out. The combined organic layers are washed with cold 3 N hydrochloric acid in order to remove pyridine. After drying over $MgSO_4$, the greater part of the solvent is distilled off at atmospheric pressure through a 40-cm Vigreux column. Distillation of the remaining liquid *in vacuo* (using a single receiver cooled in an ice bath) gives 1-ethynylcyclohexene, b.p. 38°C/12 mmHg, $n_D(20°)$ 1.4968, in excellent yield.

1-Ethynylcyclopentene, b.p. ~55°C/120 mmHg, $n_D(20°)$ 1.4890, and 1-ethynylcycloheptene, b.p. 52°C/12 mmHg, $n_D(20°)$ 1.5009, are obtained in high yields from the ethynylcarbinols. The enynes polymerize slowly on storage in a refrigerator.

Notes

1. Pyridine previously dried over powdered KOH is used

2.39 1,3-Hexadien-5-yne

$$HC{\equiv}CCH_2CH(OTs)CH{=}CH_2 + KOH \xrightarrow[\text{heat}]{H_2O,\ DMSO} HC{\equiv}CCH{=}CHCH{=}CH_2 + TsOK$$

Scale: 0.30 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel/gas-inlet combination, a mechanical stirrer and a 20-cm Vigreux column, connnected to a condenser and 250-ml (single) receiver, cooled in an ice bath; all connections should be made gas-tight.

Procedure

Potassium hydroxide (110 g) is dissolved in 120 ml of water and 40 ml of DMSO. After the air in the flask has been completely replaced by nitrogen, the solution is heated in a bath at 100-110°C. When the temperature of the solution has reached 90°C, the flow of nitrogen is

regulated to 100 ml/min and the tosylate (0.30 mol, for the preparation see Chap. XII, Section 1, note 1) is added over 10-15 min to the vigorously stirred solution. During the vigorous reaction a mixture of the dienyne and water passes over. After about half an hour, only water distills out. Remaining traces of the dienyne may be forced into the condenser by temporary introduction of a vigorous stream of nitrogen for a few seconds. The contents of the receiver are shaken with anhydrous $MgSO_4$ (~5 g) in order to remove the water. The receiver is subsequently equipped for a vacuum distillation (20-cm Vigreux column, condenser, single receiver, cooled in a bath at -70°C, see fig. 14). The apparatus is evacuated using a water aspirator (10 to 20 mmHg). A mixture of *E*- and *Z*-$HC{\equiv}CCH{=}CHCH{=}CH_2$ (*E* / *Z* ratio ~1), $n_D(20°)$ 1.5045, condenses in the receiver. The yield is usually greater than 80%.

Other volatile enynes, *e.g.* $HC{\equiv}CCH{=}CHCH_3$ and $HC{\equiv}CCH{=}CHC_2H_5$ can be prepared (yields >80%) in a similar way from the corresponding tosylates. Comparable amounts of the *E* and *Z*-isomers are obtained. These compounds can be redistilled at atmospheric pressure: $HC{\equiv}CCH{=}CHCH_3$, b.p. 44-51°C/760 mmHg; $HC{\equiv}CCH{=}CHC_2H_5$, b.p. 73-78°C/760 mmHg.

Notes

1. It is essential that the Et_2O (used in the preparation of the tosylate) is thoroughly removed: distillative separation of Et_2O from the unstable acetylenic compound at atmospheric pressure involves the risk of explosive decomposition.

2.40 3,5-Heptadien-1-yne

$$HC{\equiv}CCH_2CH(OH)CH{=}CHCH_3 + p\text{-}CH_3C_6H_4SO_2Cl + KOH \xrightarrow[Et_2O]{0°C}$$

$$\longrightarrow HC{\equiv}CCH_2CH(OTs)CH{=}CHCH_3 + KCl + H_2O$$

$$\downarrow \begin{matrix} KOH \\ Et_2O,\ 0°C \rightarrow \text{reflux} \end{matrix}$$

$$\underset{E/Z}{HC{\equiv}CCH{=}CHCH{=}}\underset{E}{CHCH_3} + p\text{-}CH_3C_6H_4SO_2OK + H_2O$$

Scale: 0.25 molar.

Apparatus: for the preparation of the tosylate; 2-l round-bottomed, three-necked flask, equipped with a powder funnel, a mechanical stirrer (fig. 3) and a thermometer; for the preparation of the enyne, the powder funnel is replaced by a gas inlet and the thermometer by a reflux condenser.

Introduction

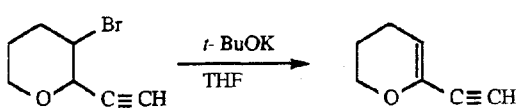
3,5-Heptadien-1-yne is less volatile and presumably more stable than 1,3-hexadien-5-yne. Distillative separation at atmospheric pressure from Et_2O should therefore be possible without involving the risk of polymerization or decomposition. This allows the preparation of the tosylate and its conversion into the dienyne in the same pot, using Et_2O as solvent. Other enynes with a b.p. >100°C/760 mmHg can be prepared in a similar way.

Procedure

A mixture of 0.25 mol of the carbinol (p. 96), 350 ml of Et_2O and 0.35 mol (excess) of tosyl chloride is placed in the flask. After dissolution of the tosylchloride, the solution is cooled to -5°C (dry-ice acetone bath). Freshly, machine-powdered KOH (140 g) is added in 5-g portions over 15 min to the vigorously stirred mixture while maintaining the temperature between -10 and 0°C. The air is then completely replaced by nitrogen and the cooling bath is removed. At about 15°C an exothermic reaction starts, and after an additional 10 to 15 min the ether begins to reflux. The mixture is heated for another hour under reflux. After cooling to room temperature, the thick slurry is poured into 500 ml of ice water and the flask rinsed with a small amount of ice water. After vigorous shaking and separation of the layers, the aqueous layer is extracted three times with small portions of Et_2O. The combined organic solutions are washed with saturated aqueous ammonium chloride and subsequently dried over $MgSO_4$. The greater part of the Et_2O is then distilled off (under a slow stream of N_2) at atmospheric pressure through a 40-cm Widmer column. The temperature of the heating bath is kept between 80 and 90°C during the last stage of this distillation. After cooling to 20°C, the remaining liquid is carefully distilled in a partial vacuum, giving the dienyne, b.p. ~30 - 40°C/40 mmHg, $n_D(20°)$ 1.5204 (*E*/*Z*-ratio ~40:60, the double bond between C-5 and C-6 has the *E*-configuration), in an excellent yield.

HC≡CCH=CHPh (*Z*/*E*-ratio ~55:45), b.p. ~55°C/0.4 mmHg, $n_D(20°)$ 1.6052, is obtained in an excellent yield from $HC{\equiv}CCH_2CH(OH)Ph$ by a similar procedure. For the preparation of the starting compound, see p. 67.

2.41 6-Ethynyl-2,3-dihydro-4H-pyran



[2]

Scale: 0.10 molar.

Apparatus: fig. 1, 500 ml.

Procedure

3-Bromo-2-ethynyltetrahydropyran (0.10 mol, p. 70) is added over 15 min to a solution of 0.20 mol of *t*-BuOK in 150 ml of THF. During this addition the reaction mixture is kept between -10 and -20°C. After an additional 15 min, the temperature is allowed to rise to 10-20°C. Finally the suspension is warmed to 40°C. A solution of 25 g of NH_4Cl in 200 ml of water is then added with vigorous stirring. After separation of the layers, three extractions with Et_2O are carried out. The combined organic solutions are washed three times with water and subsequently dried over $MgSO_4$. After concentration of the solution under reduced pressure, the remaining liquid is distilled through a 20-cm Vigreux column to give the enyne ether, b.p. 54°C/10 mmHg, $n_D(18°)$ 1.5002, in ~90% yield.

Other alkynyl bromoethers, *e.g.* $BrCH_2CH(C{\equiv}CH)OC_2H_5$, can be dehydrohalogenated in a similar way.

Chapter X
Couplings of Acetylenes, Assisted by Copper and Palladium Compounds

1. Mannich Reactions - General Introduction

Compounds with a terminal triple bond can undergo a Mannich condensation with formaldehyde and secondary aliphatic or alicyclic amines [193].

$$RC{\equiv}CH + H_2C{=}O + R'_2NH \longrightarrow RC{\equiv}CCH_2NR'_2 + H_2O$$

The formation of the acetylenic tertiary amines may be visualized as a nucleophilic attack of the acetylide-anion on the imonium ion $R'_2N\text{-}^+CH_2$ which is in equilibrium with the dialkylaminomethanol R'_2NCH_2OH. These compounds are easily formed at room temperature or slightly elevated temperatures from the secondary amines and polymeric formaldehyde (paraformaldehyde). The reaction of R'_2NCH_2OH with acetylenes is usually carried out at temperatures in the region of 100°C in an organic solvent such as dioxane. Acetylenes with a conjugated unsaturated system, RCH=CHC≡CH and RC≡CC≡CH, arylacetylenes, ArC≡CH, and ethynyl sulfides, HC≡CSR, react more easily than do alkylacetylenes, in which the ethynyl proton is less "mobile". The reaction times, which are quite long for alkylacetylenes, can be shortened to one or a few hours by carrying out the reactions in the presence of a small amount of a copper salt ($Cu(OAc)_2$, $CuCl_2$, Cu_2Cl_2) [15]. This forms a copper(I) compound with the acetylene. The copper acetylide is often visible as a yellow solid during the reaction; this solid disappears or is replaced by a red suspension of copper, when the conversion, carried out with an excess of R'_2NCH_2OH, is complete. It is advisable, however, to use no, or only a small excess of the secondary amine and paraformaldehyde, because the presence of R'_2NCH_2OH may give rise to difficulties during the purification of the aminoacetylenes (partial decomposition during distillation) especially in the cases of the more volatile representatives. The yields of the copper-catalysed Mannich reactions with acetylenic derivatives are usually high. The reactions with volatile acetylenes (especially gasses) require a more careful performance than those with b.p. of 60°C (at atmospheric pressure) or higher. Too fast addition, or introduction of the gas may lead to incomplete conversion (lowering of the attainable temperature in the reaction mixture).

1.1 Preparation of Dimethylaminomethanol and Diethylaminomethanol

$$H_2C{=}O + R'_2NH \xrightarrow{\text{dioxane}} R'_2NCH_2OH \qquad (R' = CH_3 \text{ or } C_2H_5)$$

Scale: 1.0 molar.

Apparatus: 1-l three-necked, round-bottomed flask, equipped with a stopper (which is temporarily removed during the addition of the amine), a mechanical stirrer and a combination of a thermometer and a vent.

Procedure

Pure dioxane (70 ml) and powdered paraformaldehyde (30 g, corresponding to 1 mol of the monomer) are placed in the flask. Liquified dimethylamine (~0.3 mol), or diethylamine (~ 0.3 mol) is added at room temperature. The temperature of the mixture rises gradually to ~ 45°C. After cooling to room temperature, a second portion of ~ 0.3 mol of the amine is added. When the ensuing exothermic reaction has subsided, the remainder of the 1.2 mol of the amine is added at ~ 20°C. The conversion is completed by heating the mixture for 30 min at ~ 50°C. A slightly turbid solution is formed.

1.2 Mannich Reactions with Gaseous Acetylenes

$$RC{\equiv}CH + R'_2NCH_2OH \xrightarrow[90 - 100°C]{\text{dioxane, } Cu(OAc)_2} RC{\equiv}CCH_2NR'_2 + H_2O$$

Scale: 1.0 molar.

Apparatus: 1-l three-necked, round-bottomed flask, equipped with a gas inlet tube (reaching beneath the surface of the solution), a gas-tight mechanical stirrer and a reflux condenser; the inlet tube is connected with a trap containing the liquified acetylene, and the top of the condenser with a trap placed in a bath at -78°C; all connections are fixed well and made gas-tight.

Procedure

Copper(II) acetate (4 g) is added to the solution prepared in exp. 1. The mixture is brought to ~ 95°C by heating in an oil bath (at 100-105°C). The trap containing the acetylene (1.2-1.3 mol) is placed in a bath at 0-5°C (in the case of propyne) or 20-25°C (in the case of butyne and vinylacetylene). During the introduction of the acetylene, which takes ~ 1 h, the mixture is agitated vigorously. As soon as the trap has become empty, the two traps are interchanged. As a rule, only a small amount of unconverted acetylene appears to be present in the second trap. The introduction of gas and heating at ~100°C are continued until the amount of condensed acetylene in the second trap has become negligible. The brown suspension (in some cases yellow) is then cooled to room temperature. Although it is possible to isolate the product via an aqueous work-up, we prefer the following procedure (note 1). The reaction flask is equipped for a vacuum distillation, using a short Vigreux column, condenser and *single* receiver cooled in a bath at < -40°C (compare fig. 14). The apparatus is evacuated using a water aspirator (10-20 mmHg) and the reaction flask warmed in an oil bath (initial temperature

20°C), until the distillation has stopped completely. After some cooling, nitrogen is admitted. A small brown residue remains in the reaction flask. The distillate, a mixture of dioxane, water (~1 mol) and the desired product, is vigorously shaken with ~ 50 g of K_2CO_3 in order to remove the water. After suction filtration through sintered glass and thorough rinsing of the K_2CO_3 with Et_2O, a very careful distillation (note 2) through a 40-cm Widmer column is carried out. The amines R' = C_2H_5, R = CH_3, b.p. 45°C/12 mmHg, $n_D(20°)$ 1.4438, R = R' = C_2H_5, b.p. 63°C/10mmHg, $n_D(20°)$ 1.4432 and R = $H_2C{=}CH$, R' = C_2H_5, b.p. 68°C/10 mmHg, $n_D(20°)$ 1.4711, are obtained in high yields (mostly > 80%).

Notes

1. In the cases of the lower homologues, which have a reasonably good solubility in water, several extractions with Et_2O have to be carried out. The presence of insoluble copper compounds may give rise to difficulties with the separation of the layers.
2. In view of serious foaming, a relatively large distillation flask is used.

1.3 Mannich Reactions with Liquid Acetylenes

$$RC{\equiv}CH + R'_2NCH_2OH \xrightarrow[70 - 80 \text{ or } \sim 100°C]{\text{dioxane, } Cu(OAc)_2} RC{\equiv}CCH_2NR'_2 + H_2O$$

Scale: 0.5 molar.

Apparatus: for reactive acetylenes ($RC{\equiv}CC{\equiv}CH$, $RCH{=}CHC{\equiv}CH$, Aryl-$C{\equiv}CH$, Hetero-aryl-$C{\equiv}CH$, $RSC{\equiv}CH$, $RSCH{=}CHC{\equiv}CH$): fig. 1, 500 ml; for other acetylenes: a reflux condenser instead of the thermometer in fig. 1.

Procedure

After addition of 2 g of $Cu(OAc)_2$, the solution of R'_2NCH_2OH (half the amount of that prepared in exp. 1.1 is used) is brought to ~70°C, then the reactive acetylenic compound (0.55 mol) is added over ~ 20 min, while keeping the temperature between 70 and 80°C. The conversion is terminated by heating the mixture (brown suspension) for an additional half hour at 90°C, after which it is cooled to room temperature.

In the other cases, the reaction mixture is heated in a bath at 85°C and the acetylene is added dropwise over 30 min. Subsequently, the bath temperature is raised to 100-110°C. After an additional period of 2-2.5 h the mixture is cooled to room temperature.

In all cases the reaction mixture is poured into 500 ml of water, after which a sufficient number of extractions with Et_2O are carried out. The unwashed organic solutions are dried well over K_2CO_3 (shaking or stirring with ~ 60 g of K_2CO_3 for 15 min, then suction filtration and rinsing of the drying agent with Et_2O). The isolation is carried out as described in the previous procedure. Yields are generally higher than 80%.

The following compounds have been prepared: $C_4H_9C{\equiv}CCH_2N(CH_3)_2$, b.p. 60°C/12 mmHg, $n_D(20°)$ 1.4432; $C_4H_9C{\equiv}CCH_2N(C_2H_5)_2$, b.p. 86°C/12 mmHg, $n_D(20°)$ 1.4481; $C_2H_5CH{=}CHC{\equiv}CCH_2N(C_2H_5)_2$, b.p. 92-98°C/12 mmHg (*E*:*Z* ~ 1:1), $n_D(20°)$ 1.4754; *Z*-$C_2H_5SCH{=}CHC{\equiv}CCH_2N(C_2H_5)_2$, b.p. 142°C/12 mmHg (short Vigreux column), $n_D(20°)$ 1.5298; $C_4H_9C{\equiv}CC{\equiv}CCH_2N(C_2H_5)_2$, b.p. ~90°C/0.5 mmHg (20-cm Vigreux column), $n_D(20°)$ 1.5000; $CH_3OCH_2C{\equiv}CCH_2N(CH_3)_2$, b.p. 60°C/15 mmHg, $n_D(20°)$ 1.4450; $CH_3OCH_2C{\equiv}CCH_2N(C_2H_5)_2$, b.p. 77°C/15 mmHg, $n_D(20°)$ 1.4500.

2. Cadiot-Chodkiewicz Couplings - General Introduction

Compounds with a terminal acetylenic function, RC≡CH, react with 1-bromoalkynes, R'C≡CBr in the presence of an aliphatic amine and a catalytic amount of a copper(I) salt to give the coupling products RC≡CC≡CR'. This useful reaction, discovered by Cadiot and Chodkiewicz [195], gives a ready access to a number of poly-unsaturated systems. The usual procedure involves dropwise addition of the bromoacetylene R'C≡CBr to a mixture of the acetylene RC≡CH, ethylamine, ethanol or methanol, a catalytic amount of copper(I) chloride or bromide and a small amount of hydroxylamine.HCl. This reducing agent prevents the oxidation to copper(II). The reaction is usually very fast at temperatures in the region of 30°C. Since much heat is evolved, the reaction can be monitored easily by temperature observation.

$$RC{\equiv}CH + R'C{\equiv}CBr + EtNH_2 \xrightarrow{Cu^+} RC{\equiv}CC{\equiv}CR' + EtNH_2.HBr$$

A rather fast side-reaction, the formation of the symmetrical diyne R'C≡CC≡CR' from R'C≡CBr and Cu^+, can be suppressed by keeping the concentration of R'C≡CBr low.

$$2\ R'C{\equiv}CBr + Cu^+ \rightarrow \quad \rightarrow \quad \rightarrow\ R'C{\equiv}CC{\equiv}CR' + CuBr_2$$

This side-reaction is most serious in the case of acetylenes RC≡CH with a relatively low acidity: aliphatic 1-alkynes, *e.g.* 1-octyne, and acetylenic alcohols $HC{\equiv}C(CH_2)_nOH$ with n > 2, give reduced yields (40-50%) in the coupling reaction. In many other reactions, yields are high. Since the bromoalkyne usually has the highest "added value", economical considerations prescribe the use of an excess of the free acetylene, especially when it is inexpensive, e.g. propargyl alcohol. The mechanism of the Cadiot-Chodkiewicz reaction has not been studied in detail, but is seems likely that a copper acetylide RC≡CCu is formed first: it often appears as a yellowish suspension.

2.1 General procedure for Cadiot-Chodkiewicz Couplings

$$RC{\equiv}CH + R'C{\equiv}CBr + EtNH_2 \xrightarrow[NH_2OH.HCl,\ 30\text{-}40°C]{CH_3OH,\ H_2O,\ CuCl} RC{\equiv}CC{\equiv}CR' + EtNH_2.HBr$$

Scale: 0.20 molar.

Apparatus: fig. 1, 500 ml.

Procedure

Methanol (100 ml, note 1), a solution of 10 g of hydroxylamine.HCl in 35 ml of water, 80 ml of a 70% aqueous solution of ethylamine, and 1.5 g of copper(I)chloride are placed in the flask. The air is completely replaced by nitrogen, then stirring is started and the acetylene (0.20 mol + variable excess, note 2) is added in one portion. A yellowish solution or suspension is formed. The bromoalkyne (0.20 mol, see Chap VIII) is added over about 1 h, while maintaining an atmosphere of nitrogen and keeping the temperature between 30 and 35°C. After an additional 15 min (at ~ 40°C) a solution of 5 g of KCN and 20 g of NH_4Cl in 300 ml of water is added with vigorous stirring (note 3). The product is isolated by extraction with Et_2O, washing of the extracts with water or concentrated aqueous NH_4Cl, drying over $MgSO_4$ or K_2CO_3 and distillation *in vacuo*. The following products have been prepared:

$C_4H_9C{\equiv}CC{\equiv}CCH_2OH$ (from $C_4H_9C{\equiv}CBr$ and $HC{\equiv}CCH_2OH$), b.p. ~80°C/0.1 mmHg, $n_D(20°)$ 1.5173;
$C_2H_5C{\equiv}CC{\equiv}CCH_2CH_2OH$ (from $HC{\equiv}CCH_2CH_2OH$ and $C_2H_5C{\equiv}CBr$), b.p. ~80°C/0.5 mmHg, $n_D(20°)$ 1.5196;
t-$BuC{\equiv}CC{\equiv}CC(CH_3)_2OH$ (from *t*-$BuC{\equiv}CBr$ and $HC{\equiv}CC(CH_3)_2OH$), purification not carried out;
$C_2H_5C{\equiv}CC{\equiv}C(CH_2)_9OH$ (from $C_2H_5C{\equiv}CBr$ and $HC{\equiv}C(CH_2)_9OH$), b.p. ~150°C/0.5 mmHg;
$C_2H_5C{\equiv}CC{\equiv}CCH_2N(C_2H_5)_2$ (from $C_2H_5C{\equiv}CBr$ and $HC{\equiv}CCH_2N(C_2H_5)_2$, b.p. 113°C/15 mmHg, $n_D(21°)$ 1.4989;
$C_5H_{11}C{\equiv}CC{\equiv}CCH_2OCH(CH_3)OC_2H_5$ (from $C_5H_{11}C{\equiv}CBr$ and $HC{\equiv}CCH_2OCH(CH_3)OC_2H_5$), b.p. 125°C/15 mmHg, $n_D(20°)$ 1.4819;
t-$BuC{\equiv}CC{\equiv}CCH{=}CHSC_2H_5$ (from *Z*-$HC{\equiv}CCH{=}CHSC_2H_5$ and *t*-$BuC{\equiv}CBr$), $n_D(20°)$ 1.5810 (not distilled);
$C_2H_5C{\equiv}CC{\equiv}CC_6H_{13}$ (from $C_2H_5C{\equiv}CBr$ and $C_6H_{13}C{\equiv}CH$), b.p. 120°C/15 mmHg;
$C_2H_5C{\equiv}CC{\equiv}CPh$ (from $PhC{\equiv}CH$ and $C_2H_5C{\equiv}CBr$), b.p. 130°C/15 mmHg, $n_D(23°)$ 1.6146;
ortho-$(CH{=}O)$-$C_6H_4C{\equiv}CC{\equiv}CC_2H_5$ (from *ortho*$(CH{=}O)C_6H_4C{\equiv}CH$ and $C_2H_5C{\equiv}CBr$) b.p. 120°C/0.2 mmHg, $n_D(20°)$ 1.5840.
Yields were between 80 and 90%, except in the following cases: $C_2H_5C{\equiv}CC{\equiv}C(CH_2)_9OH$ (45%); $C_2H_5C{\equiv}CC{\equiv}CCH_2CH_2OH$ (68%); $C_2H_5C{\equiv}CC{\equiv}CC_6H_{13}$ (50%).

Notes

1. In the cases of acetylenic compounds with high molecular weights more methanol is used.
2. Propargyl alcohol and the carbinol $HC{\equiv}CC(CH_3)_2OH$ are cheap, commercially

available compounds and may be used in 10 - 30% excess. In most other cases, the excess is only 10%. If the desired product has a low thermal stability (making distillation risky), and the acetylene RC≡CH is not too volatile, one may decide to carry out the reaction with equimolar amounts of the acetylene and bromoalkyne or with a slight excess of the bromoalkyne (e.g. in the case of $HC{\equiv}CCH{=}CHSC_2H_5$ and *t*-BuC≡CBr). For acetylenes that react sluggishly and are readily available (e.g. aliphatic 1-alkynes), their use in excess seems rational.

3. The following procedure may be used when the product is expected to have a good solubility in water-methanol mixtures: the greater part of the methanol is first removed under reduced pressure using a rotary evaporator, then the aqueous solution of KCN and NH_4Cl is added.

3. Pd^0-Catalysed Couplings of Acetylenes with sp^2-Halogen Compounds - General Introduction

Several acetylenic compounds undergo successful coupling with halogen compounds in which halogen is linked to sp^2-carbon (vinylic, allenic, aromatic and heteroaromatic halogen compounds). In all cases a stoichiometrical amount of a copper(I) salt appears to be necessary, which makes the syntheses less attractive for performance on a larger scale [196].

During the past ten to fifteen years, considerable progress has been made with transition metal-mediated organic syntheses. Two important new methods are available for the coupling of acetylenes with the halogen compounds mentioned above.

a. Reaction of metallated acetylenes, preferably alkynylzinc halides, with the halogen compounds in the presence of catalytic amounts of Pd^{II} or Pd^0 compounds [56a].

$$RC{\equiv}C\text{-}ZnX + X\text{-}C{=}C \xrightarrow{Pd^0 \text{ or } Pd^{II}} RC{\equiv}CC{=}C + ZnX_2$$

(X = halogen)

(For a successful coupling with an acetylenic *Grignard* compound see ref. 56b).

b. Reaction of the free acetylene with the halide in the presence of catalytic amounts of Pd^0 or Pd^{II} compounds, a copper(I) halide and an excess of an amine (to "neutralize" the hydrogen halide) [56,198].

$$RC{\equiv}CH + XC{=}C + Et_2NH \xrightarrow{Pd^0 \text{ or } Pd^{II},\ CuX} RC{\equiv}CC{=}C + Et_2NH.HX$$

As usual, the reactivity order with respect to halogen in C=C-X is I > Br > Cl. The organic halide in the couplings with alkynylzinc halides is usually an iodide, though also activated vinylic bromides (e.g. $BrCH{=}CHCOOC_2H_5$) have been found to react smoothly. We

obtained good results in Pd^0-catalyzed reactions of RC≡CZnCl with a number of aryl and heteroaryl *bromides* [2]. The conversions were carried out at slightly elevated temperatures or in refluxing THF and took a few hours.

Free acetylenes have been successfully coupled with organic bromides and iodides. Even some activated chloro compounds react satisfactorily [199]. A number of couplings of vinylic bromides or iodides with acetylenes have been carried out under phase-transfer conditions [200]. The Pd-catalysts most often used in the reactions of schemes a and b are $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2.(PPh_3)_2$. The amount of the catalyst is preferably kept as low as possible, firstly for economic reasons, secondly because palladium residues can give rise to problems during the work-up and the purification of the product. Many literature procedures are carried out on a small scale and the Pd-compound is usually removed with column chromatography. Larger amounts of products can often be purified more quickly by distillation (*in vacuo*) provided that the amount of Pd-residue in the distillation flask is small.

3.1 Pd^0-Catalysed Reaction of Trimethylsilylethynylzinc Chloride with Iodo-heteroaromates

$$Me_3SiC{\equiv}CZnCl + RI \xrightarrow[Pd(PPh_3)_4,\ 0 \rightarrow 40°C]{\text{THF-hexane}} Me_3SiC{\equiv}CR + ClZnI \qquad R = \text{Heteroaryl}$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Procedure

A solution of $Me_3SiC{\equiv}CLi$ (0.12 mol) in THF (50 ml) and hexane (85 ml) is prepared by adding BuLi in hexane to a mixture of $Me_3SiC{\equiv}CH$ and THF (see p. 114). Subsequently a solution of 0.12 mol of anhydrous zinc chloride in 50 ml of THF is added at ~ 0°C (p. 36, followed by a solution of 1 g of $Pd(PPh_3)_4$ in 20 ml of THF and 0.10 mol of the iodo compound. The cooling bath is removed and the temperature allowed to rise: if the flask is insulated by cotton wool, 40°C may be reached. After an additional 2 to 3 h (at 30-35°C) the solution is cooled to room temperature and pentane (300 ml, note 1) and a saturated aqueous solution of ammonium chloride (150 ml) are successively added with vigorous stirring. After separation of the layers, the aqueous layer is extracted with pentane. The combined solutions are washed five times with 200 ml portions of water (note 1) and subsequently dried over $MgSO_4$. The brown liquid remaining after concentration of the solution *in vacuo* is first subjected to a flash distillation (see fig. 14) at 0.1 mmHg or lower pressure (note 2). The contents of the receiver are redistilled.

1-Methyl-2-(trimethylsilylethynyl)pyrrole, b.p. ~ 70°C/0.5 mmHg, $n_D(21°)$ 1.5235, and 2-(trimethylsilylethynyl)furan, b.p. ~ 30°C/0.5 mmHg, $n_D(21°)$ 1.4995, can be obtained

in greater than 70% yields by this procedure.

$CH_3C{\equiv}CC{\equiv}CZnCl$ and 2-iodothiophene react under similar conditions to give the expected coupling product, b.p. ~70°C/0.5 mmHg, in an excellent yield. The additional time of heating at ~35°C in this case is 30 min.

Notes

1. The addition of a relatively large amount of pentane causes precipitation of part of the catalyst, which adheres to the glass wall of the separating funnel. Another part precipitates when the THF is removed in the wash procedure. The precipitate dissolves readily in acetone.
2. Under the mild conditions of this distillation, the chance of decomposition of the product under the influence of traces of Pd-compounds is small.

3.2 Pd^0-Catalysed Reactions of Trimethylsilylethynylzinc Chloride with Aryl and Heteroaryl Bromides

$$Me_3SiC{\equiv}CZnCl + RBr \xrightarrow[Pd(PPh_3)_4,\ 30°C \rightarrow \text{reflux}]{\text{THF, hexane}} Me_3SiC{\equiv}CR + ZnClBr$$

R = Aryl- or Heteroaryl-

Scale: 0.10 molar (RBr) or 0.05 molar (2,5-dibromothiophene).

Apparatus: fig. 1, 1 l.

Procedure

A solution of 1 g of $Pd(PPh_3)_4$ in 20 ml of THF is added to the solution of $Me_3SiC{\equiv}CZnCl$ (0.12 mol) in THF and hexane (see previous exp.). The bromo compound (0.10 mol, or 0.05 mol in the case of 2,5-dibromothiophene) is added in one portion at 30°C. The flask is insulated by cotton wool. In the cases of bromo heteroaromates, the reaction is clearly visible from a gradual rise of the temperature to ~ 45°C over about half an hour, dibromothiophene reacts very fast and the temperature of the mixture rises to 60°C within 15 min. At this stage the thermometer is quickly replaced with a reflux condenser. Aryl bromides (1-bromonaphthalene, 1-bromo-2-chlorobenzene, 1-bromo-3-fluorobenzene) react more slowly and the heating effect is hardly visible in spite of the insulation. The reactions with the heteroaromates are completed by heating the solutions under reflux for an additional 2.5 h (for 2,5-dibromothiophene 0.5 -1 h is sufficient), in the cases of the bromoaromates at least 4 h reflux is necessary (an additional amount of catalyst may be added to shorten the reaction time). An atmosphere of nitrogen is carefully maintained during the reactions. The work-up is carried out in a manner similar to that described in the previous experiment.

The following compounds have been obtained by this procedure in yields of at least 70% (3-bromopyridine gave the lowest yield): 1-(trimethylsilylethynyl)naphthalene, b.p. ~

110°C/0.5 mmHg (a careful distillation is necessary to separate unconverted bromonaphthalene from the product); 1-chloro-2-(trimethylsilylethynyl)benzene (from 1-bromo-2-chlorobenzene), b.p. 116°C/15 mmHg, $n_D(22°)$ 1.5372 (in this case, 2 g of Pd-catalyst was used); 3-(trimethylsilylethynyl)thiophene, b.p. 72°C/0.5 mmHg, $n_D(21°)$ 1.5360; 3-(trimethylsilylethynyl)pyridine,b.p. ~60°C/0.5 mmHg, $n_D(21°)$ 1.5282; 2,5-bis(trimethylsilylethynyl)thiophene (solid, not further purified, ^1H NMR showed a satisfactory purity); 1-fluoro-3-(trimethylsilylethynyl)benzene (qualitative experiment, purification not carried out).

n-$C_6H_{13}C{\equiv}CCH{=}CH_2$, b.p. 70°C/15 mmHg, $n_D(21°)$ 1.4583, was prepared in ~ 80% yield from $C_6H_{13}C{\equiv}CZnCl$ and $H_2C{=}CHBr$; the bromide was added in ~ 30% excess at 35°C. The reaction was completed by stirring for 3 h at 40-45°C and 30 min at 60°C.

3.3 Coupling of 2-Iodothiophene with O-Protected Propargyl Alcohol in the Presence of Catalytic Amounts of $Pd(PPh_3)_4$ and CuI

$$R'I + HC{\equiv}CCH_2OR + Et_2NH \xrightarrow[Pd(PPh_3)_4,\ 35°C]{Et_2O,\ Et_2NH,\ CuI} R'C{\equiv}CCH_2OR + Et_2NH.HI\downarrow$$

(R = -O-CH(CH_3)OC_2H_5, R' = 2-thienyl)

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Procedure

Diethylamine (80 ml, dried over machine-powdered KOH), the O-protected propargyl alcohol (0.11 mol, see p. 265), Et_2O (30 ml) and copper(I)iodide (0.7 g) are placed in the flask. A solution of 1 g of $Pd(PPh_3)_4$ in 15 ml of THF is added. After the air in the flask has been completely replaced by nitrogen, the mixture is warmed to 30°C and iodothiophene (0.10 mol) is added over 15 min, while keeping the temperature between 30 and 35°C. The turbid mixture is stirred for an additional 4 h at 30-35°C, then the excess of diethylamine and the Et_2O are removed under reduced pressure (rotary evaporator). The salt is dissolved by adding water (200 ml), whereupon the mixture is extracted with pentane. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated under reduced pressure. The remaining liquid is distilled through a short Vigreux column. The desired coupling product, b.p. ~ 100°C/1 mmHg, $n_D(20°)$ 1.5369, is obtained in an excellent yield.

3.4 Coupling of Vinyl Bromide with Propargyl Alcohol in the Presence of Catalytic Amounts of $Pd(PPh_3)_4$ and CuI

$$HC{\equiv}CCH_2OH + H_2C{=}CHBr + Et_2NH \xrightarrow[Pd(PPh_3)_4]{Et_2O,Et_2NH,\ CuI} H_2C{=}CHC{\equiv}CCH_2OH + Et_2NH.HBr{\downarrow}$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Procedure

Diethylamine (100 ml, dried over powdered KOH), $Pd(PPh_3)_4$ (0.5 g) and CuI (0.5 g) are placed in the flask. Redistilled propargyl alcohol (0.20 mol) is added, after which the temperature is raised to 45°C. Then a mixture of 0.30 mol (excess) of vinyl bromide and 30 ml of Et_2O (cooled at 5 to 10°C) is added portionwise over 30 min, while maintaining the temperature between 45 and 50°C (occasional cooling or heating). After 5 to 10 min, salt begins to separate from the solution. After the addition, the thermometer is replaced by a reflux condenser and the mixture is heated for another hour under gentle reflux. During this period Et_2O (~70 ml) is added in a number of portions in order to facilitate stirring. The suspension is filtered on sintered glass and the salt rinsed well with Et_2O. The filtrate is concentrated under reduced pressure (rotary evaporator, bath temperature ≤ 30°C). The remaining liquid is shaken with 150 ml of an aqueous solution of 30 g of ammonium chloride, after which ten extractions with Et_2O are carried out. The unwashed ethereal solution (light brown) is concentrated *in vacuo* and the remaining liquid subjected to a flash distillation at < 1 mmHg and the product collected in a single, strongly cooled receiver (fig 14). Redistillation gives the enyne alcohol, b.p. 60°C/10 mmHg, $n_D(20°)$ 1.4974, in ~ 80% yield.

$C_5H_{11}C{\equiv}CCH{=}CH_2$, b.p. 45°C/15 mmHg, $n_D(20°)$ 1.4582, is obtained in an excellent yield by a similar procedure. Instead of carrying out the filtration procedure, the reaction mixture is poured into ice water, after which the solution is extracted with pentane. The combined organic solutions are washed with cold dilute hydrochloric acid and then dried over $MgSO_4$. The greater part of the solvent is distilled off at atmospheric pressure (40-cm Vigreux column) and the remaining liquid distilled in a water-pump vacuum.

$(CH_3)_2C{=}CHBr$ and $HC{\equiv}CCH_2OH$ do not react in the presence of $Pd(PPh_3)_4$ and CuI. $(CH_3)_2C{=}C{=}CHBr$ (0.10 mol, [4]) and $HC{\equiv}CSiMe_3$ (0.12 mol, see p. 114) react smoothly at 25 to 35°C. During the reaction, the mixture is diluted with Et_2O (~ 50 ml) in order to facilate stirring. After an additional half hour (at 30-35°C) the product is isolated as described for $H_2C{=}CHC{\equiv}CCH_2OH$. $(CH_3)_2C{=}C{=}CHC{\equiv}CSiMe_3$, b.p. ~ 55°C/0.5 mmHg, $n_D(20°)$ 1.4942, is obtained in greater than 70% yield.

3.5 Coupling of *p*-Bromonitrobenzene with Trimethylsilylacetylene in the Presence of Catalytic Amounts of $Pd(PPh_3)_4$ and CuI

$$O_2N\text{-}C_6H_4\text{-}p\text{-}Br + HC{\equiv}CSiMe_3 + Et_2NH \xrightarrow[Et_2O,\ Et_2NH,40°C]{Pd(PPh_3)_4,\ CuI} O_2N\text{-}C_6H_4\text{-}p\text{-}C{\equiv}CSiMe_3 + Et_2NH.HBr{\downarrow}$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Procedure

p-Bromonitrobenzene (0.10 mol), diethylamine (120 ml, dried over powdered KOH) and CuI (0.5 g) are placed in the flask. After the air in the flask has been completely replaced by N_2, $Pd(PPh_3)_4$, (note 1) (1.5 g) is introduced. Trimethylsilylacetylene (0.12 mol, p. 114) is added over a few min. The temperature of the mixture is kept between 35 and 40°C. After an additional hour (at ~ 35°C), 200 ml of Et_2O is added to the suspension and the mixture is cooled to between 0 and 10°C. Then the salt is filtered off on a sintered-glass funnel and rinsed well with Et_2O. The solution is concentrated under reduced pressure, keeping the temperature of the heating bath below 30°C (all diethylamine should be removed). The residue is dissolved again in Et_2O (~ 100 ml) and the solution is washed with water (small amounts of $Et_2NH.HBr$ are removed in this way). After drying over $MgSO_4$, the solution is concentrated *in vacuo* to give the fairly pure substitution product (brown crystals, note 2), in an excellent yield. Purification of a small amount by column chromatography over Al_2O_3 (neutral or acid) gives light-yellow crystals, m.p. 95-97°C, after crystallization from a 2:1 mixture of pentane and Et_2O.

Notes

1. In the literature procedure [198] $PdCl_2(PPh_3)_2$ is used. Also in other reactions $Pd(PPh_3)_4$ could be used instead of bivalent Pd-catalysts.
2. The brown colour may be caused by traces of palladium or Pd^0 compounds. If the product has a reasonable thermal stability and the boiling point is not too high, purification may be carried out more quickly by distillation *in vacuo*.

4. Oxidative Couplings of Acetylenic Compounds - General Introduction

The oxidative coupling of acetylenes $RC{\equiv}CH$ to $RC{\equiv}CC{\equiv}CR$ under the influence of copper salts discovered in 1869 by Glaser has, *via* some modifications, evolved to the method reported in 1960 by Hay [201]. In the Hay-procedure, oxygen or air is passed through a solution of the acetylene and a catalytic amount of a copper(I) salt in a complex-forming solvent, such as pyridine and *N,N,N',N'*-tetramethylethane diamine (TMEDA). Reppe described in 1955 [15] the oxidative coupling of propargyl alcohol in water containing

ammonium chloride (as a complexator for Cu^I) and catalytic amounts of copper(I) chloride. The Hay-couplings can be carried out under atmospheric pressure at temperatures in the range 20-50°C, while for the oxidative "dimerization" of propargyl alcohol a slightly (up to 1.5 atm) elevated pressure is more favourable.

The oxidative coupling with catalytic quantities of Cu^I salts in pyridine or other suitable amines has a wide scope. There are a few cases of less successful reactions. We obtained low yields of $Me_3SiC{\equiv}CC{\equiv}CSiMe_3$ from the reaction of $Me_3SiC{\equiv}CH$ with oxygen in pyridine or TMEDA in the presence of CuCl and moderate yields of $Me_3SiCH_2C{\equiv}CC{\equiv}CCH_2SiMe_3$ in the oxidation of $Me_3SiCH_2C{\equiv}CH$ under similar conditions.

An essential step in the process is the (reversible) formation of the "anion" $RC{\equiv}\underline{C}$. Alkylacetylenes, which are less acidic than most other acetylenic derivatives, react less readily. We found that the oxidation of alkylacetylenes such as $C_2H_5C{\equiv}CH$ can be carried out at a convenient rate when to the solution in pyridine a small amount of diazabicycloundecene (DBU) is added. This condensed bicyclic amine is a stronger base than other amines and is expected to facilitate the proton removal from the acetylene.

During the oxidative couplings a considerable amount of heat is evolved which makes the reaction easy to follow: the point of complete conversion can often be determined with an "accuracy" of about 10 min. An additional indication for the end point in many of the oxidations is the marked change in colour: when all $RC{\equiv}CH$ has been consumed, copper remains present as Cu^{II}, which has another colour than Cu^I. Careful observation of the reaction thus, can prevent attack of sensitive "dimers" $RC{\equiv}CC{\equiv}CR$ by oxygen.

The procedure of working-up is simple: the pyridine solution of the product may be poured into a large amount of water, after which the product is extracted. When the desired compound has a good solubility in water or has a high boiling point, it may be desirable or practical to distill off the greater part of the pyridine first.

4.1 General Procedure for the Oxidative Coupling of Acetylenic Compounds

$$2\ RC{\equiv}CH + O_2 \xrightarrow[40\text{-}45^\circ C]{\text{pyridine, CuCl}} RC{\equiv}CC{\equiv}CR + H_2O$$

Scale: 0.20 molar.

Apparatus: fig. 16, 1 l; stirrer: fig. 3.

Procedure

Powdered copper(I) chloride (2 g, technical quality) is dissolved in 120 ml of pyridine. The acetylene (0.20 mol) is added. Oxygen is introduced at a rate of 300 ml/min (the use of a fritt connected to the inlet tube is recommended) with vigorous agitation of the solution. The temperature is kept between 40 and 45°C by occasional cooling. After about half an hour the reaction has ceased and the temperature begins to drop. In some cases, a change of the colour

is observed. The introduction of oxygen is continued for an additional 5 to 10 min. The greater part of the pyridine (about 80%) is then distilled off under reduced pressure using a rotary evaporator and keeping the temperature of the heating bath below 60°C. To the remaining liquid is added 200 ml of an aqueous solution of 5 g of $KC{\equiv}N$ and 20 g of NH_4Cl. After vigorous shaking, the solution is extracted with Et_2O. The organic solution is washed with dilute aqueous hydrochloric acid (2N) or with saturated aqueous NH_4Cl (in the case of acetylenic *amines*) and subsequently dried over $MgSO_4$ or K_2CO_3. The desired product is collected by vacuum distillation or crystallization. Yields are mostly high. Examples of successful oxidative couplings:

$PhC{\equiv}CC{\equiv}CPh$, mp. 87-88°C (crystallization from a mixture of Et_2O and pentane);
$t\text{-}Bu(C{\equiv}C)_4t\text{-}Bu$, mp. 99-100°C (crystallization from Et_2O);
$CH_3OCH_2(C{\equiv}C)_2CH_2OCH_3$, b.p. – 75°C/0.5 mmHg, $n_D(20°)$ 1.4988;
$(C_2H_5)_2NCH_2(C{\equiv}C)_2CH_2N(C_2H_5)_2$, b.p. 120°C/15 mmHg, $n_D(21°)$ 1.5005;
$(CH_3O)_2CH(C{\equiv}C)_2CH(OCH_3)_2$, $n_D(20°)$ 1.4778 (distillation not carried out).

Aliphatic alkynes, e.g. $HC{\equiv}CC_5H_{11}$ and $HC{\equiv}CCH_2SiMe_3$ react slowly. If a small amount (~ 3 ml) of diazabicycloundecene (DBU) is added, a smooth reaction takes place and the diyne $C_5H_{11}(C{\equiv}C)_2C_5H_{11}$ is obtained in an excellent yield. The yield of Me_3SiCH_2-$(C{\equiv}C)_2CH_2SiMe_3$ (b.p. 105°C/15 mmHg, solid at room temperature) is only about 50%. There is a considerable amount of high-boiling residue.

4.2 Oxidative Coupling of 1-Butyne. Preparation of 3,5-Octadiyne

$$2\ C_2H_5C{\equiv}CH + O_2 \xrightarrow[\text{pyridine, 30-35°C}]{\text{CuCl, DBU}} C_2H_5C{\equiv}CC{\equiv}CC_2H_5 + H_2O$$

Scale: 1.0 molar.

Apparatus: fig. 16, 1 l, stirrer: fig. 3; the gas outlet is connected to a trap, cooled at -78°C; the flow of oxygen is estimated by passing the gas through a washing bottle filled with paraffin oil; all connections are made gas-tight.

Procedure

Pyridine (250 ml), copper(I)chloride (4 g, technical quality) and diazabicycloundecene (5 ml, commercially available) are placed in the flask. The mixture is brought to 25°C and 1-butyne (~10 ml, p. 165), liquified in a trap cooled at -78°C, is quickly poured into the stirred solution. Oxygen is then introduced (~ 200 ml/min) with vigorous agitation (an inlet tube equipped with a fritt should be used). The temperature of the solution is kept between 30 and 35°C (occasional cooling). When the exothermic reaction has subsided, the mixture is cooled to 25°C, an additional 10 ml of the total amount of 1.0 mol of butyne is poured into the solution, and the introduction of oxygen is continued. When, after addition of the last portion of butyne, the temperature has dropped to below 30°C, the contents of the cold trap (usually

only a few ml) are poured into the reaction mixture and the introduction of oxygen (now at a rate of about 100 ml/min) is continued for an additional 20 min. Then the reaction mixture is poured into 1 l of ice water. Potassium cyanide (10 g) and ammonium chloride (25 g) are added. After vigorous shaking, ten extractions with small portions of pentane are carried out. The combined organic solutions are washed with dilute hydrochloric acid and subsequently dried over $MgSO_4$. The greater part of the solvent is distilled off at atmospheric pressure through a 40-cm Vigreux column. After cooling to room temperature, the remaining liquid is distilled. 3,5-Octadiyne, b.p. 45°C/15 mmHg, $n_D(20°)$ 1.4907, is collected in a single receiver cooled in a bath at 0°C (fig. 14). The yield is ~90%.

4.3 Oxidative Coupling of Propargyl Alcohol. Preparation of 2,4-Hexadiyn-1,6-diol

$$2\ HC{\equiv}CCH_2OH + O_2 \xrightarrow{H_2O,\ NH_4Cl,\ CuCl} HOCH_2(C{\equiv}C)_2CH_2OH + H_2O$$

Scale: 1.0 molar.

Apparatus: 1-l round-bottomed flask, connected through well-fixed rubber vacuum tubes to a U-like tube filled with mercury and a cylinder of oxygen; the flask is fixed on a platform which is moved by a shaking machine.

Procedure

The flask is charged with 12 g of powdered copper(I)chloride (technical grade), 40 g of ammonium chloride, 130 ml of water and ~ 0.35 mol of porpargyl alcohol (freshly distilled under reduced pressure). After the air in the flask has been completely replaced by oxygen , the connection with the supply of oxygen is made. The pressure on the apparatus is adjusted at 1.5 atm (0.5 atm. over-pressure) and vigorous shaking is started. The solution gradually becomes warm (35-40°C) while the pressure drops. After 30 to 60 min, when the levels in the manometer have become equal, an additional amount of ~ 0.35 mol of porpargyl alcohol is added and the solution is cooled to 20°C. The pressure is brought at 1.5 atm and the shaking operation repeated. After consumption of the oxygen, the remainder of the 1.0 mol of propargyl alcohol is converted. The end of the reaction is indicated by a marked change in colour (formation of Cu(OH)Cl by oxidation of CuCl). The mixture is cooled to 20°C , after which a small amount (~10 ml) of 36% aqueous hydrochloric acid is added (with swirling) in order to convert Cu(OH)Cl into the soluble $CuCl_2$ (green solution). The solution is extracted ten times with THF (total amount ~ 400 ml). The brown extract is dried over ~ 150 g of K_2CO_3. After suction filtration through sintered glass and rinsing of the drying agent with THF, the filtrate is concentrated *in vacuo* to a volume of about 100 ml. After dilution with 70 ml of Et_2O, the solution is placed in the refrigerator at -25 to -30°C. This gives a first crop of slightly coloured crystalline material (purity about 95%). Concentration of the mother liquor, dilution with Et_2O and cooling to -30°C, gives additional amounts of reasonably pure diol,

bringing the yield at ~90%. The m.p. after several crystallizations from Et_2O is 108-109°C.

$HOC(CH_3)_2(C{\equiv}C)_2C(CH_3)_2OH$ (m.p. 129-130°C after crystallization from a Et_2O-pentane mixture) is obtained in almost quantitative yield from $HC{\equiv}CC(CH_3)_2OH$ (commercially available, see also p. 89) by a similar procedure. The extraction is carried out with Et_2O.

The oxidations can also be carried out under 1 atm oxygen pressure, using a 1-l three-necked, round bottomed flask, equipped with a gas inlet tube, a gas-tight mechanical stirrer and a gas outlet. The inlet and outlet are connected with washing bottles filled with paraffin oil (for controlling the flow of O_2). After the air has been completely replaced by oxygen, this gas is introduced at a rate such that only a very weak flow is leaving the flask. The propargyl alcohol is added in three portions. Complete conversion may take several hours.

5. Copper(I)-Catalysed Coupling of Acetylenes with Allylic or Propargylic Halides or Tosylates - General Introduction

Reaction of alkali acetylides with allylic halides ($C{=}C\text{-}CH_2\text{-}X$) or propargylic halides ($C{\equiv}C\text{-}CH_2X$) is not a satisfactory way to prepare compounds with the structure systems $C{\equiv}C\text{-}C\text{-}C{=}C$ and $C{\equiv}C\text{-}C\text{-}C{\equiv}C$. The initial products with a "skipped" methylene group undergo a fast subsequent deprotonation at the skipped carbon atom, either followed by formation of conjugated unsaturated systems or by further reaction with the allylic or propargylic halide. The result generally is a complicated mixture of compounds. Acetylenic magnesium halides, $RC{\equiv}CMgX$, normally do not react with allylic or propargylic halides or tosylates, but in the presence of catalytic amounts of copper(I)halide a smooth coupling reaction takes place. The reaction is carried out most conveniently in THF, and yields are generally good [202,203].

$$RC{\equiv}CMgX + C{=}CHCH_2X \xrightarrow{CuX} RC{\equiv}CCH_2CH{=}C$$

$$RC{\equiv}CMgX + C{\equiv}CCH_2X \longrightarrow RC{\equiv}CCH_2C{\equiv}C$$

(X = Cl, Br or O-tosyl)

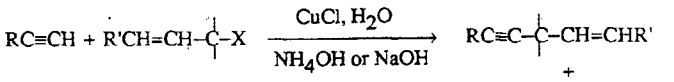
Tosylates react somewhat more easily than bromides [2], which permits the reactions to be carried out at temperatures in the region of 5°C. Under these conditions the chance of the following subsequent reaction is small:

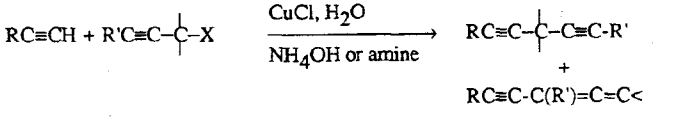
$$RC{\equiv}CCH_2C{\equiv}CH \xrightarrow{RC{\equiv}CMgBr} RC{\equiv}CCH_2C{\equiv}CMgBr \xrightarrow{HC{\equiv}CCH_2X} RC{\equiv}CCH_2C{\equiv}CCH_2C{\equiv}CH$$

The reactions of propargyl bromide or propargyl tosylate with alkynylmagnesium bromide gives small amounts of 1,3-substitution products, allenynes, $RC{\equiv}C\text{-}CH{=}C{=}C$. These can be removed however, by heating the product mixture. During this treatment, the allenynes

selectively polymerize or dimerize. Homologues of propargyl tosylate, $RC{\equiv}CCH_2OTs$, generally afford only the 1,1-substitution products, $RC{\equiv}CCH_2C{\equiv}CR'$, so the reaction of $HC{\equiv}CMgBr$ with $RC{\equiv}CCH_2OTs$ should be considered as s serious alternative, if preparation of pure $RC{\equiv}CCH_2C{\equiv}CH$ is intended.

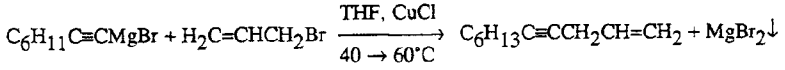
Coupling of allylic or propargylic halides and terminal acetylenes can also be realized under completely catalytic conditions [204,205]. The reactions are carried out in aqueous medium in the presence of catalytic amounts of copper(I)halide. The hydrogen halide liberated in the reaction is neutralized with ammonia, an amine or alkali hydroxide. In many cases both the 1,1- and the 1,3-coupling product is obtained:





The ratio of the 1,1- and 1,3-substitution products depends largely upon the substitution in the allylic and propargylic halide. Propargyl chloride, $HC{\equiv}CCH_2Cl$, and the branched compounds $HC{\equiv}CCH(R')Cl$ give exclusively allenyne systems by 1,3-substitution, while the homologues, $R'C{\equiv}CCH_2Cl$, couple only in a 1,1-fashion. Substituted allyl chloride in general gives 1,1- and 1,3-coupling products.

5.1 Preparation of 1-Undecen-4-yne by Reaction of Octynylmagnesium Bromide with Allyl Bromide in the Presence of Copper(I)Chloride



Scale: 0.30 molar.

Apparatus: fig. 1, 1 l.

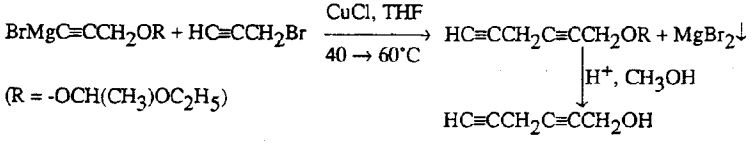
Procedure

A solution of 0.30 mol of octynylmagnesium bromide in ~ 300 ml of THF is prepared starting from 0.35 mol of ethyl bromide and 0.30 mol of 1-octyne (for the procedure see p. 29). Powdered copper(I)chloride (2 g, technical grade) is added at room temperature. After 15 min

allyl bromide (0.37 mol) is added dropwise over 15 min, while keeping the temperature of the green suspension between 40 and 50°C. The conversion is completed by heating the mixture for an additional half hour at 60°C. After cooling to 20°C, the suspension is poured into 250 ml of an aqueous solution of 5 g of KCN or NaCN and 40 g of NH_4Cl. The mixture is vigorously shaken, after which the layers are separated. The aqueous layer is extracted twice with pentane or Et_2O. The combined organic solutions are washed with aqueous NH_4Cl, dried over $MgSO_4$ and subsequently concentrated under reduced pressure. Distillation through a 40-cm Vigreux column gives the enyne, b.p. 79°C/10 mmHg, $n_D(20°)$ 1.4480, in high yields. There is a small high-boiling residue.

$C_5H_{11}C{\equiv}CCH_2C{\equiv}CH$, b.p. 69°C/10 mmHg, $n_D(20°)$ 1.4566, is obtained in reasonable yields (between 55 and 60%) by a similar procedure from $C_5H_{11}C{\equiv}CMgBr$ and $HC{\equiv}CCH_2Br$ (20 mol% excess). The greater part of the THF and extraction solvent are distilled off at atmospheric pressure through a 40-cm Vigreux column (bath temperature maximally 80°C). During this distillation the allenyne $C_5H_{11}C{\equiv}CCH{=}C{=}CH_2$ is converted into high-boiling products. The remaining liquid is first subjected to a flash distillation *in vacuo* (10-15 mmHg) using a 20-cm Vigreux column and a single receiver, cooled at -70°C (see fig. 14). The considerable high-boiling residue is discarded. Careful redistillation of the contents of the receiver gives the 1,4-diyne.

5.2 Coupling of Propargyl Bromide with the Grignard Derivative of the O-Protected Propargyl Alcohol in the Presence of Copper(I)Chloride. Synthesis of 2,5-Pentadiyn-1-ol



Scale: 0.50 molar.

Apparatus: fig. 1, 1 l.

Procedure

The adduct from propargyl alcohol and ethyl vinyl ether (0.50 mol, see p. 265) is converted into the Grignard derivative (p. 29), starting from 0.58 mol of ethyl bromide. The volume of THF used is 400 ml. Powdered copper(I)chloride (2.5 g, technical grade) is added at room temperature and after 15 min propargyl bromide (0.6 mol, see p. 247) is added dropwise over 20 min, while keeping the temperature between 40 and 50°C. After heating the suspension for an additional 1 hour at 60°C, it is cooled to room temperature and then poured into 500 ml of an aqueous solution of 10 g of NaCN or KCN and 75 g of NH_4Cl. After vigorous shaking and separation of the layers, three extractions with Et_2O are carried out. The combined

organic solutions are washed with saturated aqueous NH_4Cl and subsequently dried over $MgSO_4$. Diethylamine or triethylamine (1 ml, note 1) is added, after which the filtered solution is concentrated under reduced pressure. Paraffin oil (30 ml, note 2) is added and a quick distillation in a high vacuum is carried out, using a very short Vigreux column and a single receiver cooled in a bath at -78°C (fig 14). Before carrying out the distillation, the glass ware is rinsed with a dilute solution of diethylamine or triethylamine in acetone (note 1). Redistillation of the contents of the receiver gives the coupling product, b.p. ~ 55°C/0.01 mmHg, $n_D(20°)$ 1.4580, in ~ 70% yield.

The distillate is mixed with 120 ml of methanol and 1 ml of 36% hydrochloric acid is added. After warming the mixture for 20 min at 50°C, the methanol and the acetal $CH_3CH(OCH_3)OC_2H_5$ (compare p. 288) are removed under reduced pressure using a rotary evaporator. To the remaining liquid is added 100 ml of concentrated aqueous NH_4Cl. After addtion of 3 ml of concentrated aqueous ammonia, ten extractions with Et_2O are carried out. The unwashed organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Parrafin oil (10 ml, note 2) is added, after which the product is distilled in a high-vacuum. $HC{\equiv}CCH_2C{\equiv}CCH_2OH$, b.p. ~ 50°C/0.1 mmHg, $n_D(20°)$ 1.4949, is obtained in overall yields of about 60%.

Notes

1. The amine is added to ensure the neutralization of traces of acid, which might catalyze cleavage of the acetal function.
2. The paraffin oil is added to prevent vigorous decomposition of the residue during the last stage of the distillation. The residue now remains in a dispersed form.

5.3 Preparation of 1,4-Pentadiyne by Copper(I)halide-Catalysed Reaction of Propargyl Tosylate with Ethynylmagnesium Bromide

$$HC{\equiv}CCH_2OTs + HC{\equiv}CMgBr \xrightarrow[0 \rightarrow 15°C]{THF,\ CuBr} HC{\equiv}CCH_2C{\equiv}CH + TsOMgBr$$

Scale: 0.50 molar.

Apparatus: fig. 1, 2 l.

Procedure

A solution of ethynylmagnesium bromide in about 1 l of THF is prepared by the procedure described in ref [35], starting from 0.80 mol of ethyl bromide and 1.2 mol of magnesium. The solution obtained is assumed to contain about 0.65 mol of $HC{\equiv}CMgBr$. After cooling the solution to 0°C (a suspension is formed), 2 g of powdered copper(I)bromide (or chloride) is added. After 15 min, 0.50 mol of propargyl tosylate (p. 256) is added over 10 min. while keeping the temperature between 0 and 5°C. After the additon, the cooling bath is removed

and the temperature is allowed to rise over 1 h to 15°C (occasional cooling may be necessary). Most of the suspended material dissolves. High-boiling petroleum ether (200 ml, b.p. > 170°C) is added to the brown solution. The mixture is then poured into 2 l of 2 N aqueous hydrochloric acid. After vigorous shaking, the layers are separated and the organic layer is washed 15 times with 300 ml portions of 4 N aqueous HCl. The combined washings and first aqueous layer are extracted twice with 30-ml portions of petroleum ether. The two petroleum ether solutions are combined and washed five times with 200 ml-portions of 4 N HCl. After drying over $MgSO_4$, the combined organic solutions are subjected to a flash distillation at 10 to 20 mmHg pressure (see fig. 14) and the volatile diyne is collected in the strongly cooled receiver. The "distillation" is stopped after about 10 ml of petroleum ether has passed over (b.p. 50-60°C/15 mmHg). The distillate is heated under reflux for 30 min under nitrogen, then the flash distillation is repeated, now leaving a small amount of petroleum ether in the distillation flask. Redistillation of the contents of the receiver under N_2 at atmospheric pressure through a 20-cm Vigreux column gives the desired product, b.p. 62°C/760 mmHg, $n_D(23°)$ 1.4283, in ~60% yield. About 5% of $HC{\equiv}CCH{=}C{=}CH_2$ may still be present, and in some cases THF. This solvent can be removed by shaking the product with cold 4N aqueous HCl in a small dropping funnel.

$CH_3C{\equiv}CCH_2C{\equiv}CH$, b.p. ~ 55°C/100 mmHg, is obtained in greater than 70% yields from $HC{\equiv}CMgBr$ and $CH_3C{\equiv}CCH_2OTs$ by a similar procedure. The compound can also be prepared from $CH_3C{\equiv}CMgBr$ and $HC{\equiv}CCH_2OTs$, but in that case the desired compound is contaminated with $CH_3C{\equiv}CCH{=}C{=}CH_2$, which has to be removed by heating the crude product.

$Me_3SiC{\equiv}CCH_2C{\equiv}CH$, b.p. ~35°C/10 mmHg (single receiver, cooled at 0°C), $n_D(18°)$ 1.4497 (containing 5-7% of $Me_3SiC{\equiv}CCH{=}C{=}CH_2$), is obtained in ~ 70% yield from the reaction of $Me_3SiC{\equiv}CMgBr$ (0.40 mol) in THF with $HC{\equiv}CCH_2OTs$ (0.35 mol) at 0 to 15°C. After addition of 300 ml of pentane, the reaction mixture is hydrolyzed and the greater part of the THF is removed by the washing procedure described above. Most of the solvent is distilled off at atmospheric pressure (under N_2) through a 40-cm Vigreux column (bath temperature 120°C at the end). After cooling to room temperature, the remaining liquid is carefully distilled in a water-pump vacuum.

$C_2H_5OC{\equiv}CMgBr$ and $CH_3C{\equiv}CCH_2OTs$ react in THF at 0 to 15°C to give $C_2H_5OC{\equiv}CCH_2C{\equiv}CCH_3$. This compound (b.p. 50°C/15 mmHg, $n_D(20°)$ 1.4550) is isolated in an excellent yield *via* the conventional procedure of working up (extraction with Et_2O or pentane after hydrolysis, washing, drying, removal of the solvent *in vacuo*, then distillation).

It should be possible to prepare allylacetylene, $HC{\equiv}CCH_2CH{=}CH_2$, b.p. 42°C/760 mmHg, from $HC{\equiv}CMgBr$ and $H_2C{=}CHCH_2OTs$ by a procedure similar to that applied for $HC{\equiv}CCH_2C{\equiv}CH$.

5.4 Copper(I)Chloride-Catalysed Reaction of Propargyl Alcohol with Propargyl Chloride in Aqueous Medium. Preparation of 4,5-Hexadien-2-yn-1-ol

$$HC{\equiv}CCH_2OH + HC{\equiv}CCH_2Cl \xrightarrow[NH_2OH.HCl,\ 25\text{-}30^\circ C]{CuCl,\ CH_3OH,\ H_2O,\ NH_4OH} H_2C{=}C{=}CHC{\equiv}CCH_2OH + HCl$$

Scale: 0.25 molar.

Apparatus: fig. 1, 500 ml.

Procedure

Methanol (70 ml), 25% aqueous NH_3 solution (50 ml), freshly distilled propargyl alcohol (0.50 mol) powdered CuCl (1.5 g, technical grade) and hydroxylamine.HCl (2 g) are placed in the flask. The air in the flask is completely replaced by nitrogen. A mixture of 0.25 mol of propargyl chloride and 40 ml of methanol is added dropwise over 1 h, while keeping the temperature between 25 and 30°C. After an additional 45 min a solution of 5 g of KCN or NaCN in 150 ml of water is added with vigorous stirring. Subsequently ten extractions with Et_2O are carried out. The combined ethereal solutions are washed once with saturated aqueous NH_4Cl and are subsequently dried over $MgSO_4$. After complete removal of the solvent and other volatile compounds (some $HC{\equiv}CCH_2OH$) in water-pump vacuum, almost pure $H_2C{=}C{=}CHC{\equiv}CCH_2OH$, $n_D(20^\circ)$ 1.5405 is obtained in ~ 80% yield. If desired, the compound can be distilled in a high-vacuum, using a short column and a single receiver, cooled to below -20°C. Prior to carrying out the distillation, 40 ml of paraffin oil (note 1) should be added.

$H_2C{=}C{=}CHC{\equiv}CC(CH_3)_2OH$, $n_D(22.5^\circ)$ 1.5147 (undistilled), is obtained in ~ 70% yield by a similar procedure from $HC{\equiv}CC(CH_3)_2OH$ and $HC{\equiv}CCH_2Cl$.

Notes

1. See exp. 2, note 2.

6. Preparation of Alkynenitriles from 1-Bromoalkynes and Copper(I) Cyanide

Alkynenitriles, $RC{\equiv}CC{\equiv}N$, with $R \neq H$ can be obtained in high yields from the reaction of lithiated alkynes, $RC{\equiv}CLi$, and cyanogen chloride, $ClC{\equiv}N$ (see Chap. VIII, exp. 7). Many chemists however, will be very hesitant in using the very toxic cyanogen chloride. Another synthetic method involves the dehydration of acetylenic carboxamides, $RC{\equiv}CC(=O)NH_2$ with phosphorous pentoxide. The carboxamides are prepared by reaction of the corresponding acetylenic esters with aqueous ammonia. Although this dehydration is the only available

method for $HC{\equiv}CC{\equiv}N$ and $N{\equiv}CC{\equiv}CC{\equiv}N$, it is not an attractive method for two reasons. Firstly, the route, which in most cases starts with the acetylene $RC{\equiv}CH$, is rather lengthy, secondly, the heterogeneous conditions are not very elegant. The high temperatures required for the dehydration may give rise to decomposition of sensitive alkynenitriles. A third method, which seems to have a general applicability, consists of the reaction of a 1-bromoalkyne with copper(I)cyanide in THF: the reaction is started by addition of a small amount of anhydrous lithium bromide, which solubilizes the copper(I)cyanide.

$$RC{\equiv}CBr + CuCN \xrightarrow[40 \rightarrow 80^\circ C]{THF,\ LiBr} RC{\equiv}CC{\equiv}N + CuBr$$

The conversion takes place under relatively mild conditions and gives the alkynenitriles in high yields.

6.1 Preparation of Alkynenitriles by Reaction of 1-Bromoalkynes with Copper(I) Cyanide in the Presence of Lithium Bromide

$$RC{\equiv}CBr + CuCN \xrightarrow[40 \rightarrow 70^\circ C]{THF,\ LiBr} RC{\equiv}CC{\equiv}N + CuBr$$

Scale: 0.20 molar ($RC{\equiv}CBr$).

Apparatus: fig. 1, 250 ml.

Procedure

The 1-bromoalkyne (0.20 mol, see p. 149, 150 and 157), dry THF (80 ml) and dry powdered copper(I)cyanide (0.25 mol) are placed in the flask. The mixture is warmed to 40°C and a solution of 6 g of anhydrous lithium bromide (the commercial anhydrous salt is heated for 30 min at 150°C in a vacuum of 10 to 20 mmHg) in 20 ml of THF is added. As a rule, the reaction starts within a few min (heating to 50-55°C may be necessary) and (with stirring at a moderate rate) the temperature may rise to higher than 60°C. Occasional cooling is applied to keep the temperature between 65 and 70°C. After the reaction has subsided, the mixture is heated for an additional half hour at 70°C. Most of the solid has then passed into solution. The solution is poured into 200 ml of a cold (0°C) aqueous solution of 20 g of KCN (or 15 g of NaCN) and 30 g of NH_4Cl. After vigorous shaking, the solution is extracted four times with Et_2O. The combined ethereal solutions are washed with concentrated aqueous NH_4Cl and subsequently dried over $MgSO_4$. After removal of the solvent under reduced pressure, the remaining liquid is first subjected to a flash distillation (fig. 14) in a high-vacuum and the distillate collected in a strongly cooled (< -30°C) receiver. Redistillation gives the nitriles in ~ 75% yield.

Examples of nitriles, which have been obtained by this procedure: $PhC{\equiv}CC{\equiv}N$, b.p.

95°C/15 mmHg, the distillate solidifies at room temperature; 1-Cyclohexenyl-C≡CC≡N, b.p. 100°C/15 mmHg, n_D(19°) 1.5437; $C_4H_9C{\equiv}CC{\equiv}N$, b.p. 56°C/15 mmHg, n_D(20°) 1.4492.

Chapter XI
Base-Promoted Interconversions of Acetylenes

1. Base-Catalysed Isomerizations

Interaction between an acetylenic compound and a (catalytic amount of a) base can give rise to isomerization to an unsaturated system with the same number of π-electrons. The result is often a (pseudo-) equilibrium mixture of the starting compound and isomeric acetylenes and allenes. The composition of the mixture is determined by the relative thermodynamic stabilities of the isomers. Under more forcing conditions a conjugated diene or polyene is formed (provided that the carbon chain is sufficiently long) while in some cases cyclic compounds are the end products. Since it is, in general, very difficult to separate the isomeric compounds, the synthetic importance of the base-catalysed isomerizations is confined to conversions that afford predominantly one compound. The ratio of the isomers in the equilibrium mixture may vary strongly with the substituents. Reaction of $HC{\equiv}CCH_2NEt_2$ with *t*-BuOK in DMSO gives an equilibrium mixture of *ca.* 80% of $CH_3C{\equiv}CNEt_2$ and *ca.* 20% of $H_2C{=}C{=}CHNEt_2$ [2]. Under similar conditions the *dimethyl*amino compound $HC{\equiv}CCH_2NMe_2$ is converted into a mixture containing only *ca.* 20% of the yneamine $CH_3C{\equiv}CNMe_2$ [176]. The base-catalysed isomerization of alkyl propargyl ethers, $HC{\equiv}CCH_2OR$, into allenic ethers, $H_2C{=}C{=}CHOR$, can be easily brought about by warming with solid *t*-BuOK [177]. Attempts at further conversion into $CH_3C{\equiv}COR$ have resulted in decomposition [2]. Propargylic sulfides, $HC{\equiv}CCH_2SR$ (R = alkyl or aryl), can be completely converted into 1-propynyl sulfides, $CH_3C{\equiv}CSR$, under mild conditions ($NaOC_2H_5$ in liquid ammonia [178] or in ethanol [179]). Compounds with the structure $HC{\equiv}CCH_2CH_2R$, in which R may represent alkyl, aryl or a variety of other groups, isomerize smoothly to the 2-alkyne systems $CH_3C{\equiv}CCH_2R$ upon treatment with *t*-BuOK in DMSO at 20°C or slightly elevated temperatures [2].

In addition to the reactions mentioned, many other acetylenic compounds with a conjugated or non-conjugated unsaturated system have been carried out. The experimental procedures in this chapter are a selection of conversions which, in our opinion, are relevant from a preparative point of view.

2. Isomerizations *via* Metallated Intermediates

Some acetylenic (with a non-terminal triple bond) or allenic compounds, $RCH{=}C{=}CH_2$, can be transformed into alkali metal derivatives of terminal acetylenes by treatment with a very strong base. Treatment of an acetylenic compound with the grouping $CH_3C{\equiv}C$- or $CH_3C{\equiv}CCH{=}CH$- with one equivalent of an alkali amide (preferably the soluble potassium

amide) in liquid ammonia results in the formation of the alkali acetylide $MC{\equiv}CCH_2$- or $MC{\equiv}CCH{=}CHCH_2$ [180]. Subsequent hydrolysis (after removal of the ammonia) in many cases gives the isomers ($HC{\equiv}CCH_2$- or $HC{\equiv}CCH{=}CHCH_2$-) in high yields. This "contrathermodynamic" isomerization may be explained by assuming that the set of equilibria between the various isomers is shifted towards the slightly soluble alkali metal acetylide. Wotitz and Brown [181,182] found that the triple bond can shift over several carbons to the terminal position under the influence of sodamide in 1,2-diaminoethane or potassium aminopropylamide in 1,3-diaminopropane. In this way, acetylenic alcohols with a long carbon chain between the triple bond and the OH-function can be prepared in good yields from the easily accessible alcohols $CH_3(CH_2)_nC{\equiv}CCH_2OH$ [191].

$$CH_3(CH_2)_nC{\equiv}CCH_2OH \xrightarrow[H_2N(CH_2)_3NH_2]{2\ KNH(CH_2)_3NH_2} \text{intermediate isomers} \longrightarrow$$

$$KC{\equiv}C(CH_2)_{n+2}OK \xrightarrow{H_2O} HC{\equiv}C(CH_2)_{n+2}OH$$

Enyne systems $C_nH_{2n+1}C{\equiv}CCH{=}CH_2$ give intractable product mixtures and tar [2].

Reaction of 2-alkynoic acids with an excess of sodamide in liquid ammonia followed by treatment with mineral acid (after evaporation of the ammonia) gives 3-alkynoic acids in excellent yields [183]. Presumably, the 2-alkynoic acid is converted into the disodium compound of the 3-alkynoic acid *via* a process of proton removal and proton donation:

$$RCH_2C{\equiv}CCOOH \xrightarrow[\text{liq. } NH_3]{2\ NaNH_2} R\bar{C}HC{\equiv}CCOO^- \rightarrow RCH{=}C{=}CHCOO^- \rightarrow R\bar{C}{=}C{=}CHCOO^-$$
$$\updownarrow \qquad\qquad \updownarrow$$
$$RCH{=}C{=}\bar{C}COO^- \qquad\qquad RC{\equiv}C\bar{C}HCOO^-$$

The same 3-alkynoic acids can also be obtained (in lower yields) by heating 2-alkynoic acids with an excess of aqueous potassium hydroxide [184].

A remarkable reversal of the enyne system takes place if the enyne amines $H_2C{=}CHC{\equiv}CNR_2$ are treated with potassium amide in liquid ammonia. The reaction must proceed through the butatrienyl amines $H_2C{=}C{=}C{=}CHNR_2$ [185]:

$$H_2C{=}CHC{\equiv}CNR_2 \xrightarrow[\text{liq. } NH_3]{KNH_2} H_2C{=}\bar{C}C{\equiv}CNR_2 \longrightarrow H_2C{=}C{=}C{=}CHNR_2 \xrightarrow{KNH_2}$$
$$\updownarrow$$
$$H_2C{=}C{=}C{=}\bar{C}NR_2$$

$$H\bar{C}{=}C{=}C{=}CHNR_2 \longrightarrow KC{\equiv}CCH{=}CHNR_2 \xrightarrow[\text{liq. } NH_3]{NH_4Cl} HC{\equiv}CCH{=}CHNR_2$$
$$\updownarrow$$
$$HC{\equiv}C\bar{C}{=}CHNR_2$$

Enyne sulfides, $H_2C{=}CHC{\equiv}CSR$, and hydrocarbons, $H_2C{=}CHC{\equiv}CR$ (R = alkyl or aryl), give intractable reaction mixtures under similar conditions [2]. The same isomerization is observed under catalytic conditions, *i.e.* with *t*-BuOK in DMSO or HMPT [185].

Allenes, $H_2C{=}C{=}CHR$ (R = alkyl), are metallated regioselectively at the terminal C-atom by butyllithium in THF at low temperatures [186]. Above 0°C, the metallated allenes rearrange to lithium alkynylides:

$$H_2C{=}C{=}CHR \xrightarrow{BuLi} LiCH{=}C{=}CHR \xrightarrow{>0°C} LiC{\equiv}CCH_2R \xrightarrow{H_2O} HC{\equiv}CCH_2R$$

3. Experiments

All temperatures are internal, unless indicated otherwise

3.1 Base-Catalysed Isomerization of 1-Alkynes to 2-Alkynes

$$HC{\equiv}CCH_2R \xrightarrow[DMSO,\ 20\text{-}30°C]{t\text{-BuOK}} CH_3C{\equiv}CR$$

Scale: 0.5 molar.

Apparatus: 1-l round-bottomed, two-necked flask and thermometer; magnetic stirrer.

Introduction

1-Alkynes are smoothly converted into 2-alkynes under the influence of a catalytic amount of *t*-BuOK in DMSO at temperatures between 20 and 40°C. Using about 20 mol % of base and concentrations of the alkyne between 1 and 5 mol/liter of DMSO, the conversion is complete within 30 min. From the modest enthalpy difference of 1- and 2-alkynes (roughly 5 kcal/mol [187]) and the heat capacity of the solvent and alkyne (~ 0.5 cal/°C. g) a rough estimate can be made of the amount of heat evolved when 0.5 mol of 1-alkyne is isomerized to the 2-alkyne in about 150 ml of DMSO. This leads to the conclusion that the 1-alkyne can be added over a short period, while (occasional) cooling in a water bath at 10-15°C will be sufficient to keep the temperature of the solution between 25 and 40°C (in the case of the volatile 1- and 2-butyne, the temperature should not be allowed to rise above 30°C). There is little danger of a further isomerization into a conjugated diene in this temperature range.

Procedure

Dry (note 1) DMSO (150 ml) and *t*-BuOK (5 g) are placed in the flask. Stirring is started and the solution is brought at a temperature of ca. 20°C. Liquified 1-butyne (0.50 mol, see p. 165) or 1-hexyne (0.50 mol, see p. 52) is added in portions of about 10 g with intervals of 3 to 5 min, while keeping the temperature of the mixture between 25 and 30°C (cooling in a water bath at ~10° to 15°C). After an additional 30-min period of stirring at ~30°C, the

2-alkynes are isolated. In the case of 2-butyne the flask is connected (*via* a vacuum tube) to a trap cooled in a bath with liquid nitrogen. The connection is made in such a way that during the evacuation with the water aspirator the vapour of the 2-alkyne enters the large annular space of the trap: in this way, clogging is avoided. During the evacuation, the temperature of the bath is gradually raised to 50°C. Air is then admitted to the system and the solid 2-butyne is allowed to melt. Subsequent distillation at atmospheric pressure using a short Vigreux column and a receiver, cooled below 0°C gives pure 2-butyne b.p. ~27°C, $n_D(20°)$ 1.394 in greater than 85% yield. For the isolation of 2-hexyne the reaction flask is equipped for a vacuum distillation: 40-cm Vigreux column, condenser and receiver cooled in a bath at -70°C (fig. 14). The system is evacuated (water aspirator) and the flask gradually heated, until the DMSO begins to reflux in the column. Redistillation of the contents of the receiver at atmospheric pressure gives 2-hexyne, b.p., $n_D(20°)$, in ~90% yield. The IR spectra of the product shows the absence of 1-hexyne.

2-Heptyne and 2-octyne can be isolated in a similar way, in the case of less volatile 2-alkynes it is more convenient to dilute the reaction mixture with water (500 ml) and to extract the product with pentane.

Notes

1. Dry DMSO may be obtained by dissolving *t*-BuOK (5 g) in 300 ml of the commercial solvent (≥ 99%) and subsequently distilling at 0.5 to 1 mmHg (b.p. 40-50°C).

3.2 Base-Catalysed Isomerization of 10-Undecyn-1-ol to 9-Undecyn-1-ol

$$HC{\equiv}C(CH_2)_9OH \xrightarrow[DMSO,\ 20 \rightarrow 80°C]{t\text{-BuOK}} CH_3C{\equiv}C(CH_2)_8OH$$

Scale: 0.10 molar.

Apparatus: 250-ml round-bottomed flask and thermometer; manual swirling.

Procedure

10-Undecyn-1-ol (0.10 mol, see exp. 11) is added in one portion to a solution of 2 g of *t*-BuOK in 200 ml of dry DMSO (see exp. 1, note 1). The temperature rises from 20 to about 30°C within 1 to 2 min and a white precipitate is formed. The mixture is subsequently heated to 80°C and held at this temperature for 2 min. The precipitate dissolves completely. After cooling to 20°C, the solution is poured into 500 ml of water and six extractions with a mixture (1:1) of Et_2O and pentane are carried out. The combined organic solutions are washed twice with water and subsequently dried over $MgSO_4$, after which the solvent is removed in a water-pump vacuum. Distillation of the remaining liquid through a short Vigreux column gives 9-undecyn-1-ol, b.p. 100°C/15 mmHg, $n_D(20°)$ 1.4653, in greater than 90% yield.

3.3 Base-Catalysed Isomerization of Propargyl Diethylamine to 1-(*N*,*N*-Diethylamino)--1-propyne

$$HC{\equiv}CCH_2N(C_2H_5)_2 \xrightarrow[DMSO,\ 20 \rightarrow 50°C]{t\text{-BuOK}} \underset{80\%}{CH_3C{\equiv}CN(C_2H_5)_2} + \underset{\sim 20\%}{H_2C{=}C{=}CHN(C_2H_5)_2} \xrightarrow{\Delta} \text{dimer} + \text{polymer}$$

Scale: 1.0 molar.

Apparatus: 1-l round-bottomed flask and thermometer; manual swirling.

Introduction

Treatment of a propargylic tertiary amine $HC{\equiv}CCH_2NR_2$ with a catalytic amount of a basic reagent under suitable conditions generally affords an equilibrium mixture of the allenic amine, $H_2C{=}C{=}CHNR_2$, and the 1-propynylamine, $CH_3C{\equiv}CNR_2$. This cannot be separated into the components by distillation because there is only a small difference in the boiling points. There is, however, a considerable difference in thermal stability of the yneamines and allenic amines. If the 80:20 mixture of $CH_3C{\equiv}CN(C_2H_5)_2$ and $H_2C{=}C{=}CHN(C_2H_5)_2$ is heated for about half an hour at a temperature above 100°C, all allenic amine dimerizes or polymerizes. The yneamine survives this treatment and can be obtained in a good yield by vacuum distillation. Unfortunately, there are only a few cases in which the yneamine is the main component in the equilibrium mixture. Amines $HC{\equiv}CCH_2NR_2$ having one or both groups R = aryl give the yneamines in high yields [188].

Procedure

Diethyl propargylamine (1.0 mol, p. 273) is added in one portion to a solution of 5 g of *t*-BuOK in 150 ml of DMSO (dried as described in exp. 1, note 1). The temperature rises in a few min to above 45°C but is kept between 50 and 55°C by occasional cooling (with vigorous swirling) in a water bath at ~10°C. After 30 min the flask is equipped for a vacuum distillation (water-pump pressure, 40-cm Vigreux column, condenser and single receiver, cooled in a bath at -10°C, fig. 14) and the products are quickly distilled off from the dark solution. The distillation is stopped after a few ml of DMSO have passed over (b.p. ~80°C/15 mmHg). The distillate is heated (under N_2) for 30 min in a bath at 120°C. After cooling to below 30°C, the yneamine is distilled through a 40-cm Widmer column and collected in a single receiver, cooled in a bath at 0°C (fig. 14) (note 1). $CH_3C{\equiv}CN(C_2H_5)_2$, b.p. 27°C/12 mmHg, $n_D(20°)$ 1.4442, is obtained in 74-78% yield. The residue, a mixture of DMSO and the dimer and polymers of the allenic amine, is discarded. If the compound is stored in a well-closed and dry bottle, no deterioration occurs at room temperature.

Notes

1. If still some allenic amine is present, the product is heated again at 120-130°C.

3.4 Base-Catalysed Isomerization of 1-(*N,N*-Diethylamino)-4-buten-2-yne to 1-(*N,N*-Diethylamino)-3-buten-1-yne

$$H_2C{=}CHC{\equiv}CCH_2N(C_2H_5)_2 \xrightarrow[\text{DMSO, 20}\rightarrow\text{35°C}]{t\text{-BuOK}} CH_3CH{=}CHC{\equiv}CN(C_2H_5)_2$$

$$(+\ CH_3C{\equiv}CCH{=}CHN(C_2H_5)_2\ )$$

Scale: 0.40 molar.

Apparatus: 500-ml round-bottomed flask and thermometer (manual swirling).

Introduction

The conditions for the base-catalysed isomerization of $H_2C{=}CHC{\equiv}CCH_2N(C_2H_5)_2$ are similar to those applied in exp. 3. The work-up cannot be carried out in the same way, because the b.p. of the product is too close to that of DMSO. An aqueous work-up seems risky, since enyne amines have shown to be water-sensitive [2]. The somewhat peculiar manner in which the product is isolated is based on the fact that DMSO is slightly soluble in the apolar pentane. Extraction with this solvent alone would, presumably, not be very effective, therefore a 1:1 mixture of pentane and Et_2O is used. The small amount of DMSO which is co-extracted, can be easily removed by strongly cooling the extract, during which operation the DMSO crystallizes out.

The isomerization with *t*-BuOK gives also a small amount of the amine with the reversed order of the double and triple bond. Its boiling point is by 20 to 30°C higher than that of the main product, and careful fractional distillation results in a satisfactory separation of these isomers.

Procedure

The starting amine (0.40 mol, prepared by a Mannich reaction of vinylacetylene, see p. 211) is added in one portion to a solution of 3 g of *t*-BuOK in 175 ml of dry DMSO (see exp. 1, note 1). The temperature (initially ~20°C) rises within 1 to 2 min to 35°C, but is kept between 30 and 35°C by occasional cooling (with manual swirling) in a water bath at 10°C. After 30 min the brown reaction mixture is extracted 8 times with a 1:1 mixture of Et_2O and pentane (1 x 100 ml, 7 x 40 ml). The combined extracts are cooled to -80°C (with continuous swirling). Fifteen min after this temperature has been reached, the cold mixture is filtered quickly through a sintered-glass funnel (with suction) and the DMSO on the filter rinsed with a cold (-80°C) Et_2O-pentane mixture. After concentration of the extract *in vacuo* , the remaining liquid is carefully fractionated through a 40-cm Widmer column to give $CH_3CH{=}CHC{\equiv}CN(C_2H_5)_2$ (*E*:*Z* ~70:30), b.p. 70-75°C/12 mmHg, $n_D(20°)$ 1.4937, in ~80% yield. The small brown residue consists mainly of $CH_3C{\equiv}CCH{=}CHN(C_2H_5)_2$.

The amine $H_2C{=}C(CH_3)C{\equiv}CCH_2N(C_2H_5)_2$, b.p. 70°C/12 mmHg, $n_D(20°)$ 1.4670, is converted by a similar procedure into $(CH_3)_2C{=}CHC{\equiv}CN(C_2H_5)_2$, b.p. 90°C/12 mmHg, $n_D(20°)$ 1.4938, with an excellent yield. Amines with a longer carbon chain, e.g. $CH_3CH{=}CHC{\equiv}CCH_2NR_2$, give 1,3,5-trienylamines, e.g. $H_2C{=}CHCH{=}CHCH{=}CHNR_2$, under the isomerization conditions described above [189].

3.5 1-Diethylamino-1,3-pentadiyne

$$HC{\equiv}CC{\equiv}CCH_2N(C_2H_5)_2 \xrightarrow[\text{HMPT, 10°C}]{t\text{-BuOK + }t\text{-BuOH}} CH_3C{\equiv}CC{\equiv}CN(C_2H_5)_2$$

Scale: 0.20 molar.

Apparatus: 250-ml round-bottomed, three-necked flask, equipped with a gas inlet for N_2, a mechanical stirrer and a thermometer-outlet combination (compare fig. 1).

Introduction

When the amine $HC{\equiv}CC{\equiv}CCH_2N(C_2H_5)_2$ is subjected to the isomerization conditions of exp. 4., a vigorous reaction takes place and a very dark solution is formed from which only tarry products can be isolated. A moderate yield of the diyne amine $CH_3C{\equiv}CC{\equiv}CN(C_2H_5)_2$ is obtained, when the basic catalyst is "poisoned" by addition of *t*-butylalcohol (ratio *t*-BuOK/HO*t*-Bu ~1:3 by weight). Replacement of DMSO by HMPT, however, gives good results, provided that during the isomerization the temperature is carefully maintained around 10°C, and the concentration of the base is not too high. Since HMPT and pentane or Et_2O are completely mixable, a "dry" extraction procedure as described in exp. 4. cannot be applied. Fortunately, the diyne amine appears to be reasonably stable at pH >9 in water at low temperatures, so that the compound can be isolated by the usual extraction procedure.

Procedure

Dry HMPT (75 ml, for drying the commercially available solvent compare exp. 1, note 1) is placed in the flask (note 1). A solution of 1 g of *t*-BuOK and 3 g of *t*-butylalcohol in 5 ml of HMPT is added and the mixture is cooled to 7°C (ice-water bath). A mixture of 0.20 mol of the starting amine (p. 194) and 25 ml of dry HMPT, precooled to ~5°C, is added in 5 equal portions with intervals of about 3 min. The temperature of the dark mixture is maintained between 8 and 12°C (occasional cooling). Ten min after this addition a same amount of the solution of the basic catalyst in HMPT is added and stirring at 10°C is continued for an additional 10 min. The very dark solution is then poured into 500 ml of ice water and 7 extractions with a 1:1 mixture of Et_2O and pentane are carried out as quickly as possible. The combined solutions are washed twice with ice water and dried over K_2CO_3. The liquid remaining after concentration of the solution *in vacuo*, is distilled through a short Vigreux column and the distillate collected in a *single* receiver cooled in a bath at 0°C (fig. 14). The diyne amine, b.p. ~50°C/0.1 mmHg, $n_D(20°)$ 1.5264, is obtained in 78% yield.

Notes

1. HMPT is a cancer-suspect solvent, contact with the skin should be avoided. All operations should be carried out in a well-ventilated hood.

3.6 Preparation of Ethyl Propargyl Sulfide and Subsequent Base-Catalysed Isomerization to 1-Ethylthio-1-propyne

$$Na + C_2H_5SH \xrightarrow[-33^\circ C]{\text{liq. } NH_3} C_2H_5SNa + 1/2\, H_2\uparrow$$

$$C_2H_5SNa + HC{\equiv}CCH_2Cl \xrightarrow[-33^\circ C]{\text{liq. } NH_3} C_2H_5SCH_2C{\equiv}CH + NaCl\downarrow$$

$$C_2H_5SCH_2C{\equiv}CH \xrightarrow[\text{liq. } NH_3,\ -33^\circ C]{NaOC_2H_5} C_2H_5SC{\equiv}CCH_3$$

Scale: 0.50 molar.

Apparatus: fig. 4, 2 l.

Introduction

Cadiot and co-workers [179] studied the base-catalysed isomerization of propargyl sulfides, $HC{\equiv}CCH_2SR$, in ethanol at slightly elevated temperatures. The intermediate allenic sulfides, $H_2C{=}C{=}CHSR$, were found to isomerize relatively slowly to 1-propynyl sulfides, $CH_3C{\equiv}C\text{-}SR$, under the influence of sodium ethoxide. We observed [178] an extremely fast isomerization of propargylic sulfides to 1-propynyl sulfides in boiling liquid ammonia (-33°C) using sodium ethoxide as a catalyst. This base can be prepared by adding an equivalent amount of ethanol to a solution of sodium or a suspension of sodamide in liquid ammonia. The sodium ethoxide prepared in this way is not solvated by ethanol, which explains its high reactivity. Alternatively, a catalytic amount of *t*-BuOK (commercially available) may be added to a mixture of a propargyl sulfide and liquid ammonia. The propargyl sulfides can be conveniently prepared *in situ* by adding propargyl chloride to an ammoniacal solution of sodium alkanethiolate, which is obtained by adding the thiol to a solution of sodium in liquid ammonia. Thiols often contain small amounts of disulfides formed by oxidation. For the preparation of thiolates from thiols and sodium in ammonia it is not necessary to remove the disulfide by distillation (complaints about the stench!), as also the disulfide is converted by the alkali metal into thiolate. Methanethiol is very volatile (b.p. ~6°C) and it is experimentally not very attractive to prepare a solution of sodium methanethiolate in liquid ammonia from the thiol. This solution is obtained conveniently however, by adding the commercially available dimethyl disulfide, CH_3SSCH_3, to the double equivalent amount of sodium in liquid ammonia ($CH_3SSCH_3 + 2\ Na \rightarrow 2\ CH_3SNa$).

Procedure

Anhydrous liquid ammonia (1.2 l) is placed in the flask and 14 g (0.6 mol) of sodium is added in pieces of about 0.5 g. After 10 min ethanethiol is added dropwise over 20 min: slightly more than 0.60 mol is required to give a colourless solution. Subsequently, 0.50 mol of propargyl chloride is added over 15 min. Salt separates immediately from the solution. After an additional 15 min, a solution of 5 g of *t*-BuOK in 100 ml of liquid ammonia (prepared by adding the base to ammonia in a 500-ml round-bottomed or conical flask) is cautiously poured into the reaction flask (note 1). The mixture is vigorously stirred for 5 min after which the ammonia is allowed to evaporate overnight (fig. 11). Water (~300 ml) is added with vigorous stirring. After dissolution of the salt, four extractions with small portions of pentane are carried out. The combined organic solutions are washed three times with water and subsequently dried over $MgSO_4$. The greater part of the pentane is distilled off at atmospheric pressure (40-cm Vigreux column, bath temperature not higher than 90°C). Distillation of the remaining liquid, using a single receiver cooled in a water bath at 0°C (fig. 14), gives 1-ethylthio-1-propyne, b.p. ~30°C/15 mmHg, $n_D(20^\circ)$ 1.4963, in ~80% yield.

$CH_3C{\equiv}CSCH_3$, b.p. ~70°C/100 mmHg, $n_D(20^\circ)$ 1.5020, is obtained in slightly lower yield (between 70 and 75%) from CH_3SNa and $HC{\equiv}CCH_2Cl$. The required solution of 0.50 mol of CH_3SNa is obtained by adding ~0.30 mol of CH_3SSCH_3 to a solution of 0.60 mol of sodium in about 1 l of liquid ammonia.

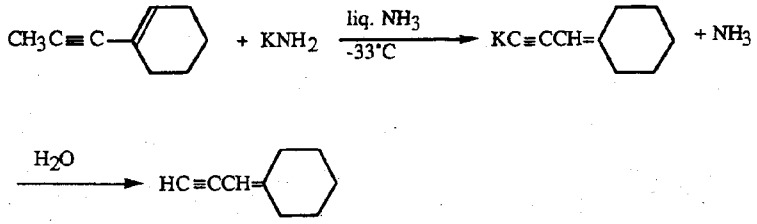
Notes

1. If no *t*-BuOK is available, a solution of 0.10 mol of sodium ethoxide in ~150 ml of liquid ammonia may be added. This solution is obtained in a 1-l round-bottomed flask by cautious addition of 0.10 to 0.13 mol of absolute ethanol to a solution of 0.10 mol of sodium or a suspension of 0.10 mol of sodamide in 150 ml of ammonia.

3.7 Conversion of 2-Alkyne and 4-En-2-yne Systems into Acetylenes with a Terminal Triple Bond by Reaction with Potassium Amide

$$CH_3C{\equiv}C\text{-}t\text{-}Bu + KNH_2 \xrightarrow[-33^\circ C]{\text{liq. } NH_3 (+ \text{HMPT})} KC{\equiv}CCH_2t\text{-}Bu\downarrow + NH_3$$

$$KC{\equiv}CCH_2t\text{-}Bu \xrightarrow{H_2O} HC{\equiv}CCH_2t\text{-}Bu$$

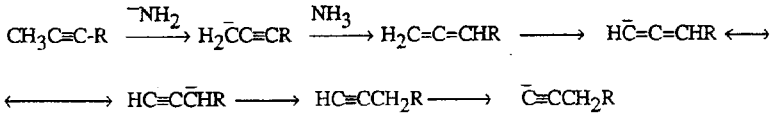


Scale: 0.50 molar.

Apparatus: fig. 4, 2 l.

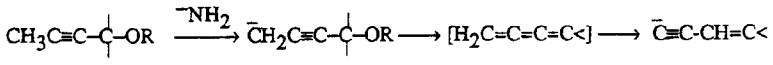
Introduction

A number of acetylenic compounds with the system $CH_3C{\equiv}C$- or $CH_3C{\equiv}CC{=}C$- can be converted into the isomers with the terminal unsaturated systems $HC{\equiv}CCH_2$- and $HC{\equiv}C$-$C{=}C$-, respectively. The procedure involves treatment with sodamide or (preferably) potassium amide in liquid ammonia, followed by protonation of the alkali acetylide, usually by addition of water (after evaporative removal of the ammonia). This isomerization also succeeds with the allene systems $H_2C{=}C{=}C{<}$ or $H_2C{=}C{=}C$-$CH{=}C$-. As a preparative method this "contrathermodynamic" isomerization is of limited significance since in many cases the compounds with terminal unsaturated systems are more readily available than the methyl compounds with the same number of carbon atoms. The conversions may be visualized as shown in the scheme below, representing the kinetically controlled formation of the kinetically stable alkynylide through a number of neutral and transient anionic intermediates:



(an analogous scheme may be drawn for the isomerization of $CH_3C{\equiv}CC{=}C{<}$ systems)

The isomerization gives good results when R represents an alkyl chain or cycloalkyl. 1-Propynyl ethers $CH_3C{\equiv}COR$ give propargylic ethers, $HC{\equiv}CCH_2OR$ [174], but with the analogous sulfides, $CH_3C{\equiv}CSR$, the conversion proceeds sluggishly, probably because of the formation of the anions $H_2C{=}C{=}\underline{C}SR$ which have a considerable kinetic stability in liquid ammonia [2,178]. When R = phenyl, only tarry products are obtained [2]. If an ether group is present in a suitable position, 1,4-elimination of HOR occurs [143], *e.g.*:



The procedures for neopentylacetylene and propynylidenecyclohexane are two synthetically useful examples of "contrathermodynamic" isomerizations.

Procedure

A solution of ~ 0.7 mol of potassium amide in about 700 ml of liquid ammonia is prepared as described in refs. 1, 3, and 4 (the solution is freed from small particles of potassium by filtration through glass wool). 1-Methyl-2-*t*-butylacetylene (0.50 mol, see p. 42) or 1-(1-propynyl)cyclohexene (0.50 mol, see p. 44) is added dropwise over 15 min with efficient stirring (note 1). A fine, white suspension of the potassium alkynylide is formed gradually. After 2 h, 200 ml of high-boiling (b.p. ≥ 170°C/760 mmHg) petroleum ether (in the case of neopentylacetylene) or 200 ml of Et_2O (in the case of propynylidenecyclohexane) is added over a few min from the dropping funnel. The flask is then placed in a water bath at 40°C. When the stream of ammonia vapour has become faint, introduction of nitrogen (~500 ml/min) is started. In the case of propynylidenecyclohexane an additional volume of 100 ml of Et_2O is added. The flask is placed in an ice-water bath and ice water (~300 ml) is added over about half an hour with vigorous stirring. After dissolution of all solid material, the layers are separated and the aqueous layer is extracted twice with small portions of petroleum ether or Et_2O. The combined organic solutions are dried over $MgSO_4$. Neopentylacetylene (b.p. 76°C/760 mmHg, $n_D(20°)$ 1.3992) is isolated from the solution in the manner described on p. 10. Yields are mostly higher than 80%. Propynylidenecyclohexane, b.p. 55°C/10 mmHg, $n_D(20°)$ 1.5060, is obtained in an excellent yield by concentrating the ethereal solution in a water-pump vacuum (bath temperature not higher than 35°C) and subsequently distilling the remaining liquid thorough a 30-cm Vigreux column.

c-$C_6H_{11}CH{=}CHC{\equiv}CH$, b.p. 71°C/10 mmHg, $n_D(20°)$ 1.4945, (only the *E*-isomer is obtained) is obtained in a similar way by treating the methyl derivative of propynylidenecyclohexane (p. 44) with KNH_2. Reaction of $CH_3C{\equiv}CCH_2N(C_2H_5)_2$ (p. 44) with KNH_2 gives a mixture of $HC{\equiv}CCH_2CH_2N(C_2H_5)_2$ and $H_2C{=}CHCH{=}CHN(C_2H_5)_2$ from which the acetylenic compound can be isolated (b.p. 33°C/10 mmHg, $n_D(20°)$ 1.4390) in ~70% yield by very careful distillation through a 40-cm Vigreux column.

Enyne alcohols $CH_3C{\equiv}CCH{=}CH(CH_2)_nOH$ can be converted with good yields into the isomers $HC{\equiv}CCH{=}CH(CH)_{n+1}OH$. From *E*-$CH_3C{\equiv}CCH{=}CHCH_2OH$ (obtained by methylation of $LiC{\equiv}CCH{=}CHCH_2OLi$ in liquid ammonia as described on p. 48) a 90:10 mixture of *Z* and *E*-$HC{\equiv}CCH{=}CHCH_2CH_2OH$ is obtained.

Notes

1. In the case of the preparation of neopentylacetylene, 50 ml of dry HMPT (see Chap. I of ref. 1, or exp. 1, note 1) is introduced prior to adding the 2-alkyne.

3.8 Conversion of 1-(*N*,*N*-Dialkylamino)-3-buten-1-yne into 1-(*N*,*N*-Dialkylamino)--1-buten-3-yne by Reaction with Potassium Amide

$$H_2C{=}CHC{\equiv}CNR_2 + KNH_2 \xrightarrow[-33^\circ C]{\text{liq. } NH_3} KC{\equiv}CCH{=}CHNR_2 \downarrow + NH_3$$

$$\xrightarrow{NH_4Cl} HC{\equiv}CCH{=}CHNR_2 \; (R = CH_3, C_2H_5)$$

Scale: 0.20 molar.'

Apparatus: fig. 4, 1 l.

Introduction (see also Section 2)

Although the isomerization $H_2C{=}CHC{\equiv}CNR_2 \rightarrow HC{\equiv}CCH{=}CHNR_2$ can be brought about with catalytic amounts of *t*-BuOK in HMPT or DMSO [185], the procedure below is more satisfactory because aqueous work-up of the water-sensitive products can be avoided. The potassium amide is consumed in the conversion into the slightly soluble potassium compound of the ynene amine. We therefore presume that an equivalent amount of KNH_2 is required for a complete conversion of the starting compound.

Procedure

The enyne amine (0.20 mol, see ref. 4) is mixed with 50 ml of dry Et_2O and the solution added over 15 min to a solution of 0.25 mol of potassium amide in 350 ml of liquid ammonia (ref. 1, 3, 4). A fine suspension is formed. After an additional hour the outlet is replaced with a powder funnel and 15 g of powdered ammonium chloride is introduced in 0.5 g portions over about 10 min. The dropping funnel is then replaced with a gas inlet and introduction of N_2 is started (~500 ml/min). The ammonia is evaporated by placing the flask in a water bath at 35-40°C. The remaining brown solid is rinsed five to eight times with small portions of dry Et_2O (which are cautiously decanted from the solid). After concentrating the solution *in vacuo*, the remaining liquid is distilled through a 30-cm Vigreux column to give the amines R = CH_3, b.p. 58°C/15 mmHg, $n_D(20^\circ)$ 1.5419, and R = C_2H_5, b.p. 78°C/15 mmHg, $n_D(20^\circ)$ 1.5277, in excellent yields. The *E*/*Z* ratio is 94:6 for both compounds.

3.9 Preparation of 3-Pentyn-1-oic Acid and 3-Heptyn-1-oic Acid by Treatment of the 2-Alkynoic Acids with Sodamide in Liquid Ammonia

$$RCH_2C{\equiv}CCOOH + 2\,NaNH_2 \xrightarrow[-33^\circ C]{\text{liq. } NH_3} R\bar{C}{=}C{=}CHCOO^- \downarrow + 2\,NH_3$$

$$\xrightarrow[2.\ H_2O,\ H^+]{1.\ NH_4Cl} RC{\equiv}CCH_2COOH \qquad (R = CH_3, C_3H_7)$$

Scale: 0.10 molar.

Scale: 0.10 molar.

Apparatus: fig. 8, 3 l; stirrer fig. 3.

Introduction

Addition of a 2-alkynoic acid to alkali amide in liquid ammonia initially gives a solution of the alkali salt of the carboxylic acid. If an excess of alkali amide is present, the weakly basic salt is further deprotonated at a position next to the triple bond [183]. This double deprotonation which may be compared with the formation of 'di-anions' from 1,3-diketones and alkali amides [71], is essentially complete. The high kinetic stability of the alkynoic acid-dianion may be explained on the basis of resonance stabilization :

$$RCH{=}C{=}\bar{C}COO^- \longleftrightarrow R\bar{C}HC{\equiv}CCOO^- \longleftrightarrow RCH{=}C{=}C{<}^{O^-}_{O^-}$$

The protolysis with ammonium chloride is apparently highly regioselective, since the product obtained after acidic work-up is almost pure 3-alkynoic acid.

Procedure

A mixture of 0.10 mol of the 2-alkynoic acid (p. 100) and 50 ml of THF is added over a few min to an efficiently stirred suspension of 0.4 mol (excess!) of sodamide [1,3,4] in 400 ml of liquid ammonia. The addition is carried out by means of a syringe, keeping the end of the needle a few cm above the surface of the ammonia. The initially formed solution quickly changes into a rather thick white suspension. After an additional 30 min, 40 g of powdered ammonium chloride is added over 5 min with vigorous stirring. The ammonia is then removed by placing the flask in a water bath at 50°C (continuous swirling by hand is necessary in order to suppress bumping). Towards the end of this operation, a rubber stopper provided with an outlet is placed on the flask. Warming is continued until the flow of ammonia from the outlet has become very faint. Et_2O (200 ml) is then added and warming at 50°C is continued until the flow of ammonia has stopped completely. After cooling to room temperature, 200 g of finely crushed ice is added. After dissolution of the solid material, 5 N hydrochloric acid is added with swirling until the pH of the solution has become lower than 3. The solution is then saturated with ammonium chloride, after which ten extractions with small portions of Et_2O are carried out. The unwashed extracts are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Traces of water are removed in a vacuum of 0.5 to 1.0 mmHg by warming the remaining liquid for 30 min at 30°C. The remaining brown solid (3-alkynoic acid, purity >95% according to ^1H NMR, yield ~90%) gives the pure acid by crystallization from pentane as described in ref [183].

3.10 Preparation of Neopentylacetylene *via* Lithiation of *t*-Butylallene

$$t\text{-BuCH=C=CH}_2 + C_2H_5Li \xrightarrow[-60 \rightarrow +25^\circ C]{Et_2O} t\text{-BuCH=C=CHLi} \longrightarrow t\text{-BuCH}_2C{\equiv}CLi$$

$$\xrightarrow{H_2O} t\text{-BuCH}_2C{\equiv}CH$$

Scale: 0.30 molar.

Apparatus: fig. 1, 1 l.

Introduction

Allene, $H_2C{=}C{=}CH_2$, and homologues with an alkyl chain, $RCH{=}C{=}CH_2$, can be easily metallated at temperatures in the region of -70°C using *n*-BuLi in a mixture of THF and hexane [186]. In most cases, a mixture of $RC(Li){=}C{=}CH_2$ and $RCH{=}C{=}CHLi$ is formed in which the latter species predominates [2]. *t*-Butylallene gives exclusively the terminally metallated intermediate [2]. There is a considerable difference in thermostability of the 1- and 3-metallated allenes. Whereas the 1-metallated allenes rearrange smoothly and completely to acetylides $RCH_2C{\equiv}CLi$ at temperatures above 0°C , the intermediates $RC(Li){=}C{=}CH_2$ (which are also formed from BuLi and 2-alkynes $RC{\equiv}CCH_3$ at room temperature) are reasonably stable under the same conditions [1,190]. Treatment of an alkylallene with alkyllithium at low temperatures, followed by aqueous work-up at room temperature is therefore expected to afford a mixture of the 1-alkyne $RCH_2C{\equiv}CH$ and the protonation products of $RC(Li){=}C{=}CH_2$ (generally a mixture of the allenes and the 2-alkyne). In the case of *t*-butylallene (and possibly also other allenes with a bulky substituent such as cyclohexyl), however, only the 1-alkyne will be formed. Since neopentylacetylene is volatile, the commercially available solution of BuLi in hexane cannot be used for the metallation. The most suitable reagent is a solution of ethyllithium in Et_2O prepared from ethyl bromide and lithium.

Procedure

A solution of 0.4 mol of ethyllithium in ~350 ml of Et_2O [1,4] is cooled to -65°C, after which 0.30 mol of *t*-butylallene [4] is added over 10 min. The cooling bath is removed and the temperature allowed to rise. The suspension disappears gradually. When the temperature has reached -10°C, the solution is warmed to 25°C. After an additional 15 min the solution is cooled to below 0°C and 50 ml of a saturated solution of NH_4Cl is added dropwise with vigorous stirring. After separation of the layers, two extractions with small portions of Et_2O are carried out. The combined organic solutions are dried over $MgSO_4$, after which the Et_2O is distilled off very slowly through an efficient (40 to 60 cm) Widmer column. The remaining liquid is distilled from a smaller flask to give neopentylacetylene, b.p. 76°C/760 mmHg, $n_D(20^\circ)$ 1.3992, in > 70% yield. Towards the end of the distillation the pressure in the apapratus is slightly lowered (water aspirator) in order to minimize the hold-up.

3.11 Preparation of 10-Undecyn-1-ol by Treatment of 2-Undecyn-1-ol with the Monopotassium Amide of 1,3-Diaminopropane

$$C_8H_{17}C{\equiv}CCH_2OH + 2\,KNH(CH_2)_3NH_2 \xrightarrow[20 \rightarrow 70^\circ C]{H_2N(CH_2)_3NH_2} KC{\equiv}C(CH_2)_9OK + 2\,H_2N(CH_2)_3NH_2$$

$$\xrightarrow{H_2O} HC{\equiv}C(CH_2)_9OH$$

Scale: 0.20 molar.

Apparatus: 2-l one-necked, round-bottomed flask.

Introduction

C.A. Brown [182] found that dialkylacetylenes can be converted into the potassium compounds of the isomeric 1-alkynes by treatment with a solution of potassium aminopropylamide, $KNH(CH_2)_3NH_2$, in 1,3-diaminopropane. Hydrolysis of the reaction mixtures gave the 1-alkynes in high yields. Chemists of Unilever [191] applied this reaction to transform acetylenic alcohols with a long alkyl chain, $CH_3(CH_2)_nC{\equiv}CCH_2OH$, into the isomers with a terminal triple bond, $HC{\equiv}C(CH_2)_{n+1}CH_2OH$. In these cases two equivalents of the amide is required. The mechanism by which the triple bond can move towards the end of the chain without isomerizing to the much more stable conjugated diene, is not well understood. The scope of this remarkable isomerization is limited.The amide was obtained by treating 1,3-diaminopropane with potassium hydride. We developed an alternative method for preparing the amide consisting of treatment of diaminopropane with potassium amide [192]. This method avoids the tedious and hazardous working with the alkali hydride which is commercially available as a suspension in mineral oil. This oil has to be removed by washing with Et_2O or pentane, after which the remaining powder has to be weighed in a dry and inert atmosphere.

Procedure

A filtered solution of 0.50 mol of potassium amide in ~300 ml of liquid ammonia is prepared as described in refs.1,3, and 4. The solution is concentrated to a volume of 100 to 150 ml by placing the flask in a water bath at 35°C (only the lower part of the flask is dipping in the water). 1,3-Diaminopropane (350 ml, dried over machine-powdered KOH and subsequently distilled in a vacuum) is cautiously added to the remaining very concentrated solution of potassium amide. An efficient reflux condenser equipped with a narrow outlet (on the top) is placed on the flask, which is subsequently placed in a water bath at ~ 50°C. The flask is occasionally swirled by hand. When the stream of ammonia vapour has become very faint, the outlet is connected with a 20 cm long tube filled with KOH pellets, which in its turn is

connected with the water aspirator. The flask is evacuated and gradually warmed until the diaminopropane begins to reflux (in the beginning it may be necessary to interrupt heating when frothing becomes serious). Heating and refluxing are continued for 1 to 1.5 h until all solid has disappeared. Nitrogen is admitted and the greyish solution is cooled to 15°C. 2-Undecyn-1-ol (0.20 mol, p. 58) is added in one portion, after which the mixture is vigorously swirled by hand in order to effect homogenization. A thermometer is placed in the flask. The temperature of the solution rises within a few min to over 60°C. When the evolution of heat has stopped and the temperature begins to drop, the flask is placed in a bath at 70°C. The brown solution becomes very viscous. After 1 h the reaction mixture is cooled to room temperature and 1 l of ice water is added. After vigorous swirling, five to eight extractions with a 1:1 mixture of Et_2O and pentane are carried out. The combined organic solutions are washed twice with water and subsequently dried over $MgSO_4$. The liquid remaining after concentration of the solution *in vacuo* is distilled through a short Vigreux column to give 10-undecyn-1-ol, b.p. ~95°C/1 mmHg, $n_D(20°)$ 1.4660, in good to excellent yields.

Chapter XII
Miscellaneous Preparations of Acetylenic Derivatives

1. Halogen Compounds, Sulfinates, Sulfonates and Acetates

All temperatures are internal, unless indicated otherwise

1.1 Propargyl Bromide from Propargyl Alcohol and Phosphorous Tribromide

$$3\ HC{\equiv}CCH_2OH + PBr_3 \xrightarrow[\text{reflux}]{Et_2O\ (\text{pyridine})} 3\ HC{\equiv}CCH_2Br + P(OH)_3$$

Scale: 3.0 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer and a reflux condenser.

Introduction

The most convenient way to prepare propargyl bromide on a laboratory scale consists of reacting the corresponding alcohol with phosphorous tribromide in the presence of a small amount of pyridine. The formation of the bromide proceeds through a number of intermediates. In the first step $HC{\equiv}CCH_2OPBr_2$ and HBr are formed, which react further to $HC{\equiv}CCH_2Br$ and $HOPBr_2$. The reaction with $HOPBr_2$ proceeds in a way that is analogous to the first step. The nucleophilic attack of bromide on propargylic carbon in the bromophosphites, resulting in the formation of propargyl bromide, is catalysed by pyridine: this binds part of the HBr, thus converting it into the more nucleophilic Br^-. In addition to propargyl bromide, appreciable amounts of the dibromo compound $H_2C{=}C(Br)CH_2Br$ are formed, especially when no solvent is used. The formation of this compound may be visualized as an electrophilic addition of HBr to the triple bond in $HC{\equiv}CCH_2OH$ or some intermediate, followed by reaction with PBr_3. Diethyl ether suppresses this electrophilic addition by forming the oxonium complex $Et_2O^+H.Br^-$ with HBr. It is possible to obtain propargyl bromide in high yields by slowly adding PBr_3 to a strongly cooled mixture of $HC{\equiv}CCH_2OH$ and Et_2O and subsequently allowing the temperature to rise very slowly. In the procedure described below, the reaction is carried out in refluxing Et_2O, giving propargyl bromide in *ca.* 70% yield. In the procedure followed by Gaudemar [206], propargyl alcohol is added dropwise to propargyl bromide containing a small amount of pyridine. We experienced this procedure as inconvenient because much HBr escaped from the reaction mixture during the addition of the alcohol.

Warning!

Contact of $HC{\equiv}CCH_2Br$ (and homologues) with the skin causes a painful irritation. It is absolutely necessary to wear protective gloves and to work in a well-ventilated hood.

Procedure

A mixture of 3.0 mol of propargyl alcohol, 400 ml of dry Et_2O and 10 ml of pyridine is placed in the flask. Phosphorous tribromide (1.1 mol) is added dropwise over 1.5 h without external cooling while stirring at a moderate rate. After the addition, the reaction mixture is heated for an additional 1 h under reflux. The greater part of the ether is then quickly distilled off (during ~45 min) at atmospheric pressure through a 40-cm Vigreux column, keeping the bath temperature below 100°C. The remaining liquid is cooled to below 30°C, after which the volatile components are distilled off in a water-pump vacuum (10 to 20 mmHg). The vapours are condensed in a single receiver, cooled in a bath at -50°C, or lower temperature (fig 14). The distillation is stopped when (at a pressure of 10-20 mmHg) the temperature in the head of the column rises above 35°C. Careful redistillation at 760 mmHg of the contents of the receiver through a 40-cm Widmer column gives the main portion of propargyl bromide, passing over between 80 and 95°C. The residue is mainly $H_2C{=}C(Br)CH_2Br$. Fractional distillation of the ethereal distillate (see above) gives an additional small amount of propargyl bromide, bringing the yield at about 70%. Pure propargyl bromide, b.p. 84°C/760 mmHg, $n_D(20°)$ 1.491, is obtained by redistillation.

$HC{\equiv}CCH{=}CHCH_2Br$, b.p. ~40°C/15 mmHg, $n_D(20°)$ 1.5350 (*E*:*Z* ~85:15), is obtained in ~70% yield by a similar procedure from the corresponding alcohol (p. 64). During the addition of PBr_3 the solution turns very dark. The enyne bromide is a very lachrymatory compound. Contact of the liquid or vapour with the skin has a similar effect as in the case of propargyl bromide and other acetylenic bromides.

1.2 Homologues of Propargyl Bromide from Propargylic Alcohols and Phosphorous Tribromide

$$3\ RC{\equiv}CCH_2OH + PBr_3 \xrightarrow[-30°C \rightarrow \text{reflux}]{Et_2O\ (\text{pyridine})} 3\ RC{\equiv}CCH_2Br + P(OH)_3\downarrow \quad (R = \text{alkyl})$$

Scale: 0.90 molar.

Apparatus: fig. 1, 1 l.

Introduction: see exp. 1.

Procedure (for warning see exp. 1)

A mixture of 0.90 mol of the acetylenic alcohol, 250 ml of dry Et_2O (note 1) and 5 ml of pyridine is cooled to -35°C. Phosphorous tribromide (0.32 mol) is added dropwise over 45 min, while keeping the temperature between -25 and -35°C (note 2). The reaction mixture is stirred for an additional 2 h at -20 to -25°C, after which the temperature is allowed to rise over 2 h to 20°C. The conversion is completed by heating the reaction mixture for 30 min under reflux. A saturated aqueous solution of NaCl is then added with vigorous stirring. After separation of the layers, one extraction with a small portion or Et_2O is carried out. The organic solution is dried over $MgSO_4$, after which the greater part of the solvent is distilled off at atmospheric pressure through a 40-cm Vigreux column or removed under reduced pressure (in the case of less volatile bromo compounds). Careful distillation of the remaining liquid gives the bromo compounds in yields between 75 and 85%: $CH_3C{\equiv}CCH_2Br$, b.p. ~60°C/80 mmHg, $n_D(20°)$ 1.5062; $C_2H_5C{\equiv}CCH_2Br$, b.p. 38°C/10 mmHg, $n_D(20°)$ 1.4980; $C_4H_9C{\equiv}CCH_2Br$, b.p. 72°/12 mmHg, $n_D(20°)$ 1.4936.

Notes

1. When smaller amounts of Et_2O are used, yields are lower and more of the dibromo compound (compare exp. 1) is formed.
2. If the addition of PBr_3 is carried out under reflux (compare exp. 1), yields are 5 to 10% lower.

1.3 3-Bromo-3-methyl-1-butyne from the Corresponding Carbinol and Phosphorous Tribromide

$$3\ HC{\equiv}CC(CH_3)_2OH + PBr_3 \xrightarrow[15\text{-}20°C]{} 3\ HC{\equiv}CC(CH_3)_2Br + P(OH)_3$$

Scale: 0.30 molar.

Apparatus: fig. 1, 500 ml.

Procedure (compare exps. 1 and 2)

Phosphorous tribromide (0.11 mol) is added dropwise over 20 min to 0.30 mol of the acetylenic carbinol (commercially available, see also p. 89), while keeping the temperature between 10 and 20°C. During the addition, which is carried out over 15 min, the solid on the glass wall (carbinol) gradually liquifies. Fifteen minutes after the addition, 100 ml of water is added with vigorous stirring. The organic layer is dried over a small amount of $MgSO_4$ and subsequently transferred into a 500-ml round-bottomed flask which is equipped for a vacuum distillation using a 40-cm Widmer column, a condenser and a single receiver cooled in a bath at -10°C (fig. 14). The product passing over below 45°C/15 mmHg (a mixture of the desired compound and $H_2C{=}C(Br)C(CH_3)_2Br$) is carefully redistilled in the same apparatus. The distillate with b.p. up to 30°C/15 mmHg, $n_D(20°)$ 1.4668, is practically pure $HC{\equiv}CC(CH_3)_2Br$. The yield is *ca.* 50% (note 1).

Notes

1. It should be possible to obtain higher yields by adding PBr_3 at low temperatures to a mixture of the carbinol and Et_2O and gradually raising the temperature (compare exp. 2).

1.4 3-Bromo-1-nonyne from the Corresponding Tosylate and Lithium Bromide in Acetone

$$HC{\equiv}CCH(OTs)C_6H_{13} + LiBr \xrightarrow[\text{reflux}]{\text{acetone}} HC{\equiv}CCH(Br)C_6H_{13} + TsOLi\downarrow$$

Scale: 0.30 molar.

Apparatus: 1-l two-necked, round-bottomed flask, equipped with a mechanical stirrer and a reflux condenser.

Introduction

The procedure for 3-bromo-1-nonyne illustrates an excellent method for the preparation of primary and secondary propargylic bromides [207]. The preparation of the tosylates as well as their conversion into the bromides are very clean reactions giving high overall yields. In fact, distillative purification is not necessary if the proper conditions are applied for the preparation of the tosylates and their conversion into the bromo compounds. For these reasons, this method is more suitable than the PBr_3-method for the preparation of propargylic bromides with a low volatility or low thermal stability. Propargylic iodides may be prepared similarly, using NaI in acetone or ethanol. It should be noted that the substitution is regio-specific, *i.e.* 1,3-substitution ("propargylic rearrangement") does not take place at all.

Procedure

A solution of 0.40 mol of anhydrous lithium bromide in 150 ml of dry acetone is added to a mixture of 0.30 mol of the tosylate (see exp. 1.11) and 100 ml of acetone. After refluxing for 1 h, 600 ml of ice water is added to the suspension and eight extractions with small (1 x 150 ml, 7 x 50 ml) portions of pentane are carried out. The combined extracts are washed with water and subsequently dried over $MgSO_4$. After removing the pentane under reduced pressure, the remaining liquid is distilled through a 30-cm Vigreux column to give the acetylenic bromide, b.p. 82°C/15 mmHg, $n_D(16°)$ 1.4742, in an excellent yield.

1.5 Homopropargyl Bromide from the Corresponding Tosylate and Lithium Bromide in DMSO

$$HC{\equiv}CCH_2CH_2OTs + LiBr \xrightarrow[\text{distillation}]{\text{DMSO}} HC{\equiv}CCH_2CH_2Br + LiOTs$$

Scale: 0.50 molar.

Apparatus: fig. 14, 1 l, a 40-cm Vigreux column is used.

Introduction

This method for the conversion of tosylates into the corresponding bromides is a variant of the method described in the previous experiment. It is more suitable for volatile bromides (with boiling points up to ~55°C/15 mmHg) than the acetone-method because the isolation procedure is more convenient (no frequent extraction with pentane or Et_2O, no time-consuming distillative separation from the extraction solvent).

Procedure

The tosylate (0.50 mol, freed from traces of Et_2O by evacuation, see exp. 1.11) is added with manual swirling to a solution (partly suspension) of 0.70 mol of anhydrous lithium bromide in 250 ml of DMSO. The apparatus is evacuated (water aspirator) and the flask heated in an oil bath. The volatile acetylenic bromide is trapped in the strongly cooled (-40°C) receiver (fig. 14). The temperature of the bath is gradually raised until DMSO begins to distill (b.p. ~80°C/15 mmHg). The distillation is stopped when about 20 ml of DMSO has passed over. The contents of the receiver are washed three times with 30 ml portions of water in a small dropping funnel and the lower layer is subsequently dried over a small amount of $MgSO_4$. Pure $HC{\equiv}CCH_2CH_2Br$, $n_D(20°)$ 1.4827, distillation unnecessary, is obtained in greater than 80% overall yields.

$HC{\equiv}CCH(CH_3)Br$, $n_D(20°)$ 1.4735, is obtained in an excellent yield by a similar procedure starting from $HC{\equiv}CCH(CH_3)OH$. This alcohol is commercially available as a 50% solution in water. The alcohol can be separated from the water by saturating the aqueous solution with K_2CO_3 and subsequently drying the upper layer over K_2CO_3.

The chloro compound $HC{\equiv}CCH(CH_3)Cl$, b.p. 74°C/760 mmHg, $n_D(20°)$ 1.4250, can be prepared analogously, using anhydrous lithium *chloride*.

In the preparation of $HC{\equiv}C(CH_2)_4Br$ from the alcohol by the same method, a 40-cm Widmer column is used instead of the Vigreux column. The distillation is stopped when about 50 ml of DMSO has been collected in the receiver (cooled at 0°C). The wash procedure gives the pure bromide, $n_D(20°)$ 1.4812, in ~80% overall yield.

Acetylic bromides with a b.p. in the region of 80°C/15 mmHg or higher may be prepared by heating the solution of LiBr and the tosylate in DMSO for 1 h at 70-80°C and subsequently adding water to the reaction mixture. The bromo compound is then isolated via extraction with Et_2O. It is, however, also possible to prepare less volatile bromides by heating the corresponding tosylates with a 10 to 20% excess of anhydrous LiBr in refluxing acetone or THF, as described in exp. 1.4.

1.6 5-Chloro-3-hexen-1-yne and 5-Bromo-3-hexen-1-yne from 3-Hydroxy-4-hexen-1-yne and Concentrated Aqueous HCl or HBr

$$HC{\equiv}CCH(OH)CH{=}CHCH_3 + HX \longrightarrow HC{\equiv}CCH{=}CHCH(X)CH_3 + H_2O \quad (X = Cl \text{ or } Br)$$

Scale: 0.50 molar.

Apparatus: 1-l three-necked, round-bottomed flask, equipped with a dropping funnel, a mechanical stirrer and a thermometer.

Procedure (compare [208])

The acetylenic alcohol (0.50 mol, see p. 87) is added over 30 min to 250 ml of a concentrated aqueous solution of HCl (37%) or HBr (note 1), while keeping the temperature at 20°C or 5 to 10°C, respectively. The heating effect is weak. After an additional 30 min (at the temperature indicated), 250 ml of ice water is added. The product is extracted six times with a 1:1 mixture of Et_2O and pentane (a sufficient amount of solvent should be used for the first extraction of the bromo compound in order to effect a satisfactory separation of the layers). The combined organic solutions are washed with water and subsequently dried over $MgSO_4$. The greater part of the solvent is then distilled off at atmospheric pressure through a 40-cm Widmer column, keeping the bath temperature below 80°C. Distillation of the remaining liquid *in vacuo* through the same column gives $HC{\equiv}CCH{=}CHCH(Cl)CH_3$, (*Z*/*E* ~30:70), b.p. 55-60°C/50 mmHg, $n_D(20°)$ 1.4829, or $HC{\equiv}CCH{=}CHCH(Br)CH_3$, (*Z*/*E* ~30:70), b.p. 44-50°C/10 mmHg, $n_D(20°)$ 1.5242, in yields of 72 and 90%, respectively. $H_2C{=}CH$-$CH(OH)C{\equiv}CH$ and concentrated HBr give a 30/70 mixture of $HC{\equiv}CCH(Br)CH{=}CH_2$ and $HC{\equiv}CCH{=}CHCH_2Br$, in 60% yield.

Notes

1. The solution of HBr is obtained by stirring a mixture of 250 ml of 48% HBr with 50 g of PBr_3 at ~40°C until the solution has become homogeneous.

1.7 3-Chloro-3-methyl-1-butyne from the Corresponding Carbinol and Concentrated HCl

$$HC{\equiv}CC(CH_3)_2OH + HCl \xrightarrow[-15°C]{H_2O,\ NH_4Cl,\ Cu_2Cl_2} HC{\equiv}CC(CH_3)_2Cl + H_2O$$

Scale: 0.50 molar.

Apparatus: 1-l wide-necked, conical flask and thermometer.

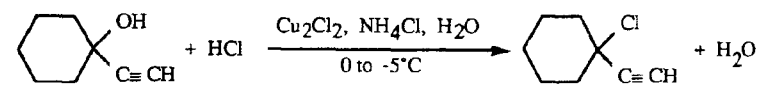
Procedure (compare [209])

Concentrated aqueous HCl (37%, 200 ml) powdered NH_4Cl (50 g), copper(I)chloride (10 g, technical grade) and copper bronze (2 g, note 1) are placed in the flask. The mixture is cooled to -20°C and 0.50 mol of the acetylenic carbinol (commercially available, see also p. 89) is added over a few min with manual swirling. Subsequently gaseous HCl (40 g, weight increase) is introduced over 10 min with manual swirling, while keeping the temperature below -10°C (note 2). The flask is then placed in a bath at -10°C. After 1 h (occasional swirling by hand) 300 ml of ice water is added. The layers are separated as completely as possible. The upper layer, crude $HC{\equiv}CC(CH_3)_2Cl$ (45 to 48 g, $n_D(20°)$ 1.421-1.423), is swirled with ~10 g of anhydrous K_2CO_3 (note 3) in a 500-ml round-bottomed flask. This flask is equipped for a vacuum distillation using a 40-cm Vigreux column, a condenser and a single receiver cooled in a bath at -70°C (fig. 14). A tube filled with $CaCl_2$ lumps is placed between the distillation apparatus and the water aspirator. The apparatus is evacuated (10 to 20 mmHg) and the flask containing the crude chloro compound and the drying agent warmed in a bath at 30 to 40°C. Careful redistillation of the contents of the receiver through a 40-cm Widmer column gives 3-chloro-3-methyl-1-butyne, b.p. 75-79°C/760 mmHg, $n_D(20°)$ 1.4168-1.4182, in 70 to 74% yield, with a purity of *ca.* 95%.

Notes

1. We presume that the metal serves to convert $CuCl_2$, formed by oxidation, into Cu_2Cl_2.
2. At higher temperatures the tertiary chloride undergoes a rearrangement under the influence of CuCl giving a chloride with a conjugated diene system. This isomer has a considerably higher refractive index.
3. Traces of HCl or CuCl are neutralized or adsorbed.

1.8 1-Chloro-1-ethynylcyclohexane from 1-Ethynylcyclohexanol and Concentrated HCl



Scale: 0.50 molar.

Apparatus: 1-l three-necked, round-bottomed flask, equipped with a mechanical stirrer, a powder funnel and a thermometer.

Procedure (compare [209])

A mixture of concentrated HCl, Cu_2Cl_2, copper bronze (see note 1 of exp. 7) and NH_4Cl is prepared in a 1-l conical flask as described in the previous experiment. Gaseous HCl (~40 g)

is then quickly introduced at -15°C (see exp. 7). The cold mixture is poured into the reaction flask. Ethynylcyclohexanol (0.50 mol, commercially available, see also p. 93) is then added over 2 min with stirring and cooling between -5 and -10°C. Stirring at 0 to -5°C is continued for an additional 1 h. Ice water (just enough to effect dissolution of the salt) is then added, followed by ~50 ml of pentane. After separation of the layers, one extraction with a small amount of pentane is carried out. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Careful distillation of the remaining liquid through a 40-cm Widmer column gives the tertiary chloride, b.p. 55°C/15 mmHg, $n_D(22°)$ 1.4804, in high yields.

1.9 1,4-Dichloro-2-butyne from the Corresponding Diol and Thionyl Chloride

$$HOCH_2C{\equiv}CCH_2OH + 2\,SOCl_2 \longrightarrow ClOSOCH_2C{\equiv}CCH_2OSOCl\ (+2\ HCl\uparrow) \rightarrow$$

$$\longrightarrow ClCH_2C{\equiv}CCH_2Cl + 2\,SO_2\uparrow$$

Scale: 2.0 molar.

Apparatus: 3-l three-necked flask, equipped with a dropping funnel, a mechanical stirrer and a thermometer-gas outlet combination.

Introduction

The reaction of primary or secondary alcohols with thionyl chloride is a general method for preparing the corresponding chloro compounds. In the first step a chlorosulfite ROSOCl is formed from which SO_2 is eliminated in a relatively slow step. This decomposition is facilitated by a tertiary amine, *e.g.* pyridine. The ammonium salt $RO\text{-}SON^+....Cl^-$ formed from the chlorosulfite is subsequently attacked on carbon (in R) by Cl^-. Since nucleophilic substitutions on propargylic carbon proceed more easily than on carbon in saturated compounds, it may be expected that the conversion of propargylic chlorosulfites into the chlorides will take place under relatively mild conditions.

The thionyl chloride method can be applied successfully to prepare primary and secondary propargylic chlorides. The isolation and purification of volatile chlorides is less convenient (contamination with $SOCl_2$!) than in the cases of higher-boiling compounds (simple distillation from the reaction mixture). The *tosylate method* (exp. 1.5) seems more attractive for the preparation of chlorides such as $HC{\equiv}CCH(CH_3)Cl$ (b.p. 74°C/760 mmHg) and $CH_3C{\equiv}CCH_2Cl$ (b.p. 101°C/760 mmHg) on a modest (up to ~0.5 molar) scale. For the preparation of "non-propargylic" chlorides from the corresponding alcohols, *e.g.* $HC{\equiv}C(CH_2)_4Cl$ from $HC{\equiv}C(CH_2)_4OH$, the reaction conditions are expected to be comparable with those necessary for the formation of saturated alkyl chlorides (refluxing for a few hours).

Warning

Dichlorobutyne is a skin-irritating compound; it is advised to wear protective gloves during the experiment.

Procedure (compare [231])

Powdered butynediol (2.0 mol, technical grade, light brown colour) and pyridine (15 ml) are placed in the flask. Thionyl chloride (4.3 mol, precooled at -40°C) is added in a number of portions over 30 min. During this addition, the flask is cooled in a bath at -30 to -40°C. The addition is accompanied by abundant evolution of hydrogen chloride. As a result, the net heating effect is very small. Temperature control in the first stage of the addition is therefore not very essential. Stirring becomes more easy when the greater part of the thionyl chloride has been added and part of the butynediol has dissolved. After the addition, stirring at 0 to -10°C is continued for an additional 2 h, then the flask is placed in a large (10 to 15 l if available) bath with ice and ice water. The gas outlet is connected with a tube, loosely filled with $CaCl_2$-lumps. The stirrer is replaced by a stopper. After ~12 h the brown reaction mixture is poured into a 1-l round-bottomed flask, which is equipped for a vacuum distillation, using a 40-cm Widmer column, a condenser and a single receiver, cooled in an ice bath (compare fig. 14). The system is evacuated (water aspirator) and the temperature of the heating bath (during the first hour of the evacuation 25°C) gradually raised to ~40°C. When the pressure has dropped to below 40 mmHg, the bath temperature is gradually raised until dichlorobutyne begins to pass over. Exhaustive distillation of the remaining viscous brown residue (partly pyridine.HCl) should not be attempted because decomposition may ensue (note 1). Careful redistillation affords 1,4-dichloro-2-butyne, b.p. 57°C/12 mmHg, $n_D(20°)$ 1.5054 in ~80% yield. If purified butynediol (recrystallized from a 3:10 mixture of THF and Et_2O) is used, yields may be higher than 90%.

Notes

1. Treatment of the residue with water, followed by extraction with Et_2O gives an additional small amount of product.

1.10 1,6-Dichloro-2,4-hexadiyne from the 1,6-Diol and Thionyl Chloride

$$HOCH_2(C{\equiv}C)_2CH_2OH + 2\,SOCl_2 \longrightarrow ClOSOCH_2(C{\equiv}C)_2CH_2OSOCl\ (+2\,HCl\uparrow)$$

$$\longrightarrow ClCH_2(C{\equiv}C)_2CH_2Cl + 2\,SO_2\uparrow$$

Scale: 0.30 molar.

Apparatus: 500-ml flask, see exp. 1.9.

Procedure (for warning see previous experiment)

The diol (0.30 mol, p. 222) and pyridine (3 ml) are placed in the flask. Thionyl chloride (80 g, precooled to -30°C) is added in 10-g portions over 20 min, while cooling the flask in a bath at -30°C. Stirring is started as soon as possible. After the addition the cooling bath is removed and the temperature of the reaction mixture is allowed to rise over ~4 h (occasional cooling is applied if the temperature rises too fast) to +30°C. The flask is then placed in a bath at 40-45°C. The equipment is removed and the flask is evacuated using a water aspirator. After about 1 h, the evacuating operation is terminated and Et_2O (200 ml) is added to the remaining brown liquid. The solution is vigorously shaken with a mixture of 200 ml of ice water and 20 ml of pyridine. After separation of the layers, two extracions with Et_2O are carried out. The combined organic solutions are successively washed with 3 N HCl and water and then dried over $MgSO_4$. The Et_2O is removed *in vacuo* and the remaining liquid distilled through a short Vigreux column to give the pure dichloride, b.p. ~50°C/0.2 mmHg, $n_D(20°)$ 1.5750, in an excellent yield.

1.11 General Procedure for the Preparation of *p*-Toluenesulfonates

$$ROH + p\text{-}CH_3\text{-}C_6H_4\text{-}SO_2Cl + KOH \xrightarrow[\sim 0°C]{Et_2O} RO\text{-}SO_2\text{-}C_6H_4\text{-}p\text{-}CH_3 + KCl + H_2O$$

Scale: 0.50 molar.

Apparatus: 2-l round-bottomed, three-necked flask, equipped with a powder funnel, a mechanical stirrer (fig. 3) and a thermometer.

Introduction

Esters of arenesulfonic acids are prepared by reaction of the corresponding alcohol with the arenesulfonyl chloride in the presence of a basic reagent, which has the function of activating the alcohol and binding the hydrogen chloride. The reaction is often carried out with pyridine, which is used as solvent. In the procedure for tosylates of primary aliphatic alcohols, described in A.I. Vogel, A Textbook of Practical Organic Chemistry, an aqueous solution of sodium hydroxide is used. Esters of primary alcohols are formed more easily than secondary-alkyl esters, while tertiary alcohols cannot be esterified under the usual conditions.

The procedure described below is quite general and uses finely, freshly machine--powdered KOH, which is added to a solution of the primary or secondary (acetylenic) alcohol and a 10-15% molar excess of tosyl chloride in Et_2O, kept around 0°C. The excess of tosyl chloride is destroyed during the reaction of the excess of KOH. Side- and subsequent reactions ("saponification" of the ester by KOH and 1,2-elimination of *p*-toluenesulfonic acid from the ester) can be suppressed by keeping the temperature of the reaction mixture below 5°C. This procedure can be carried out within 2 h and generally gives excellent (often almost quantitative) yields of the tosylates. Purification of acetylenic tosylates by distillation, which is risky because of the limited thermal stability of the esters, is not necessary because the

"crude" products have a satisfactory purity (> 95%) for further synthetic work. If not used immediately, the tosylates should be stored in the refrigerator, where deterioration is negligible.

Warning

Tosyl chloride may irritate the skin; protective gloves should be worn.

Procedure

Tosyl chloride (0.60 mol in the case of primary alcohols or 0.65 mol for secondary alcohols) is dissolved in 1 l of Et_2O. The alcohol (0.50 mol) is then added and the mixture is cooled to between -5 and -10°C (bath with dry ice and acetone). Freshly and finely machine-powdered KOH (250 g) is added with efficient stirring. The addition is initially carried out in 5 g portions with intervals of 2 min. The evolution of heat is considerable and efficient cooling is necessary to maintain the temperature between -5 and 0°C (for primary alcohols) or between 0 and +5°C (for secondary alcohols). After some 50 g of KOH has been added over the first 20 min, the remainder is added over an additional 10 min. The mixture is then stirred for half an hour or 1 h at the temperature indicated in the cases of primary or secondary alcohols, respectively. Working up is carried out by pouring the mixture into 1.5 l of ice water (the solid remaining in the flask is quickly hydrolysed with ice water and subsequently added to the bulk of the solution. After vigorous shaking, the layers are separated. The organic layer and two ethereal extracts are dried over $MgSO_4$, after which the ether is thoroughly removed *in vacuo*, keeping the temperature of the heating bath below 80°C. Yields are usually greater than 90%.

1.12 General Procedure for the Preparation of Methanesulfinates and Methanesulfonates

$$CH_3SOCl + ROH + Et_3N \xrightarrow[-50°C]{CH_2Cl_2} CH_3SO\text{–}OR + Et_3N.HCl\downarrow$$

$$CH_3SO_2Cl + ROH + Et_3N \xrightarrow[-50°C]{CH_2Cl_2} CH_3SO_2\text{–}OR + Et_3N.HCl\downarrow$$

Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Introduction

Esters of acetylenic alcohols and methanesulfinic and methanesulfonic acid have been used as synthetic intermediates in our laboratory, mainly for S_N2'-like substitution reactions leading to allenic derivatives [see for example refs. 210,211]. Although pyridine is recommended as

solvent for the preparation of these esters [234], the procedure given in this experiment, which uses dichloromethane as solvent and a relatively small excess of triethylamine or pyridine, seems more simple. Yields are generally excellent as in the case of the *p*-toluenesulfonic esters (exp. 11). Also acetylenic tertiary alcohols RC≡CC(R')(R")OH have been successfully converted by this procedure into the methanesulfinates. The esters from tertiary alcohols and methanesul*fonic* acid $CH_3SO_2OC(R')(R")C{\equiv}CR$ are unstable at room temperature and can only be prepared at low temperatues in an organic solvent from the lithium alkoxides and CH_3SO_2Cl.

Procedure

Methanesulfinyl chloride (0.25 mol, see ref 235) or methanesulfonyl chloride (0.25 mol, commercially available) is added dropwise over 10-15 min to a mixture of the acetylenic alcohol (0.20 mol), dry dichloromethane (300 ml) and dry triethylamine (0.35 mol). After the addition, which is carried out at ~ -50°C, the temperature is allowed to rise to 0°C. Ice water (200 ml) is added with vigorous stirring to the white suspension. The aqueous layer is extracted twice with small portions of dichloromethane. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo* keeping the bath temperature below 70°C. The last traces of solvent may be removed in a high-vacuum (bath temperature 30 to 40°C). Yields of the products (purity > 95%) are usually greater than 90%. If not used directly, the esters should be stored in the refrigerator (-20°C).

1.13 General Procedure for the Preparation of Acetates

$$RC{\equiv}CC(R')(R")OH + CH_3C(=O)Cl + PhNEt_2 \rightarrow RC{\equiv}CC(R')(R")OC(=O)CH_3 + PhNEt_2.HCl\downarrow$$

(R = H; R' = R' = CH_3 or R'R"C = cyclohexyl)

Scale: 0.30 molar.

Apparatus: 500-ml three-necked round-bottomed flask, equipped with a dropping funnel, a mechanical stirrer and a combination of a thermometer and a vent.

Procedure (compare [212])

N,N-Diethylaniline (0.70 mol) and redistilled acetyl chloride (0.37 mol) are placed in the flask. The acetylenic alcohol (0.30 mol) is added over a few min while heating the mixture at *ca.* 40°C. An exothermic reaction starts and the temperature rises to 120°C in a few min. Occasional cooling is necessary to keep the temperature at that level. After the exothermic reaction has subsided, the mixture is heated for an additional 15 min at ~ 130°C (immersion of the flask in the heating bath is necessary to prevent solidification of the reaction mixture on the glass wall). After cooling to 50°C (stirring has been stopped), a mixture of 300 ml of ice

water and 30 ml of 36% hydrochloric acid is added. A small amount of Et_2O is added, after which the mxiture is vigorously shaken (or stirred). After separation of the layers, two extractions with Et_2O are carried out. The combined organic solutions are washed with water and then dried over $MgSO_4$. The liquid remaining after concentration of the solution in vacuum, is distilled through a 30-cm Vigreux column. The acetate R = H, R' = R" = CH_3, b.p. 45°C/27 mmHg, $n_D(20°)$ 1.4193, and the acetate R = H, R'R"C = cyclohexyl, b.p. 87°C/15 mmHg, $n_D(20°)$ 1.4669, are obtained in excellent yields.

With primary and secondary alcohols the reaction presumably proceeds much more easily and a sufficient amount of a solvent *e.g.* Et_2O, may be necessary. The reaction may be carried out in the refluxing solvent.

2. Ethers, Sulfides and Thiols

2.1 Methyl Propargyl Ether from Propargyl Alcohol, Dimethyl Sulfate and NaOH

$$2\ HC{\equiv}CCH_2OH + (CH_3)_2SO_4 + 2\ NaOH \xrightarrow[55°C]{H_2O} 2\ HC{\equiv}CCH_2OCH_3 + Na_2SO_4 + 2\ H_2O$$

Scale: 3.0 molar.

Apparatus: 2-l round-bottomed, three-necked flask, equipped with a dropping funnel, a gas-tight mechanical stirrer (fig 3), an efficient reflux condenser and a thermometer (combined with the reflux condenser or dropping funnel).

Procedure (compare [15])

A solution of 200 g of sodium hydroxide (note 1) in 300 ml of water and 3.0 mol of propargyl acohol are placed in the flask. Dimethyl sulfate (250 g) is added at such a rate that the temperature is maintained between 50 and 55°C (some cooling may be necessary). This addition takes about 2 h. The reflux condenser is then replaced with a 40-cm Vigreux column, which is connected to an efficient condenser and a receiver, cooled at 0°C. The propargylic ether is distilled off as quickly as possible, while the temperature of the heating bath is gradually raised). The distillation is stopped when the thermometer in the head of the distillation column indicates 95°C. In order to remove some methanol, the contents of the receiver are washed three times with cold aqueous NH_4Cl in a small separatory funnel. The upper layer is dried over a small amount of $MgSO_4$. Yields are generally higher than 70%. Redistillation (under N_2) may be carried out (b.p. 61°C/760 mmHg, $n_D(20°)$ 1.3969), but is not necessary. The product must be stored under N_2 in a perfectly closed bottle, placed in the refrigerator (-20°C) (note 2).

$HC{\equiv}CCH_2OC_2H_5$, $n_D(20°)$ 1.4039, b.p. 80°C/760 mmHg, is obtained in a similar way (yields > 70%) using Et_2SO_4. During the addition of this reagent, the temperature of the

reaction mixture is maintained between 60 and 70°C. The reaction is brought to completion by heating the reaction mixture for 2 h under reflux.

Notes

1. The use of *potassium* hydroxide is less convenient since a very thick suspension of K_2SO_4 is formed.
2. Auto-oxidation with formation of $HC{\equiv}CCH(OOH)OCH_3$ takes place very readily. Samples that have been stored for a few days at room temperature under air (instead of N_2) contain detectable amounts of the hydroperoxide. The presence of this compound appears most convincingly by shaking 1 ml of the ether with an aqueous solution of KI. A brown colour is developed immediately, but disappears when shaking is continued (due to addition or some other reaction with I_2). The presence of much hydroperoxide (after prolonged storage at room temperature or even in the refrigerator) appears from the considerably higher refractive index. Samples that show a positive KI test, should **never** be redistilled at atmospheric pressure. A good qualitative test consists in shaking 2 to 3 ml with *t*-BuOK: if a dark brown colour is developed and much heat is evolved (in that case the $n_D(20°)$ is considerably higher then 1.40) the sample should be poured into the waste container (after dilution with an equal volume of acetone). One of the coworkers in our laboratory had an extremely vigorous explosion during a distillation of a sizable (~500 g) amount of $HC{\equiv}CCH_2OCH_3$, which had been stored for a few weeks at room temperature (not under N_2). Samples that contain small amounts of hydroperoxide ($n_D(20°) < 1.403$, slight evolution of heat upon shaking with *t*-BuOK) can best be purified by adding a small amount of paraffin oil (20 ml on each 100 ml of $HC{\equiv}CCH_2OCH_3$) and subsequently "distilling" the volatile ether at 10 to 20 mmHg. The vapour is condensed in a strongly cooled receiver (see fig. 14).

2.2 1,4-Dimethoxy-2-butyne from 1,4-Butynediol, Dimethyl Sulfate and NaOH

$$HOCH_2C{\equiv}CCH_2OH + 2\,(CH_3)_2SO_4 + 2\,NaOH \xrightarrow[35 \rightarrow 90°C]{H_2O}$$

$$\longrightarrow CH_3OCH_2C{\equiv}CCH_2OCH_3 + Na_2SO_4 + 2\,H_2O$$

Scale: 1.0 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer (fig 3) and a combination of a thermometer and a vent.

Procedure (compare [236])

A solution of 1.0 mol of butynediol in 160 ml of water is placed in the flask. Sodium hydroxide pellets (100 g, note 1) and dimethyl sulfate (2.5 mol) are added in turn in ~20 equal portions over 1.5 h. During the addition, the temperature of the reaction mixture is kept between 30 and 40°C (occasional cooling). After the addition, the mixture is heated for an additional 3 h in a bath at 90°C. Ice water (150 ml) is then added and, after cooling to 20°C, five extractions with Et_2O are carried out. The unwashed organic solutions are dried over K_2CO_3, after which they are concentrated *in vacuo*. Distillation of the remaining liquid through a 40-cm Vigreux column gives the bis-ether b.p. 54°C/12 mmHg, $n_D(20°)$ 1.4392, in yields of at least 80% (depending on the quality of butynediol).

$C_2H_5OCH_2C{\equiv}CCH_2OC_2H_5$, b.p. 76°C/12 mmHg, $n_D(20°)$ 1.4338, is prepared in a similar way, with comparable yields.

The bis-ether should be stored under N_2 in the refrigirator.

Notes

1. See note 1 of previous experiment.

2.3 Dipropargyl ether from Propargyl Alcohol, Propargyl Bromide and NaOH

$$HC{\equiv}CCH_2Br + HC{\equiv}CCH_2OH + NaOH \longrightarrow (HC{\equiv}CCH_2)_2O + NaBr + H_2O$$

Scale: 0.50 molar.

Apparatus: 1-l three-necked, round-bottomed flask, equipped with a powder funnel, a mechanical stirrer and a combination of thermometer and vent; after the addition of NaOH, the powder funnel is replaced with a stopper.

Procedure

Propargyl alcohol (0.70 mol) and propargyl bromide (0.50 mol) are placed in the flask. Freshly and finely machine-powdered sodium hydroxide (30 g) is added in small portions with vigorous stirring (note 1). The heating effect is rather strong so that occasional cooling is necessary to keep the temperature between 60 and 70°C. When, after addition of the NaOH, the reaction has subsided, the mixture is heated for an additional 1 h in a bath at 70-80°C. After cooling to 30°C, 500 ml of ice water is added with vigorous stirring. The product is isolated by extraction with Et_2O and the extract washed with water. After drying the organic solution over $MgSO_4$, most of the Et_2O is distilled off at normal pressure. The remaining liquid is distilled through a 30-cm Vigreux column to give dipropargyl ether, b.p. 67°C/85 mmHg, $n_D(20°)$ 1.4428, in an excellent yield.

Notes

1. Small amounts of THF may be added if stirring becomes difficult.

2.4 *O*-Methylation of the Carbinol from Acetylene and Acetone in DMSO

$$2\ HC{\equiv}CC(CH_3)_2OH + (CH_3)_2SO_4 + 2\ KOH \xrightarrow[60°C]{DMSO} 2\ HC{\equiv}CC(CH_3)_2OCH_3 + K_2SO_4$$

Scale: 1.0 molar.

Apparatus: fig. 1, 1 l.

Introduction

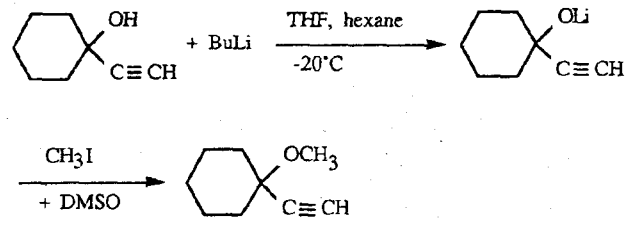
Tertiary and secondary alcohols are less acidic than primary alcohols. Methylation of $HC{\equiv}CC(CH_3)_2OH$ with Me_2SO_4 and alkali hydroxide in aqueous medium, analogous to the procedure for $HC{\equiv}CCH_2OCH_3$ (exp. 2.1), is therefore expected to give a poor result. In the aprotic DMSO, however, the concentration of the alkoxide $HC{\equiv}CC(CH_3)_2OK$ will be sufficient, while the alkylation will proceed smoothly in this strongly polar solvent. Undoubtedly, part of the dimethyl sulfate will react with KOH to give methanol (which may further react to dimethyl ether). Therefore, an excess of Me_2SO_4 and KOH is used.

The procedure for the tertiary propargylic ether seems to be generally applicable. If alkyl groups other than methyl or ethyl are to be introduced, modification of the reaction conditions will be necessary. For example, for the preparation of $HC{\equiv}CCH_2OC_4H_9$, powdered KOH might be added portion-wise to a heated mixture of $HC{\equiv}CCH_2OH$ (excess), butyl bromide and DMSO. The volatile butyl propargyl ether can be isolated from the reaction mixture by evacuation. In the cases of higher-boiling ethers, isolation can be carried out after addition of water to the reaction mixture and extraction with Et_2O or pentane. Methylation or ethylation of *primary* alcohols can also be performed in Et_2O, provided that the b.p. of the desired ether is sufficiently high to allow a satisfactory distillative separation from Et_2O. The procedure may consist in adding the alkylating reagent (CH_3I or Me_2SO_4, C_2H_5I or Et_2SO_4) to a mixture of the primary alcohol, excess of finely powdered KOH and Et_2O (or THF).

Procedure (compare [213])

DMSO (technical grade, 250 ml) and machine-powdered KOH (1.5 mol) are placed in the flask. The acetylenic alcohol (1.0 mol, commercially available) is added over a few min. Subsequently 1.0 mol of dimethyl sulfate is added dropwise with vigorous stirring, while keeping the temperature in the region of 60°C (~45 min). After the exothermic reaction has ceased, stirring and heating at ~60°C are continued for an additional half hour. The flask is then equipped for a vacuum distillation using a 40-cm Vigreux column, a condenser and a single receiver cooled in a bath at -70°C (fig. 14). The system is evacuated (water aspirator) and the flask heated in a bath at 70°C. The volatile ether condenses in the strongly cooled receiver. The contents of the receiver are washed twice with saturated aqueous ammonium chloride and subsequently dried over $MgSO_4$. Pure $HC{\equiv}CC(CH_3)_2OCH_3$, $n_D(20°)$ 1.3997, is obtained in ~65% yield. Distillation is not necessary.

2.5 *O*-Methylation of 1-Ethynylcyclohexanol with Methyl Iodide in THF-DMSO



Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

Introduction

Although the procedure for the O-methylation of the carbinol from acetylene and acetone (exp. 2.4) gives a fair yield, it is less suitable for the O-methylation of alcohols that are not available in large amounts. In such cases there is need for a very clean high-yield method. The procedure for the O-methylation of ethynylcyclohexanol meets this condition. Ethynylcyclohexanol can be O-lithiated quantitatively by BuLi in a mixture of THF and hexane. Since O-alkylations of lithium alkoxides in solvents of moderate polarity proceed very sluggishly (even in the case of methyl iodide), a sufficient amount of the polar DMSO has to be added as a co-solvent. The methylation with methyl iodide can then be accomplished under relatively mild conditions and there is no indication for decomposition of the lithium carbinolate into $LiC{\equiv}CH$ and cyclohexanone.

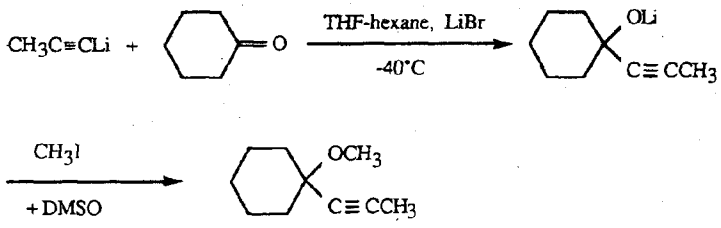
Procedure (compare [47])

THF (140 ml) is added to a solution of 0.21 mol of BuLi (note 1) in 150 ml of hexane with cooling below 0°C. A mixture of 0.20 mol of 1-ethynylcyclohexanol (p. 92) and 20 ml of THF is then added at -25°C, followed by 75 ml of dry DMSO (distilled from a few g of *t*-BuOK at 0.5 mmHg and subsequently redistilled at 10-20 mmHg). Five min later, 0.32 mol (excess) of CH_3I is added in one portion at ~0°C. The mixture is successively stirred for 1 h at 10°C and 1 h at 45°C, then it is poured into 400 ml of a saturated aqueous solution of NaCl. The aqueous layer is extracted three times with Et_2O. The combined organic solutions are washed four times with brine and are subsequently dried over $MgSO_4$. The greater part of the solvent is then distilled off at atmospheric pressure through a 40-cm Vigreux column. Careful distillation of the remaining liquid through a 40-cm Widmer column gives the methyl ether, b.p. 56°C/18 mmHg, $n_D(20°)$ 1.4620, in an excellent yield.

Notes

1. The excess of BuLi is used to compensate for losses due to the presence of traces of oxygen and moisture.

2.6 Methylation of an *In Situ* Prepared Lithium Carbinolate



Scale: 0.20 molar.

Apparatus: fig. 1, 1 l.

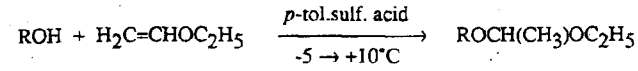
Procedure

A suspension of 0.20 mol of $CH_3C{\equiv}CLi$ in 140 ml of hexane and 140 ml of THF is prepared (p. 24). To this suspension is added at 0°C a solution of 0.1 mol of anhydrous lithium bromide (note 1) (prepared by heating the commercial anhydrous salt for 30 min at 150°C in a vacuum of 0.5 mmHg or lower) in 40 ml of THF. The mixture is then cooled to -40°C and 0.20 mol of cyclohexanone is added over 10 min, while maintaining the temperature between -35 and -45°C. After the addition, the cooling bath is removed and the temperature allowed to rise to -5°C. Methyl iodide (0.28 mol) and dry DMSO (160 ml, dried by distillation from a few g of *t*-BuOK under 0.5 mmHg, followed by redistillation at 10-20 mmHg) are then added successively. The temperature rises to about 35°C, while salt separates from the solution. After heating for an additional 1.5 h at 50°C and stopping of the stirrer , two clear layers have formed. Ice water (500 ml) is added and, after separation of the layers, the aqueous layer is extracted four times with Et_2O. The combined organic solutions are washed four times with saturated aqueous NH_4Cl and subsequently dried over $MgSO_4$. Removal of the solvent *in vacuo* followed by careful distillation through a 30-cm Vigreux column gives the methyl ether, b.p. 80°C/12 mmHg, $n_D(20°)$ 1.4701, in greater than 80% yield.

Notes

1. The LiBr is added to solubilize part of the propynyllithium. If no LiBr is added, the coupling with ketones is slower and part of the ketone is converted into the enolate. In the cases of soluble lithium alkynylides, the addition of LiBr is not necessary.

2.7 Protection of the OH Group in Alcohols with Ethyl Vinyl Ether



Scale: 0.20 molar.

Apparatus: fig. 1, 500 ml.

Introduction

Although many organic chemists still use 3,4-dihydro-2H-pyran [214,215] for the protection of OH groups, protection with ethyl vinyl ether has distinct advantages. Ethyl vinyl ether [216] is much cheaper than the cyclic ether, but chemists working in a university will perhaps find the advantage of the easier protection and deprotection more important. Furthermore, ^1H NMR-spectroscopic analysis of the adducts from ethyl vinyl ether in many cases will be easier.

The reaction of alcohols (and phenols) with ethyl vinyl ether proceeds readily at temperatures in the region of 0°C. For obtaining good yields (often almost quantitative) it is essential to use *water-free* alcohols and to keep the temperature below 10°C during the protection reaction. The use of an excess of ethyl vinyl ether allows the reaction to be completed within 30 min, irrespective whether primary, secondary or tertiary alcohols are used. It should be pointed out that the reaction is by no means limited to *acetylenic* alcohols. Traces of acid, which often adhere to the glass, should be neutralized. This can be done most easily and effectively by rinsing the glass ware with gaseous ammonia or a solution of an aliphatic amine in acetone.

Procedure

Freshly distilled ethyl vinyl ether (0.3 to 0.4 mol) is cooled to -5°C and ~100 mg of *p*-toluenesulfonic acid (monohydrate or anhydrous) is added with efficient stirring. The dry alcohol (0.20 mol) is then added over about 15 min, while keeping the temperature between 0 and 5°C (a cooling bath at -70°C is advisable, since it provides more flexibility in controlling the temperature). After the addition, the mixture is stirred for an additional 15 min at 5 to 10°C. Then it is cooled to 0°C and an additional 100 mg of *p*-toluenesulfonic acid is added while watching the temperature carefully. If, without external cooling, no significant rise in temperature ensues, a solution of 5 g of K_2CO_3 in 50 ml of water is added with vigorous stirring (for 1 min). The organic layer is dried over K_2CO_3, 1 ml of diethylamine is added ,after which it is concentrated concentrated *in vacuo* . As a rule, the remaining liquid needs not be distilled because the purity is higher than 95%. Distillation (if desired) is often accompanied by foaming; it is therefore advisable to use a distillation flask of 500 ml. Impure or water-containing alcohols often react sluggishly (no distinct rise of the temperature upon addition of ~5 g of the alcohol in one portion). It is then tempting to add more acid catalyst,

which may result in a sudden rise of the temperature and development of a brown colour. Purification by distillation is then difficult and yields are considerably lower.

Solid alcohols can best be liquified by addition of a small amount of Et_2O or THF (*e.g.* $HOCH_2C{\equiv}CCH_2OH$).

2.8 Preparation of *t*-Butyl Propargyl Ether by Acid-catalysed Addition of Propargyl Alcohol to Isobutene

$$H_2C{=}C(CH_3)_2 + HC{\equiv}CCH_2OH \xrightarrow[30\text{-}40^\circ C]{H_2SO_4} HC{\equiv}CCH_2O\text{-}t\text{-}Bu$$

Scale: 1.5 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a gas inlet tube, a mechanical stirrer and a thermometer-gas outlet combination; the gas inlet and outlet are connected to a cylinder with isobutene and a washing bottle filled with paraffin oil, respectively; all connections are made gas-tight.

Procedure (compare [217])

Concentrated sulfuric acid (1.5 to 2 ml) is added with vigorous stirring to 1.5 mol of propargyl alcohol (redistilled under reduced pressure). The alcohol is then warmed to 35°C and isobutene is introduced at a rate such that a slow stream (~10 to 20 ml/min) is emitted from the outlet. The temperature is kept between 40 and 45°C (occasional cooling, later occasional warming). The flow of isobutene should be continuously controlled: in the beginning the rate of absorbance increases with the temperature due to the higher rate of reaction, when the reaction subsides the rate of absorbance decreases. After about 1.5 h (depending *inter alia* upon the efficiency of stirring) the reaction begins to subside and the temperature to drop. Stirring at 40 to 45°C is then continued for another 1.5 h, while introducing isobutene at a rate of ~ 75 ml/min. The light-brown solution is poured into 500 ml of ice water, containing a sufficient amount of KOH. After vigorous shaking in a small separatory funnel, the upper layer is dried over K_2CO_3 and subsequently distilled. The desired ether, b.p. ~70°/90C mmHg, $n_D(20°)$ 1.4182, is obtained in ~70% yield. The compound should be stored under nitrogen in a well-closed bottle at -20°C (compare note 2 of exp. 2.1!).

2.9 Formation of Acetylenic Epoxides from the Corresponding Chlorohydrines and KOH

$$RC{\equiv}C{-}\underset{\displaystyle OH}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}{-}CH_2Cl \xrightarrow[Et_2O]{KOH} RC{\equiv}C{-}\overset{\displaystyle CH_3}{\overset{|}{C}}\!\!<\!\!\begin{matrix}O\\ \diagdown\\ \diagup\\ CH_2\end{matrix} + KCl + H_2O$$

Scale: 0.20 molar.

Apparatus: 1-l round-bottomed flask, equipped with a powder funnel, a mechanical stirrer and a thermometer-vent combination; after the addition of KOH, the powder funnel is replaced with a stopper.

Procedure

Redistilled chloroacetone (0.20 mol) is added over a few min to a solution (or suspension) of 0.20 mol of the lithiated acetylene in 140 ml of THF and 140 ml of hexane (p. 24), with cooling between -80 and -70°C. Ten min after the addition the mixture is poured into 300 ml of an aqueous solution of 5 g of NH_4Cl (in the cases of lithium alkynylides with slight solubility, stirring is continued at -60°C for an additional 15 min before the mixture is hydrolysed). After separation of the layers, extraction of the aqueous layer with Et_2O and drying of the organic solutions over $MgSO_4$ the solvent is removed *in vacuo* and the remaining liquid distilled. The distilled chlorohydrine (0.20 mol) is mixed with 200 ml of Et_2O, and 150 g of finely, freshly machine-powdered KOH is added over 30 min with efficient stirring, while maintaining the temperature between 5 and 15 °C. After an addditional half hour, the mixture is poured into water. The organic layer and the ethereal extract of the aqueous layer are dried over K_2CO_3, after which the solvent is removed in a water-pump vacuum (in the case of the volatile epoxide with R = CH_3, the greater part of the Et_2O is distilled off under atmospheric pressure. Yields are mostly excellent.

2.10 Methyl Propargyl Sulfide from Sodium Methanethiolate and Propargyl Chloride

$$CH_3SNa + HC{\equiv}CCH_2Cl \xrightarrow[0 \rightarrow 15^\circ C]{CH_3OH,\ H_2O} HC{\equiv}CCH_2SCH_3 + NaCl\downarrow$$

Scale: 0.50 molar.

Apparatus: fig. 1, 1 l.

Procedure (compare [179])

Sodium hydroxide (0.60 mol) is dissolved in 40 ml of water and 150 ml of methanol is added. Methanethiol (0.60 mol) is liquified (~-60°C) in a cold trap and 30 ml of cold (-20°C or lower temperature) methanol is added to the methanethiol. This cold mixture is added over ~15 min to the solution of sodium hydroxide while keeping the temperature between 0 and 10°C. Subsequently 0.50 mol of propargyl chloride (or bromide) is added dropwise over 20 min while keeping the temperature between 0 and 10°C. Salt separates immediately from the solution. After stirring for an additional half hour at ~15°C, 500 ml of an aqueous solution of 10 g of KOH is added (to prevent stench due to hydrolysis of the excess of sodium methanethiolate). The mixture is extracted ten times with small portions (total amount ~ 500

ml) of high-boiling (b.p. > 170°C/760 mmHg) petroleum ether. The combined extracts are washed twice with water and subsequently dried over $MgSO_4$. The solution is brought in a 1-l round-bottomed flask, which is equipped for a vacuum distillation using a 40-cm Widmer column (fig. 14). The apparatus is evacuated using a water aspirator, the receiver being cooled in a bath at -70°C. The flask is heated in a water bath which is gradually brought at a temperature of ~80°C. The evacuation is terminated when the petroleum ether begins to reflux in the top of the column. The contents of the receiver are subjected again to the flash distillation-condensing procedure, now keeping the temperature of the "heating" bath below 15°C. Methyl propargyl sulfide, $n_D(20°)$ 1.4920, is collected in ~85% yield.

Ethyl propargyl sulfide and phenyl propargyl sulfide can be prepared from the corresponding sodium thiolates and propargyl chloride or bromide. In the case of $C_2H_5SCH_2C{\equiv}CH$, the reaction conditions are similar to those described above. Pentane is used as extraction solvent. The greater part of the solvent is distilled off at normal pressure through a 40-cm Widmer column, after which the product is distilled at a pressure of 50 to 100 mmHg. In the preparation of $PhSCH_2C{\equiv}CH$, a 10% excess of propargyl halide is used. The product is extracted with a 1:1 mixture of Et_2O and pentane. The solvent is removed under reduced pressure and the sulfide distilled at ~0.5 to 1 mmHg.

2.11 1,4-Bis(methylthio)-2-butyne from 1,4-Dichloro-2-butyne and Sodium Methanethiolate

$$2\ CH_3SNa + ClCH_2C{\equiv}CCH_2Cl \xrightarrow[0 \rightarrow 20°C]{CH_3OH + H_2O} CH_3SCH_2C{\equiv}CCH_2SCH_3 + 2\ NaCl\downarrow$$

Scale: 0.20 molar.

Apparatus: fig. 1, 500 ml.

Procedure

A solution of 0.50 mol (excess) of CH_3SNa in ~40 ml of water and 150 ml of methanol is prepared as described in exp. 2.10. Dichlorobutyne (0.20 mol, see exp. 1.9) is added over 15 min, while keeping the temperature between 0 and 10°C. After an additional period of 30 min, during which the temperature is allowed to rise to 15°C, the suspension is poured into a solution of 10 g of KOH in 500 ml of water. The product is extracted with a 1:1 mixture of Et_2O and pentane, the extracts washed with water, dried over $MgSO_4$ and subsequently concentrated under reduced pressure. The bis-thioether, b.p. 116°C/14 mmHg, $n_D(20°)$ 1.5585, is obtained in ~80% yield.

2.12 2-Propyne-1-thiol (Propargyl Mercaptan) and 2-Butyne-1-thiol from Potassium Hydrogen Sulfide and the Propargylic Bromides

$$RC{\equiv}CCH_2Br + KSH \xrightarrow[0 \text{ or } 35°C]{H_2O} RC{\equiv}CCH_2SH + KBr\downarrow$$

Scale: 0.50 molar.

Apparatus: fig. 1, 1 l; stirrer: fig. 3.

Procedure (compare [222])

Potassium hydroxide (70 g, pellets) is dissolved in 100 ml of water. A rapid stream of hydrogen sulfide (1 to 2 l/min) is introduced with vigorous stirring (the dropping funnel is temporarily replaced by a gas inlet tube). The temperature, initially kept between 0 and -10°C, is gradually lowered to ~ -30°C. After disappearance of the suspension of K_2S, stirring and introduction of H_2S are continued for an additional 15 min at ~ -30°C, then the propargylic bromide (0.50 mol, exp. 1.1 and 1.2) is added over a few min, followed by 200 mg of hydrochinone (radical inhibitor). N_2 (~200 ml/min) is introduced at -5°C and the mixture is vigorously agitated: in the case of $HC{\equiv}CCH_2Br$ for 1.5 h at -2 to +2°C, in the case of $CH_3C{\equiv}CCH_2Br$ the temperature is allowed to rise to 35°C, after which stirring at this temperature is continued for an additional 1 h. The isolation is carried out as follows. Water (200 ml, perfused with N_2) and 0.5 g of hydrochinone are added to the first reaction mixture, after which the upper layer is separated off (in a small separating funnel) and transferred into a 500 ml round-bottomed flask, containing ~5 g of $MgSO_4$. The volatile thiol is then isolated by a flash distillation in a water-pump vacuum (fig. 14), using a 30-cm Vigreux column, condenser and single receiver (containing a trace of hydrochinone) cooled in a bath at -70°C. During the distillation the temperature of the heating bath is gradually raised to 80°C. The residue consists mainly of $(HC{\equiv}CCH_2)_2S$. The receiver contains reasonably (~95%) pure $HC{\equiv}CCH_2SH$, $n_D(20°)$ 1.5026. The yield is about 50%. The compound can be kept unchanged for a few days, provided that it is stored at -30°C (refrigerator) under N_2.

$CH_3C{\equiv}CCH_2SH$, $n_D(20°)$ 1.5104, is obtained by a similar work-up and flash distillation procedure (raising the bath temperature to above 100°C). The compound is obtained in a good (~80%) yield.

Notes

1. All operations should be carried out under N_2. Especially $HC{\equiv}CCH_2SH$ polymerizes rapidly in the presence of oxygen. The thiols have a disagreeable smell.

2.13 1-Methylthio-1-buten-3-yne and 1-Ethylthio-1-buten-3-yne from Sodium Alkanethiolate and Butadiyne

$$HC{\equiv}CC{\equiv}CH + RSNa \xrightarrow[-10 \rightarrow 20°C]{CH_3OH} HC{\equiv}CCH{=}CHSR$$

Scale: 0.50 molar.

Apparatus: fig. 1, 1 l.

Procedure

A solution of 0.60 mol of butadiyne in ~150 ml of methanol is prepared as described on p. 179 (the diacetylene is condensed in a cold trap containing 100 ml of methanol, a corresponding volume of the obtained solution is diluted to 150 ml). A solution of 0.50 mol of CH_3SNa or C_2H_5SNa in 150 ml of methanol (prepared by adding the thiol at 0°C to a solution of 0.50 mol of NaOH or $NaOCH_3$ in methanol) is added to the solution of diacetylene over 10 min, while keeping the temperature between 0 and -10°C. The reaction mixture is then allowed to warm up to 20°C. After an additional 3 h it is poured into 1.5 l of water and ten extractions with small portions of pentane are carried out. The combined organic solutions are washed with water, dried over $MgSO_4$ and then concentrated in a water-pump vacuum. The remaining (brown) liquid is distilled through a 30-cm Vigreux column to give the Z-enyne sulfides, b.p. 46°C/15 mm, $n_D(20°)$ 1.5595, and b.p. 65°C/16 mmHg, $n_D(20°)$ 1.5423, in high yields.

2.14 Propargyl Vinyl ether

$$HC{\equiv}CCH_2OH + HCl + (CH_3CH{=}O)_3 \xrightarrow[-10°C]{} HC{\equiv}CCH_2OCH(Cl)CH_3 + H_2O$$

$$HC{\equiv}CCH_2OCH(Cl)CH_3 + PhNEt_2 \xrightarrow[100°C]{} HC{\equiv}CCH_2OCH{=}CH_2 + PhNEt_2.HCl\downarrow$$

Scale: 1.0 molar.

Apparatus: First reaction: fig. 16, 1 l.
Second reaction: fig. 1, 2 l.

Procedure

Gaseous hydrogen chloride (2 to 3 l/min) is introduced into a mixture of 1.0 mol of propargyl alcohol (freshly distilled under reduced pressure) and 0.33 mol of paraldehyde, while keeping the temperature between -15 and -5°C. The introduction of gas is stopped when copious fumes escape from the outlet. The auxiliary equipment is removed and the flask allowed to stand for several min in a bath at -70°C. After solidification of the lower layer (concentrated aqueous HCl), the upper layer is cautiously decanted from the ice mass and vigorously

shaken with a small amount (~5 g) of $MgSO_4$. The clear liquid, crude $HC{\equiv}CCH_2$-$-OCH(Cl)CH_3$, is added in 4 equal portions, with 5 min intervals, to 2.0 mol of *N,N*-diethylaniline, heated between 95 and 105°C. Occassional cooling or heating may be necessary to maintain this temperature range. After heating for an additional 30 min at 95 - 100°C, the reaction mixture is cooled to between 60 and 70°C. The flask is equipped for a vacuum distillation, using a 40-cm Vigreux column, condenser and single receiver, cooled in a bath at -78°C (compare fig. 14). During evacuation (water aspirator) the volatile product is trapped in the strongly cooled receiver. The semi-solid mass is gradually heated until diethylaniline (note 1) begins to reflux in the upper part of the Vigreux column. Nitrogen is then admitted and the contents of the receiver are vigorously shaken during about 10 min with 20 g of KOH pellets (note 2). The evacuation procedure is then repeated (see fig. 14) to give pure propargyl vinyl ether, $n_D(20°)$ 1.4373, in ~50 % overall yield. The b.p. at 760 mmHg is 82°C.

Notes

1. The greater part of the diethylaniline can be recovered by adding a sufficient amount of a 20 % aqueous KOH solution (after cooling) to the crystalline mass, separating the layers, drying the organic layer over KOH pellets or K_2CO_3 and distilling it in a water-pump vacuum (b.p. ~95°C/15 mmHg).
2. A small amount of acetaldehyde formed during the dehydrohalogenation reaction is removed by resinification under the influence of KOH.

2.15 Propargyl Vinyl Sulfide

$$H_2C{=}CHSC_2H_5 + 2\,Li \xrightarrow[-33°C]{\text{liq. } NH_3} H_2C{=}CHSLi + C_2H_6\uparrow + LiNH_2\downarrow$$

$$LiNH_2 + NH_4Cl \longrightarrow LiCl\downarrow + 2\,NH_3$$

$$H_2C{=}CHSLi + HC{\equiv}CCH_2Br \longrightarrow H_2C{=}CHSCH_2C{\equiv}CH$$

Scale: 0.50 molar.

Apparatus: cleavage reaction and addition of NH_4Cl: fig.4, 2 l; stirrer: fig. 3; for the reaction with $HC{\equiv}CCH_2Br$: 2-l round-bottomed, three-necked flask, equipped with a powder funnel and a mechanical stirrer; the third neck is open.

Procedure

Dry liquid ammonia (1.2 l) is placed in the flask after which lithium (1.0 mol, 7.0 g, freshly cut in pieces of ~0.5 g) is introduced. After stirring for 15 min, ethyl vinyl sulfide [1, 233] is added dropwise over 30 min. Close to the stoichiometrical amount of 0.50 mol is needed to course a complete disappearance of the blue colour. The dropping funnel is then replaced with

a powder funnel, and an additional amount of liquid ammonia is introduced to bring the volume of the solution at ~0.7 l. Subsequently, powdered ammonium chloride (0.50 mol) is added over 15 min in portions of ~1 g with efficient stirring. The obtained reaction mixture (suspension) is then cautiously poured over 5 min (note 1) into the second reaction flask which contains a mixture of 100 ml of methanol (note 2), 300 ml of liquid ammonia and 0.6 mol of propargyl bromide (exp. 1.1). This mixture has been prepared just before this addition is carried out (compare note 1). The ensuing reaction is vigorous. The mixture is stirred for an additional hour (note 3), after which it is cautiously poured on to 500 g of finely crushed ice in 3 to 5-l wide-necked conical flask or round-bottomed flask. After melting of the ice, six extractions with pentane (b.p. ~35°C; portions as small as possible) are carried out. The combined organic solutions are washed well with water and subsequently dried over a small amount of $MgSO_4$. The solution is then decanted from the drying agent and transferred into a 1-l round-bottomed flask, which is equipped for a distillation in a water-pump vacuum, using a 40-cm Vigreux column, a condenser and a single receiver cooled in a bath with ice water (fig. 14). During the evacuation the distillation flask is warmed in a bath of ~25°C (note 4). After the pentane has evaporated, the desired vinyl propargyl sulfide, b.p. 25 -30°C/15 mmHg, $n_D(20°)$ 1.5183, passes over. Yields of at least 70% may be obtained.

Notes

1. Since propargyl bromide is readily ammonolysed, one should carry out this addition as quickly as possible.
2. The product isomerizes readily to the allenic sulfide, $H_2C{=}C{=}CHSCH{=}CH_2$, or 1-propynyl sulfide, $CH_3C{\equiv}CSCH{=}CH_2$, under the influence of the alkenethiolate. For this reason, inversed-order addition is applied. The methanol solvates the alkenethiolate, thus rendering it less active in catalyzing the isomerization.
3. During this period the excess of $HC{\equiv}CCH_2Br$ ammonolyzes.
4. Vinyl propargyl sulfide may undergo explosive decomposition upon heating at temperatures above 70°C [2].

3. Amines, Isothiocyanates and Nitriles

3.1 Preparation of Propargylic Tertiary Amines from Propargyl Bromide and Aliphatic or Cycloaliphatic Secondary Amines

$$HC{\equiv}CCH_2Br + 2\,R_2NH \xrightarrow[20°C \rightarrow \text{reflux}]{Et_2O} HC{\equiv}CCH_2NR_2 + R_2NH.HBr\downarrow$$

Scale: 0.50 molar ($HC{\equiv}CCH_2Br$).

Apparatus: fig. 1, 1 l.

Introduction

Nucleophilic substitutions on propargylic or allylic carbon atoms generally proceed more easily than substitutions with halides in which the unsaturated system is absent or more remote from the halogen atom. This holds also for reactions with amines. The initial product in the reaction of propargyl bromides with an aliphatic or cycloaliphatic amine R_2NH is the ammonium salt $HC{\equiv}CCH_2NR_2HBr$. Since secondary amines are stronger bases than tertiary amines, it may be expected that HBr is largely transferred to the secondary amine. In order to achieve a complete conversion of propargyl bromide, it thus will be necessary to use an excess of at least 100 mol % of the secondary amine. The reactions proceed at a convenient rate in Et_2O and the ethereal solutions of the propargylic tertiary amines can be separated from the HBr salt of the secondary amine by filtration. If desired, the secondary amine used in excess can be recovered by treating the salt with concentrated aqueous KOH.

Propargyl bromide reacts sluggishly with the bulky diisopropylamine (yields are low).

Procedure (compare [218])

Propargyl bromide (0.50 mol, exp. 1.1) is added over 20 min to an efficiently stirred mixture of 1.10 mol of the amine (dried by shaking with machine-powdered KOH) and 500 ml of dry Et_2O. A suspension of salt is formed almost immediately. When the temperature of the mixture has reached 35°C, the thermometer is replaced by a reflux condenser. The reaction is completed by heating the suspension for an additional hour under reflux. The suspension is then cooled to 0°C, after which the salt is filtered off on a sintered-glass funnel and rinsed well with dry Et_2O. In the case of pyrrolidine, a viscous oil may be formed: instead of carrying out the filtration, the supernatant solution is decanted and the salt thoroughly rinsed with pentane. In all cases, the greater part of the solvent is distilled off at atmospheric pressure through a 40-cm Vigreux column (bath temperature not higher than 100°C), after which the remaining liquid is carefully fractionated through a 40-cm Widmer column. The following amines have been prepared by this procedure:

$HC{\equiv}CCH_2NEt_2$, b.p. ~60°C/150 mmHg, $n_D(20°)$ 1.4320, yield > 70%;
$HC{\equiv}CCH_2$-pyrrolidine, b.p. 42°C/10 mmHg, $n_D(20°)$ 1.4668, yield > 70%;
$HC{\equiv}CCH_2$-piperidine, b.p. 62°C/10 mmHg, $n_D(20°)$ 1.4732, yield > 85%;
$HC{\equiv}CCH_2$-morpholine, b.p. 75°C/10 mmHg, $n_D(20°)$1.4764, yield > 85%.

E-$HC{\equiv}CCH{=}CHCH_2NMe_2$, b.p. 70°C/80 mmHg, $n_D(19°)$ 1.4680, can be obtained in a high yield from $HC{\equiv}CCH{=}CHCH_2Br$ (*E*-isomer) and Me_2NH (2.5 mol equivalents) in Et_2O by a similar procedure.

3.2 Propargyl Dimethylamine from Propargyl Bromide and Dimethylamine

$$HC{\equiv}CCH_2\,Br + 2\,Me_2NH \xrightarrow[0 \rightarrow 35°C]{\text{petroleum ether}} HC{\equiv}CCH_2NMe_2 + Me_2NH.HBr\downarrow$$

Scale: 1.0 molar ($HC{\equiv}CCH_2Br$).

Apparatus: fig. 1, 2 l; stirrer: fig. 3.

Procedure (for Introduction see previous exp.)
Dimethylamine (2.1 mol) is liquified in a cold trap and subsequently poured into 500 ml of high-boiling petroleum ether (b.p. > 170°C), precooled at -5°C. Propargyl bromide (1.0 mol, see exp. 1.1) is then added dropwise over 45 min, while maintaining the temperature between 0 and 10°C. A thick suspension is gradually formed. After the addition, the temperature is allowed to rise to 35°C (occasional cooling may be necessary). After an additional 1.5 h (at 35°C, warming may be necessary) the dropping funnel and thermometer are replaced by stoppers and the flask is equipped for a vacuum distillation (fig 14: 40-cm Vigreux column, condenser and single receiver, cooled in a bath at -70°C). A tube filled with KOH pellets is placed between the receiver and the water aspirator. The system is evacuated (10-20 mmHg) and the flask gradually heated until the petroleum ether begins to pass over. The contents of the receiver are carefully redistilled at atmospheric pressure through a 40-cm Widmer column. $HC{\equiv}CCH_2NMe_2$, b.p. 82°C/760 mmHg, $n_D(20°)$ 1.4197, is obtained in greater than 80% yield.

3.3 Propargylamine from Propargyl Bromide and Liquid Ammonia

$$HC{\equiv}CCH_2Br + NH_3 \xrightarrow[-33°C]{\text{liq. } NH_3} HC{\equiv}CCH_2NH_2 + NH_4Br$$

Scale: 2.0 molar.

Apparatus: 5-l wide-necked, round-bottomed flask; after the addition a rubber stopper with a narrow hole is placed on the flask; the flask is insulated by cotton wool.

Procedure (compare [219])
Anhydrous liquid ammonia (2 l) is placed in the flask. Propargyl bromide (2.0 mol, see exp. 1.1) is added in 10-ml portions over 2 h. After addition of each portion, the flask is gently swirled by hand, after which the stopper is placed again on the flask. After completion of the addition, the stopper is replaced with a drying tube filled with KOH pellets. The ammonia is allowed to evaporate slowly (the cotton wool is left around the flask). This may take more than 12 hours. The evaporation is considered to be complete when the bottom of the flask has adapted room temperature. The remaining solid mass is dissolved in a minimum amount of water (~150 ml) and the solution transferred into a 1-l round-bottomed flask. NaOH pellets (150 g) are then added in small portions (~10 g) with swirling and cooling in a bath with ice water. The flask is then equipped for a distillation at atmospheric pressure: 40-cm Vigreux column, condenser and single receiver (contents 500 ml, cooled in an ice bath). The propargylic amine is slowly distilled off along with water. The distillation is stopped after

about 10 ml of water has passed over at 100°C. The distillate is saturated with NaOH (or KOH) by gradual addition of pellets, while swirling continuously and cooling in a bath at 0°C. When the NaOH pellets (the use of machine-powdered NaOH or KOH is preferred) no longer dissolve, the flask is equipped for a vacuum distillation (fig. 14) using a 40-cm Vigreux column, a condenser and receiver, cooled at -70°C. The apparatus is evacuated using a water aspirator, while the temperature of the heating bath is gradually raised to about 70°C. The contents of the receiver (partly solid) are brought at 0°C and machine-powdered NaOH (or KOH) is added portion-wise with swirling until the solid remains in suspension. The evacuation operation is repeated, after which the contents of the receiver are redistilled at atmospheric pressure. Propargylamine, b.p. 85°C/760 mmHg, $n_D(23°)$ 1.4478, is obtained in ~40% yield. The residue consists mainly of $(HC{\equiv}CCH_2)_2NH$, b.p. 54°C/14 mmHg, $n_D(20°)$ 1.4740 (yield ~20%).

3.4 1,4-Bis(diethylamino)2-butyne from 1,4-Dibromo-2-butyne

$$3\ HOCH_2C{\equiv}CCH_2OH + 2\ PBr_3 \xrightarrow[0\text{-}10°C]{Et_2O} 3\ BrCH_2C{\equiv}CCH_2Br + 2\ P(OH)_3$$

$$BrCH_2C{\equiv}CCH_2Br + 4\ Et_2NH \longrightarrow Et_2NCH_2C{\equiv}CCH_2NEt_2 + 2\ Et_2NH.HBr$$

Scale: 0.50 molar.

Apparatus: fig. 1, 1 l for the preparation of dibromobutyne; 1-l three-necked, round-bottomed flask, equipped with a dropping funnel, a mechanical stirrer and a reflux condenser for the conversion into the amine.

Warning
Dibromobutyne is a skin-irritating and lachrymatory compound: use protective gloves of suitable quality; the experiment should be carried out in a well-ventilated hood.

Procedure (compare exps 1.2 and 3.1)
Butynediol (0.50 mol, technical grade) is powdered and subsequently placed in the flask, containing 200 ml of Et_2O. Phosphorous tribromide (98 g, slight excess) is added dropwise over ~45 min, with cooling in a bath with ice and ice water. After the addition, the cooling bath is removed and stirring is continued for an additional 2 h (gentle refluxing may occur temporarily). Ice water (500 ml) is then added and the lower (organic) layer is dried (without washing) over $MgSO_4$. The aqueous layer is extracted twice with 40-ml portions of Et_2O. The combined ethereal solutions are added over 30 min to a mixture of 2.5 mol of diethylamine (dried over machine-powdered KOH) and 300 ml of Et_2O. The thick suspension is heated for an additonal 1 h under reflux, after which it is poured into 400 ml of an aqueous

solution of 150 g of KOH. The upper layer is dried (without washing) over K_2CO_3 together with four ethereal extracts. The Et_2O and excess of diethylamine are removed under reduced pressure and the remaining liquid distilled from a 1-l flask (a relatively big flask is used in connection with foaming during the distillation). The bis(diethylamino) compound, b.p. 110°C/10 mmHg, $n_D(20°)$ 1.4630, is obtained in yields of 65% (based on butynediol).

3.5 6-Diethylamino-1-hexyne from the Corresponding Tosylate and Diethylamine

$$HC{\equiv}C(CH_2)_4OTs + 2\,Et_2NH \xrightarrow[\text{reflux}]{\text{dioxane}} HC{\equiv}C(CH_2)_4NEt_2 + TsOH.Et_2NH{\downarrow}$$

Scale: 0.40 molar.

Apparatus: 2-l round-bottomed, three-necked flask, equipped with a thermometer (dipping in the solution), a mechanical stirrer and a reflux condenser.

Procedure

The tosylate (0.40 mol, prepared as described in exp. 1.11), dioxane (130 ml, dried over machine-powdered KOH) and diethylamine (1.0 mol, dried over machine-powdered KOH) are placed in the flask. The mixture is heated for 2 h under reflux. The temperature of the refluxing liquid rises by about 10°C over the first period of 1 h , but remains constant during the rest of the time. After stopping the stirrer a two-layer system is formed. The mixture is cooled to room temperature and then cautiously poured into a mixture of 100 ml of concentrated HCl and 100 ml of ice water. Three extractions with Et_2O are then carried out in order to remove impurities. The extracts are washed twice with 20-ml portions of water, the washings being added to the main portions of the aqueous solution. This is subsequently heated and evacuated (rotary evaporator) in order to remove as much as possible of the dioxane: the procedure is terminated when the volume of the solution has decreased to about 150 ml. After cooling to below 10°C, NaOH pellets (80 g) are added in ten equal portions with vigorous stirring and cooling in a bath with ice water. The amine is then extracted five times with Et_2O and the extracts dried over K_2CO_3 (without previous washing). After concentration of the ethereal solution under reduced pressure, the remaining liquid is carefully distilled through a 40-cm Widmer column. The amine, b.p. 73°C/14 mmHg, $n_D(20°)$ 1.4418, is obtained in greater than 80% yield.

3.6 1-Amino-2-heptyne from the Corresponding Bromo Compound and Hexamethylenetetramine

The procedure for $C_4H_9C{\equiv}CCH_2NH_2$, starting from $C_4H_9C{\equiv}CCH_2Br$ (see exp. 1.2) described in ref 129, gives good results.

3.7 3-Amino-3-methyl-1-butyne from the Corresponding Tertiary Alkynyl Chloride and Sodamide in Liquid Ammonia

$$HC{\equiv}CC(CH_3)_2Cl + 2\,NaNH_2 \xrightarrow[-33°C]{\text{liq. } NH_3} NaC{\equiv}CC(CH_3)_2NH_2{\downarrow} + 2\,NaCl{\downarrow}$$

$$NaC{\equiv}CC(CH_3)_2NH_2 \xrightarrow{H_2O} HC{\equiv}CC(CH_3)_2NH_2$$

Scale: 0.20 molar.

Apparatus: fig. 4, 1 l; stirrer: fig. 3.

Introduction

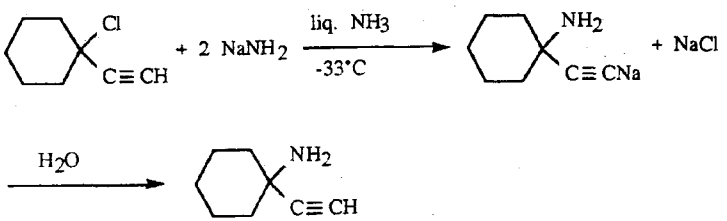
The mechanism of this remarkable reaction, in which a halogen atom in a *tertiary* acetylenic halide is substituted by the nucleophilic group NH_2 with high yields, is not completely clear. Probably the ethynyl hydrogen atom is abstracted in the first step by the strongly basic amide. The results from solvolysis experiments carried out with tertiary acetylenic bromides [22] suggest that the intermediate $^-C{\equiv}C\text{-}C(CH_3)_2Cl$ looses Cl^- to give the Zwitter-ionic intermediate $^-C{\equiv}C\text{-}C^+(CH_3)_2$. This is subsequently attacked by NH_3 or $^-NH_2$.

Procedure (compare [221])

To a suspension of 0.5 mol of sodamide in 400 ml of liquid ammonia [1,3,5] the acetylenic chloride (0.20 mol, see exp. 1.7) is added dropwise over 10 min. A thick brown suspension is formed. The ammonia is allowed to evaporate overnight (see fig. 11). The last traces of ammonia are removed by evacuating the flask for about half an hour. Nitrogen is then admitted and the flask is equipped with a gas inlet (for introduction of N_2), a dropping funnel and an outlet, connected (*via* a plastic tube) to a cold trap (-70°C). Water (120 ml) is cautiously added (over 15 min) from the dropping funnel, while a slow stream of N_2 is passed through the apparatus. It is desired to immerse the flask in a bath with ice water. After the addition of the water, the flask is swirled in order to bring the aqueous mixture into contact with the solid on the glass wall. After all solid material has dissolved, the contents of the trap are poured into the flask. The flask is then equipped with a 40-cm Vigreux column, which is connected to a condenser and a 250-ml receiver, cooled at -20°C. The flask is heated in an oil bath until the thermometer in the head of the column indicates 100°C. During this distillation, some gaseous ammonia escapes from the receiver. The liquid in the receiver is saturated with KOH (portionwise addition of pellets with manual swirling and cooling in an ice-water bath). The receiver is then equipped for a vacuum distillation (fig 14) using a 30-cm Vigreux column, a condenser and a 250 ml receiver cooled at -70°C. The volatile amine is trapped in this strongly cooled receiver by subjecting the mixture of KOH, water and the amine to a flash distillation at water-pump pressure (temperature of the heating bath not higher than 60°C). The liquid collected in the receiver still contains small amounts of water. These

can be removed by adding machine-powdered KOH (15-20 g) and repeating the flash distillation procedure. Redistillation of the condensate gives the amine, b.p. 83°C/760 mmHg, $n_D(16°)$ 1.4268, in ~60% yield.

3.8 1-Amino-1-ethynylcyclohexane from the Corresponding Tertiary Acetylenic Chloride and Sodamide in Liquid Ammonia



Scale: 0.30 molar.

Apparatus: fig. 4, 2 l; stirrer: fig. 3.

Procedure (compare previous exp.)

The tertiary chloride (0.30 mol, see exp. 1.8) is added dropwise over 15 min to an efficiently stirred suspension of 0.80 mol of sodamide and 500 ml of liquid ammonia. The reaction is very vigorous and occasional addition of small amounts of Et_2O may be necessary to suppress frothing. The ammonia is allowed to evaporate overnight (fig. 11) after which 200 ml of Et_2O is added. The mixture is then hydrolysed by cautiously adding (with swirling) 500 ml of ice water. After dissolution of the solid material and separation of the layers, three extractions with Et_2O are carried out. The unwashed ethereal solutions are dried over K_2CO_3 and subsequently concentrated *in vacuo* . Distillation of the remaining liquid gives the amine b.p. 54°C/15 mmHg, $n_D(17°)$ 1.4845, in an excellent yield.

3.9 Propargyl Isothiocyanate from Propargylamine and Thiophosgene

$$HC{\equiv}CCH_2NH_2 + S{=}CCl_2 \xrightarrow[K_2CO_3 + KOH]{CH_2Cl_2,\ H_2O} HC{\equiv}CCH_2N{=}C{=}S$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction

The reaction of primary amines with (commercially available) thiophosgene constitutes a convenient preparative method for isothiocyanates. The reaction is quite general and gives good yields [239]. The amino group attacks on the thiocarbonyl carbon atom with primary formation of a compound with the structure RNH-C(=S)Cl. This intermediate may either eliminate HCl under the influence of the amine with formation of the isothiocyanate or may undergo a second substitution of Cl with formation of the thioureum derivative $S{=}C(NHR)_2$. The latter compound can also be formed by addition of RNH_2 to the heterocumulene system of the isothiocyanate. These undesired processes can be largely avoided by keeping the concentration of the amine as low as possible during the reaction. Since part of the amine is inactivated by reaction with the HCl liberated, it is necessary to carry out the reaction in the presence of a basic reagent which neutralizes the HCl, but does not react with thiophosgene. In the procedure for propargyl isothiocyanate, which should be generally applicable, we use aqueous potassium carbonate. At a later stage, aqueous KOH is added to complete the elimination of HCl from the intermediate $HC{\equiv}CCH_2NH\text{-}C(=S)Cl$.

Procedure

A mixture of 0.11 mol of thiophosgene and 75 ml of dichloromethane is cooled to -5°C after which a solution of 0.10 mol of K_2CO_3 in 100 ml of water (5°C) is added. A mixture of 0.10 mol of propargylamine (exp. 3.3) and 20 ml of water is added dropwise over 15 min with vigorous stirring and maintaining of the temperature between 0 and 5°C. After an additional 10 min a cold (0°C) solution of 0.2 mol of KOH in 100 ml of water is added in one portion with cooling below 0°C. The organic layer and three extracts (Et_2O) are dried (without washing) over $MgSO_4$ and subsequently concentrated under reduced pressure. Distillation of the remaining liquid through a 20-cm Vigreux column gives $HC{\equiv}CCH_2N{=}C{=}S$, b.p. 55°C/15 mmHg, $n_D(20°)$ 1.5389, in ~70% yield. As most isothiocyanates, the compound is a strong lachrymator.

Poor results are obtained when the addition is carried out in a reversed sense ($CSCl_2$ to $HC{\equiv}CCH_2NH_2$, H_2O, CH_2Cl_2 and KOH or K_2CO_3).

3.10 4-Pentynenitrile from Homopropargyl Tosylate and Sodium Cyanide in DMSO

$$HC{\equiv}CCH_2CH_2OTs + NaC{\equiv}N \xrightarrow[60\text{-}70°C]{DMSO} HC{\equiv}CCH_2CH_2C{\equiv}N + NaOTs$$

Scale: 0.50 molar.

Apparatus: fig. 1, 1 l.

Procedure

Dry, powdered sodium cyanide (40 g, excess; KC≡N is not sufficiently soluble), DMSO (200 ml, dried by distillation from 5 g of *t*-BuOK at 0.5 to 1 mmHg and subsequent redistillation at 10 to 20 mmHg) and homopropargyl tosylate (0.50 mol, see exp. 1.11) are placed in the flask. The mixture is gradually heated to 70°C. A rather strong exothermic reaction occurs and occasional cooling may be necessary. After an additional half hour (at 70°C) the mixture is cooled to room temperature and then poured into 400 ml of saturated aqueous NH_4Cl. Twenty (note 1) extractions with Et_2O (2 x 100 ml, 1 x 50 ml, the other portions ~30 ml) are carried out. The combined organic solutions are washed twice with 100 ml portions of saturated aqueous NH_4Cl and subsequently dried over K_2CO_3. The Et_2O is then removed under reduced pressure. Distillation of the remaining liquid through a 40-cm Widmer column gives $HC{\equiv}CCH_2CH_2C{\equiv}N$, b.p. 60°C/10 mmHg, $n_D(20°)$ 1.4373, in high yields.

Notes

1. The presence of DMSO enhances the solubility of the nitrile. The method can also be applied to prepare other nitriles with the general structure $RC{\equiv}C(CH_2)_nC{\equiv}N$ ($n \geq 2$). In these cases the extraction procedure is less laborious.

3.11 3-Alkynenitriles from 1-Bromo-2-alkynes and Copper(I) Cyanide

$$RC{\equiv}CCH_2Br + CuCN \xrightarrow[40 \rightarrow 80°C]{LiBr,\ THF} RC{\equiv}CCH_2C{\equiv}N + CuBr \quad (R = CH_3 \text{ or } C_4H_9)$$

Scale: 0.40 molar.

Apparatus: fig. 1, 500 ml.

Introduction

Nitriles with the system $-C{\equiv}CCH_2C{\equiv}N$ cannot be prepared from the corresponding propargylic bromides or tosylates and alkali cyanide, because the basic cyanide causes a smooth isomerization to allenic nitriles ($C{=}C{=}CHC{\equiv}N$). The use of copper(I) cyanide allows the substitution reaction to be carried out under non-basic conditions. Since copper(I) cyanide is poorly soluble in THF, the reaction proceeds sluggishly in this solvent and prolonged heating at elevated temperatures presumably will be necessary. Anhydrous LiBr forms a complex with CuCN which is soluble in THF, thus creating favourable conditions for the conversion. Indeed, a sub-stoichiometrical amount of LiBr appears to cause a smooth reaction. In addition to the main product, a small amount of the 1,3-substitution product, the allenic nitrile $RC(C{\equiv}N){=}C{=}CH_2$, is formed. The two isomers can be satisfactorily separated by fractional distillation.

Procedure

Anhydrous lithium bromide (0.1 mol, freed from traces of water by heating the commercial anhydrous salt for 30 min at 150°C in a vacuum of ~15 mmHg) is dissolved in 100 ml of dry THF. Dry, powdered CuCN (0.47 mol) and the bromoalkyne (0.40 mol) are successively added, after which the suspension is warmed to between 40 and 60°C. An exothermic reaction starts gradually and occasional cooling is necessary to keep the temperature between 70 and 80°C. The greater part of the suspension disappears and a brown solution is formed. This is heated for an additional 30 min at 75-80°C, then the hot (cooling may result in partial solidification) solution is cautiously poured into a vigorously stirred solution of 50 g of NH_4Cl in 250 ml of 4 N hydrochloric acid (in another three-necked flask), which is kept between 0 and 5°C. The first flask is rinsed with the aqueous layer. The product is isolated by extraction with a 1:1 mixture of Et_2O and pentane (five to seven times). The combined organic solutions are washed with saturated aqueous NH_4Cl and subsequently dried over $MgSO_4$. The liquid remaining after removal of the solvent *in vacuo* is first subjected to a flash distillation at < 0.5 mmHg, using a short Vigreux column and a single receiver cooled in a bath at -50°C (fig.14). Redistillation of the contents of the receiver through a 30-cm Widmer column gives $CH_3C{\equiv}CCH_2C{\equiv}N$, b.p. 47°C/15 mmHg, $n_D(18°)$ 1.4432, in 62% yield (the small first fraction is mainly $CH_3C(C{\equiv}N){=}C{=}CH_2$) and $C_4H_9C{\equiv}CCH_2C{\equiv}N$, b.p. 84°C/15 mmHg, $n_D(17°)$ 1.4487, in 72% yield (the first fraction of ~5 g consists mainly of $C_4H_9C(C{\equiv}N){=}C{=}CH_2$).

4. Ketones, Sulfoxides and Sulfones

4.1 Ethynyl Ketones by Oxidation of the Corresponding Ethynyl Carbinols with Chromic Acid

$$3\,HC{\equiv}CCH(OH)R + 2\,CrO_3 + 3\,H_2SO_4 \longrightarrow 3\,HC{\equiv}CC(=O)R + Cr_2(SO_4)_3 + 6\,H_2O$$

Our experiences with the procedure described in [83] were satisfactory. For the preparation of $HC{\equiv}CCOC_3H_7$ the original procedure was slightly modified: the solution of CrO_3 was added over 45 min, while keeping the temperature between 10 and 15°C. After an additional 1.5 h (at 10 to 15°C) the mixture was extracted 8 times with Et_2O and the combined extracts were washed with saturated aqueous ammonium chloride. The conversion of $HC{\equiv}CCH(OH)CH_3$ into the ketone was carried out in the absence of acetone. Our yields were the same as those mentioned in ref [83].

Ethynyl phenyl ketone HC≡CCOPh, is prepared as follows:
Ethynyl phenyl carbinol (0.20 mol, see p. 95 is added to a mixture of 200 ml of acetone, 60 ml of water and 23.1 g of 96% sulfuric acid cooled at 10°C. A solution of 14.7 g of CrO_3 in 50 ml of water is added dropwise over 40 min, while maintaining the temperature between 10 and 15°C. After an additional 2 h (at 15 to 20°C) the greenish solution is poured into 1 l of ice

water and the product is extracted with Et_2O (five times). The combined organic solutions are washed with concentrated aqueous ammonium chloride and dried over $MgSO_4$. The solid remaining after removal of the solvent under reduced pressure is dissolved in about 250 ml of refluxing pentane. The clear solution is decanted from a small amount of brown product and put in the refrigerator (-25°C). White crystals, m.p. 49-50°C, are obtained. The mother liquor is concentrated and cooled again, giving an additional small amount of crystals. The yield is about 90%.

4.2 Conversion of 1-Ethylthio-1-propyne into the Sulfoxide

$$C_2H_5SC{\equiv}CCH_3 + NaIO_4 \xrightarrow[40°C]{H_2O\text{-}CH_3OH} C_2H_5S(=O)C{\equiv}CCH_3 + NaIO_3\downarrow$$

Scale: 0.05 molar.

Apparatus: fig. 1, 500 ml (the dropping funnel is omitted).

Procedure (compare ref [223])
Sodium periodate (0.07 mol) is dissolved in 60 ml of water and a mixure of 0.05 mol of ethylthiopropyne (p. 238) and 15 ml of CH_3OH (note 1) is added. The solution is agitated vigorously, while keeping the temperature between 40 and 45°C (initial temperature 20°C). After one hour the white suspension is cooled to 20°C and 100 ml of water is added. The solution is extracted seven times with chloroform and the combined extracts dried (without washing) over $MgSO_4$. Concentration in a water-pump vacuum (the last traces of $CHCl_3$ are removed at < 0.1 mmHg) gives the pure sulfoxide, $n_D(22°)$ 1.5012, in almost quantitative yield.

Notes

1. In the cases of the higher homologues, more methanol should be used or the reaction should be carried out at a higher temperature.

4.3 Conversion of 1-Ethylthio-1-propyne into the Sulfone

$$CH_3C{\equiv}CSC_2H_5 + H_2O_2 \xrightarrow[95°C]{CH_3COOH} CH_3C{\equiv}CSO_2C_2H_5 + H_2O$$

Scale: 0.10 molar.

Apparatus: fig. 1, 500 ml.

Warning
Contact of 33% H_2O_2 with the skin gives white spots which are very painful. Rubber gloves should be worn and the face should be protected.

Procedure (compare [224])
A mixture of 0.10 mol of ethylthiopropyne (p. 238) and 100 ml of glacial acetic acid is heated to 95°C, then 36 ml of 33% hydrogen peroxide is added over 15 min, while keeping the temperature between 95 and 100°C. After an additional 1 h the solution is cooled to room temperature. Water (200 ml) is added and the solution is extracted ten times with small portions of chloroform. The combined extracts are dried (without washing) over $MgSO_4$ and subsequently concentrated *in vacuo* (see exp. 2). The sulfone, $n_D(20°)$ 1.4745, is obtained in an excellent yield.

$(CH_3C{\equiv}C)_2SO_2$ (m.p. 98-100°C after crystallization from a Et_2O-pentane mixture) is prepared in a similar way from the sulfide with a yield of ~75%.

5. Partial Reduction of One of the Triple Bonds in Diyne Systems

5.1 Reduction of Diyne Alcohols with Lithium Alanate

$$HC{\equiv}CC{\equiv}CC(CH_3)_2OH + LiAlH_4 \xrightarrow[0\rightarrow30°C]{THF} \textit{E}\text{-}HC{\equiv}CCH{=}CHC(CH_3)_2OH$$

Scale: 0.10 molar.

Apparatus: fig. 1, 1 l.

Introduction
The procedure described in this experiment exemplifies a general method [225] for the reduction of propargylic alcohols to *E*-allylic alcohols. The first step in the reaction is the formation of the aluminium alkoxide -C≡C-C-$OAlH_3$. Subsequently one of the three hydrogen atoms attached to aluminum is transferred to the triple bond with formation of a 5-membered cyclic aluminum compound. Hydrolysis affords the *E*-allylic alcohol. In the present case an *E*-enyne alcohol is formed.

Procedure
A solution of 4.0 g (slight excess) of lithium alanate (note 1) in 50 ml of THF is added over 30 min to a mixture of 0.10 mol of the diyne alcohol (see ref. 4 and p. 84) and 75 ml of THF, while keeping the temperature between 0 and 5°C. When, after completion of the addition, the evolution of hydrogen has ceased, the cooling bath is removed and the temperature allowed to rise (occasional cooling may be necessary when a too fast rise is observed). After stirring for an additional 1 h at ~25°C, water (~10 ml) is added dropwise with vigorous stirring. The

addition is stopped when a white slurry has formed. The almost clear solution is decanted and the slurry thoroughly rinsed with Et_2O. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated under reduced pressure. The remaining liquid is distilled through a 20-cm Vigreux column to give the *E*-enyne alcohol, b.p. 65°C/10 mmHg, $n_D(18°)$ 1.4803, in an excellent yield.

Notes

1. One should be sure that the quality of the reagent is good!

5.2 Reduction of 3,5-Octadiyne with Activated Zinc Powder - Formation of *Z*-3-Octen-5-yne

$$C_2H_5C{\equiv}CC{\equiv}CC_2H_5 + Zn + 2\,C_2H_5OH \longrightarrow Z\text{-}C_2H_5CH{=}CHC{\equiv}CC_2H_5 + Zn(OC_2H_5)_2$$

Scale: 0.20 molar.

Apparatus: 250-ml round-bottomed, three-necked flask, equipped with a gas inlet (for introduction of N_2), a mechanical stirrer and a reflux condenser.

Introduction

There are several reports on the successful partial reduction of acetylenic compounds with activated zinc powder ([226] and refs mentioned). Swiss chemists [227] have explained the formation of *Z*-double bonds by assuming that the acetylene is first adsorbed on the metal. Subsequently, two electrons are successively transferred from the metal to the triple bond. Protolysis of the resulting three-membered metallocycle, in which the double bond has the *Z*-configuration, finally gives the *Z*-olefinic compound. The reaction is usually carried out in ethanol. Non-conjugated triple bonds are not reduced unless they are in the terminal position or the molecule contains a OH group, an amino, an ether or ester function. It has appeared that systems in which these functions are close to the triple bond (e.g. in the "propargylic" position) are reduced more easily than the isomers in which the heteroatom-containing group is in a more remote position. In a series of homologues, the time required for complete conversion increases with increasing length of the carbon chain. These experimental facts support the adsorption mechanism.

Triple bonds in conjugated unsaturated systems are reduced relatively easily. Depending upon the degree of activation of the zinc-powder, one or both of the triple bonds in a conjugated diyne can be reduced to a double bond. We have found that the reduction can be completely stopped at the stage of the enyne by using zinc that is activated by boiling with a small amount of 1,2-dibromoethane in ethanol. Further activation of the metal by addition of copper(I)bromide (added as a solution of CuBr.LiBr in THF) leads to reduction of the second triple bond with formation of a conjugated diene. In the case of hydrocarbon-diynes, these partial reductions give almost pure *Z*-enynes and *Z,Z*-dienes.

Procedure

Ethanol (100%, 60 ml) and zinc powder (50 g, Merck, analytical grade) are placed in the flask. 1,2-Dibromoethane (5 g) is added and the mixture is heated until refluxing begins. The heating bath is then removed. When the exothermic reaction (evolution of ethene and refluxing of the solvent) has subsided, an additional amount of 5 g of dibromoethane is added. After this has reacted, the mixture is heated for an additional 10 min under reflux. The suspension is then cooled to about 50°C, while introducing N_2. 3,5-Octadiyne (0.20 mol, see p. 55) is then added over 10 min in two or three portions. The reaction is markedly exothermic and refluxing of the ethanol may ensue. After the reaction has subsided, the mixture is heated for an additional 2 h (note 1) under reflux while a slow stream of N_2 is passed through the apparatus. The mixture is then cooled to room temperature, after which the suspended zinc is allowed to settle down. The supernatant layer is then decanted and poured into a solution of 35 g of NH_4Cl in 200 ml of water and 30 ml of concentrated aqueous ammonia. The zinc slurry in the flask is rinsed four times with 30-ml portions of hot (~50°C) ethanol and the rinsings added to the hydrolysed mixture. Subsequently four extractions with pentane (b.p. 35°C) are carried out. The combined extracts are washed with 2 N hydrochloric acid and subsequently dried over $MgSO_4$. The greater part of the solvent is then distilled off at atmospheric pressure through a 40-cm Vigreux column. After cooling to room temperature, the remaining liquid is distilled *in vacuo* and the distillate collected in a *single* receiver, cooled at 0°C (fig. 14). *Z*-3-octen-5-yne, b.p. ~40°C/15 mmHg, $n_D(20°)$ 1.4590, is obtained in greater than 70% yields.

$C_3H_7CH{=}CHC{\equiv}CC_3H_7$, b.p. 75°C/15 mmHg, $n_D(20°)$ 1.4623, can be prepared in a similar way from the diyne (p. 55). The period of reflux (~5 h in the case of using the same molar amounts of reagents as above) can be shortened to ~3 h if only 35 ml of ethanol is used.

Notes

1. Technical zinc powder reacts less easily.

5.3 Reduction of 1-Trimethylsilyl-1,3-heptadiyne with Activated Zinc Powder. Formation of 1-Trimethylsilyl-3-hepten-1-yne

$$C_3H_7C{\equiv}CC{\equiv}CSiMe_3 + Zn + 2\,C_2H_5OH \xrightarrow[\text{reflux}]{C_2H_5OH} Z\text{-}C_3H_7CH{=}CHC{\equiv}CSiMe_3 + Zn(OC_2H_5)_2$$

Scale: 0.05 molar.

Apparatus: 100-ml three-necked, round-bottomed flask, equipped with a gas inlet (for the introduction of N_2), a mechanical stirrer and a reflux condenser.

Introduction

Russian chemists [228] found that trimethylsilyl groups protect adjacent triple bonds against hydrogenation with poisoned Pd-catalysts. A similar effect is shown in reductions of trimethylsilylated 1,3-diynes with (activated) zinc powder [226]. One disadvantage of the zinc method is that the zinc salts present in the reaction mixture can cause cleavage of the ≡C-Si bond (this was shown in a separate experiment in which a trimethylsilylated 1,3-diyne was heated with a solution of zinc bromide or chloride in ethanol [2]). It seems therefore important to keep reaction times of the reductions with zinc as short as possible and to activate the zinc powder with a limited amount of dibromoethane.

Procedure

To a mixture of 30 g of zinc powder (Merck, analytical grade) and 30 ml of absolute ethanol is added 3.5 ml of 1,2-dibromoethane. The mixture is heated until an exothermic reaction (evolution of ethene and temporary reflux) starts. The activation is completed by heating the mixture for an additional 10 min under reflux. After cooling to about 50°C, the trimethylsilylated diyne (0.05 mol, see Chap. VI for silylation methods) is added in one portion. The introduction of N_2 is started and the mixture is heated for 30 min under reflux. After cooling to room temperature, the work-up is carried out in a way similar to that in exp. 2 (no aqueous ammonia is used). Z-$C_3H_7CH{=}CHC{\equiv}CSiMe_3$, b.p. 75°C/20 mmHg, $n_D(20°)$ 1.4592, is obtained in a high yield.

Z,Z-$C_2H_5SCH{=}CHCH{=}CHC{\equiv}C$-*t*-Bu (undistilled) is obtained from Z-C_2H_5S--$CH{=}CHC{\equiv}CC{\equiv}C$-*t*-Bu by a similar procedure (1 h reflux). The starting compound is prepared by Cadiot-Chodkiewicz coupling of Z-$C_2H_5SCH{=}CHC{\equiv}CH$ with $BrC{\equiv}C$-*t*-Bu (see p.213).

5.4 Conversion of 2,5-Octadiyn-1-ol into Z-2-Octen-5-yn-1-ol by Reduction with Activated Zinc Powder

$$C_2H_5C{\equiv}CCH_2C{\equiv}CCH_2OH + Zn + 2\,C_2H_5OH \longrightarrow Z\text{-}C_2H_5C{\equiv}CCH_2CH{=}CHCH_2OH + Zn(OC_2H_5)_2$$

Scale: 0.10 molar.

Apparatus: 100-ml three-necked, round-bottomed flask, equipped with a gas inlet, a mechanical stirrer and a reflux condenser.

Introduction: for the influence of a propargylic OH group see exp. 2, Introduction.

Procedure

Zinc powder (30 g, Merck, analytical grade) is activated in 30 ml of 100% ethanol as described in exp. 3. The diyne alcohol (0.10 mol, note 1) is added at ~50°C, after which the mixture is heated under reflux for about 2 h. Nitrogen is introduced during this period. After cooling to room temperature, the reaction mixture (including the excess of zinc powder) is poured into a solution of 30 g of NH_4Cl in 200 ml of water. The aqueous mixture is extracted seven times with Et_2O. The combined extracts are washed once with a saturated solution of NH_4Cl and subsequently dried over $MgSO_4$. The liquid remaining after removal of the solvent under reduced pressure is distilled through a short Vigreux column. The Z-enyne alcohol, b.p. ~60°C/1 mmHg, $n_D(20°)$ 1.4972, is obtained in an excellent yield.

Notes

1. The diyne alcohol is prepared by removal of the protecting group from $C_2H_5C{\equiv}CCH_2C{\equiv}CCH_2OCH(CH_3)OC_2H_5$ (see exp. 6.1). For the preparation of the protected alcohol compare p. 265.

5.5 Reduction of an O-Protected Alcohol with a Conjugated Diyne System

$$C_5H_{11}C{\equiv}CC{\equiv}CCH_2OR + Zn + 2\,C_2H_5OH \xrightarrow[\text{reflux}]{C_2H_5OH} Z\text{-}C_5H_{11}C{\equiv}CCH{=}CHCH_2OR + Zn(OC_2H_5)_2$$

Scale: 0.10 molar.

Apparatus: 100-ml, three-necked, round-bottomed flask, equipped with a dropping funnel-gas inlet combination, a mechanical stirrer and a reflux condenser.

Introduction

Although treatment of diyne alcohols $RC{\equiv}CC{\equiv}CCH_2OH$ with activated zinc powder in ethanol results in specific reduction of the triple bond that is closest to the OH group, the reduction is not stereospecific. In the various experiments we found significant amounts of E-$RC{\equiv}CCH{=}CHCH_2OH$ (up to 30%). It might be possible that a satisfactory stereoselectivity can be attained by using unactivated zinc (with analytical zinc powder activated with dibromoethane, the reaction is very fast). Satisfactory and reproducible results can be obtained, however, by carrying out the reduction with the *protected* diyne alcohol (either as the adduct with $H_2C{=}CHOC_2H_5$ or as an O-SiR_3 derivative, compare ref. 229).

Procedure

Zinc powder (30 g, Merck, analytical grade) is activated with dibromoethane (3.5 ml) in 100% ethanol (35 ml) as described in the previous experiments. After cooling to ~30°C, the protected diyne alcohol (0.10 mol), prepared as described in p. 213) is added in three equal portions over 5 min, while introducing N_2. The temperature of the suspension rises fast and

(as a rule) after some 10 min the ethanol begins to reflux: spontaneous refluxing ceases after 5 to 10 min. The mixture is heated for an additional 30 min under reflux (for compounds with a longer carbon chain, see Introduction of exp. 2). After cooling to room temperature and settling of the zinc powder, the supernatant solution is decanted and poured into 200 ml of an aqueous solution of 30 g of NH_4Cl to which 10 ml of concentrated aqueous ammonia has been added. The zinc powder in the flask is rinsed three times with 20-ml portions of hot (40 to 50°C) ethanol, the rinsings being added to the NH_4Cl-solution. The product is isolated by extraction with Et_2O (five times), washing the organic solution with saturated aqueous NH_4Cl, drying the solution over $MgSO_4$ and concentrating the solution *in vacuo*. Removal of the protecting group, as described in exp. 6.1. gives Z-$C_5H_{11}C{\equiv}CCH{=}CHCH_2OH$, b.p. ~80°C/0.5 mm, $n_D(20°)$ 1.4837, in ~80% yield.

$C_2H_5C{\equiv}CC{\equiv}CCH(OC_2H_5)_2$ is converted into Z-$C_2H_5C{\equiv}CCH{=}CHCH(OC_2H_5)_2$ (yield ~75%) by a similar procedure (~45 min reflux, using the same molar amounts of reagents).

6. Removal of Protecting Groups

6.1 Acid-Catalysed Conversion of Vinyl Ethyl Ether Adducts into Alcohols

$$RO\text{-}CH(CH_3)OC_2H_5 + CH_3OH \xrightarrow[50°C]{H^+} ROH + CH_3CH(OCH_3)(OC_2H_5)$$

Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed flask and thermometer.

Procedure

Concentrated aqueous HCl (36%) (0.5 ml) is added to a mixture of 0.10 mol of the vinyl ether adduct and 50 ml of methanol. The mixture is heated for ~15 min in a bath at 50°C, then the acetaldehyde acetal and the greater part of the solvent is removed using a rotary evaporator (note 1). Water (~50 ml) is added, after which the product is extracted with Et_2O. The ethereal solution is washed with water, then dried over $MgSO_4$ or K_2CO_3. The product is isolated in the usual manner.

Notes

1. When the desired alcohol has no good solubility in water, the evaporation of methanol and the acetaldehyde acetal need not be carried out and the reaction mixture can be directly treated with a sufficient amount of water.

6.2 Acid-Catalysed Conversion of an Acetylenic Acetal into the Aldehyde

$$C_4H_9C{\equiv}CCH(OC_2H_5)_2 + H_2O \xrightarrow[H^+]{H_2O,\ DMSO} C_4H_9C{\equiv}CCH{=}O + 2\,C_2H_5OH$$

Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed flask and thermometer.

Procedure

To a mixture of 4 g of 96% H_2SO_4 and 20 ml of water are successively added 40 ml of DMSO and 0.10 mol of the acetylenic acetal (p. 76). The mixture is heated for 15 to 20 min at 75°C with occasional swirling. After 5 min (at 75°C) the solution has become homogeneous. The solution is cooled to room temperature and subsequently poured into 150 ml of ice water, saturated with NH_4Cl. The product is isolated by extraction with Et_2O (10 times), washing the solution with saturated aqueous NH_4Cl, drying over $MgSO_4$ and distillation through a short Vigreux column. The aldehyde, b.p. 55°C/10 mmHg, $n_D(20°)$ 1.4518, is obtained in an excellent yield.

In the case of lower homologues, less DMSO should be used.

6.3 Base-Catalysed Removal of Trimethylsilyl Groups from Trimethylsilylalkynes

$$RC{\equiv}CSiMe_3 + CH_3OH \xrightarrow{KOH} RC{\equiv}CH + Me_3SiOCH_3$$

Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed flask and thermometer.

Procedure

The TMS-acetylene (0.10 mol) is added to a solution of 6 g of KOH in 40 ml of methanol and the mixture is heated for 30 min at 60°C. If the b.p. of the acetylene $RC{\equiv}CH$ is higher than 60°C/10 mmHg, the greater part of the methanol can be removed under reduced pressure (rotary evaporator). After addition of a sufficient amount of water, the acetylene is extracted with Et_2O or pentane. In the cases of more volatile acetylenes, the reaction mixture is poured into 300 ml of water, after which extraction with Et_2O or pentane is carried out.

Compounds with a skipped enyne or diyne system ($RCH{=}CHCH_2C{\equiv}C$- and $RC{\equiv}CCH_2C{\equiv}C$-) undergo isomerization either before or after the removal of the Me_3Si-group. *Conjugated* systems $RCH_2C{\equiv}CC{\equiv}CH$ and $RCH_2CH{=}CHC{\equiv}CH$ are also base-sensitive. In these cases, deprotection can be successfully carried out with potassium cyanide and silver nitrate [230].

6.4 Base-Catalysed Elimination of Acetone from a Carbinol. Preparation of *t*-Butylbutadiyne

$$t\text{-Bu-C}{\equiv}\text{CC}{\equiv}\text{CC(CH}_3)_2\text{OH} \xrightarrow[\text{heat, vacuum}]{\text{KOH}} t\text{-Bu-C}{\equiv}\text{CC}{\equiv}\text{CH} + (\text{CH}_3)_2\text{C=O}$$

Scale: 0.10 molar.

Apparatus: fig. 14, size of the distillation flask: 500 ml.

Procedure (compare [195])

Paraffin oil (100 ml), powdered KOH (4 g, preferably machine-powdered), the carbinol (0.10 mol, p. 213) and a few drops of an anti-foaming liquid are placed in the flask. After vigorous shaking, the flask is equipped for a vacuum distillation (fig. 14, 30-cm Vigreux column, condenser and single receiver, cooled in a bath at -70°C). The distillation apparatus is evacuated (water aspirator, 10 to 20 mmHg) and the temperature of the heating bath raised to 150-170°C. The acetone and the diyne condense in the receiver. After 45 min (at 150-170°C) nitrogen is admitted and the condensate is shaken 5 times with 10-ml portions of cold (0°C) 2 N HCl in order to remove the acetone (a small dropping funnel is used for this operation). The upper layer is then transferred into a 250-ml round-bottomed flask containing 2-3 g of $MgSO_4$. After vigorous shaking a flash distillation is carried out (see fig. 14) in a vacuum of 10 to 20 mmHg. The diyne, $n_D(20°)$ 1.4581, collected in the strongly cooled receiver, is obtained in an excellent yield.

Instructions for searching

A limited number of simple and useful compounds are tabulated in the List of Selected Compounds.

The Type-Compound-Method Index includes all compounds in this book and a few in the previous books [3] and [4] and in the literature.

The various compounds are arranged according to classes, in alphabetical order. Within a given class the various compounds are ordered as indicated. For each group of compounds or particular compound, the method of preparation is indicated in the second column. The various classes of compounds listed are the following:

List of Selected Compounds

TYPE-COMPOUND-METHOD INDEX

Z-BuC≡CCH=CHCH$_2$OH	BuC≡CC≡CCH$_2$OR + Zn, EtOH, then deprotection (R = CH(Me)OEt)	287
E-MeC≡CCH=CHCH$_2$OH	*E*-HC≡CCH=CHCH$_2$OH + 2 LiNH$_2$ + MeI, liq. NH$_3$	49
H$_2$C=C=CHC≡CCH$_2$OH	HC≡CCH$_2$Cl + HC≡CCH$_2$OH, NH$_4$OH, CuCl	228
RC≡CC≡CCH$_2$OH R = alkyl, aryl	1. RC≡CC≡CLi + $(CH_2O)_n$, THF or Et$_2$O 2. RC≡CBr + HC≡CCH$_2$OH, Cadiot-Chodkiewicz	81 213
HOCH$_2$(C≡C)$_2$CH$_2$OH	HC≡CCH$_2$OH + O$_2$, H$_2$O, CuCl, NH$_4$Cl	222
H$_2$C=CHC≡CCH$_2$CH$_2$OH MeCH=CHC≡CCH$_2$CH$_2$OH	H$_2$C=CHC≡CLi + oxirane, liq. NH$_3$ MeCH=CHC≡CLi + oxirane, liq. NH$_3$	[4
EtC≡CC≡CCH$_2$CH$_2$OH	1. EtC≡CC≡CLi + oxirane, liq. NH$_3$ 2. EtC≡CBr + HC≡CCH$_2$CH$_2$OH Cadiot-Chodkiewicz	66 213
EtC≡CC≡C(CH$_2$)$_9$OH	EtC≡CBr + HC≡C(CH$_2$)$_9$OH, Cadiot-Chodkiewicz	213
PhC≡CCH$_2$CH$_2$OH	PhC≡CLi + oxirane, THF + DMSO	67

b. Secondary

HC≡CCH(Pr)OH	HC≡CLi (liq. NH$_3$ → THF) + PrCH=O	85
HC≡CCH(R)OH R= H$_2$C=CH,CH=CHMe	HC≡CLi + RCH=O, liq. NH$_3$, -75°C	87
HC≡CCHROH, R = Ph	1. HC≡CLi + PhCH=O, liq. NH$_3$	94
R = alkyl, Ph	2. HC≡CLi.TMEDA + RCH=O, THF	82
R = alkyl, Ph	3. HC≡CMgBr + RCH=O, THF	92
BrC≡CCH(Me)OH	KOBr + HC≡CCH(Me)OH, H$_2$O	150
ClCH$_2$C≡CCH(Me)OH	ClCH$_2$C≡CLi + MeCH=O, Et$_2$O	83
HC≡CCH$_2$CH(R)OH	1. H$_2$C=C=CHMgBr + RCH=O, Et$_2$O	95
general method	2. LiC≡CH + Et-oxirane, DMSO	65

HC≡CCH$_2$CH(Ph)OH	1. HC≡CLi + styrene oxide, liq. NH$_3$ → DMSO	67
	2. H$_2$C=C=CHMgBr + PhCH=O, Et$_2$O	95
HC≡CC(=CH$_2$)CH$_2$- -CH(OH)CH$_2$-*i*-Pr	LiC≡CC(CH$_2$Li)=CH$_2$ + *i*-Pr-CH$_2$CH=O	94

c. Tertiary

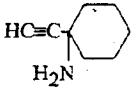
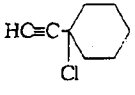
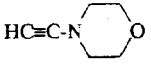
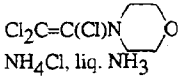
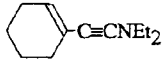
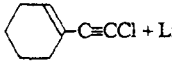
HC≡CC(R^1)(R^2)OH R^1 and R^2 = alkyl	1. HC≡CNa + R^{1}R^{2}C=O, liq. NH$_3$ 2. HC≡CH + *t*-BuOK + R^{1}R^{2}C=O, THF	88 92
HC≡CC(R^1)R^2)OH R^{1}R^{2}C = cycloalkyl	HC≡CH + *t*-BuOK + R^{1}R^{2}C=O, THF	92
HC≡CC(Me)CH=CH$_2$)OH	HC≡CLi + H$_2$C=CHCOMe, liq. NH$_3$ → THF	88
HC≡CC(Me)(β-ionyl)OH	HC≡CMgBr + β-ionone, THF	91
MeC≡CC(R^1)(R^2)OH R^{1}R^{2}C = cycloalkyl	MeC≡CLi + cycloalkanone, THF + LiBr	82
Me$_2$NCH$_2$C≡C- -C(R^1)(R^2)OH	Me$_2$NCH$_2$C≡CLi + cycloalkanone, THF + LiBr	82
BrC≡CCMe$_2$OH	KOBr + HC≡CCMe$_2$OH, H$_2$O	150
ClC≡CCMe$_2$OH	ClC≡CLi + Me$_2$C=O, liq. NH$_3$	90
EtOC≡CCMe$_2$OH	EtOC≡CLi + Me$_2$C=O, THF	82
HC≡CC≡CCMe$_2$OH	HC≡CC≡CLi + Me$_2$C=O, THF	84
E-HC≡CCH=CHCMe$_2$OH	HC≡CC≡CCMe$_2$OH + LiAlH$_4$, THF	283
H$_2$C=C=CHC≡CCMe$_2$OH	HC≡CCH$_2$Cl + HC≡CCMe$_2$OH, NH$_4$OH, CuCl	228
t-BuC≡CC≡CCMe$_2$OH	*t*-BuC≡CBr + HC≡CCMe$_2$OH, Cadiot-Chodkiewicz	213
HOCMe$_2$(C≡C)$_2$CMe$_2$OH	1. HC≡CCMe$_2$OH + O$_2$, NH$_4$Cl, CuCl H$_2$O	222
	2. ClCH$_2$C≡CCH$_2$Cl + 4 NaNH$_2$ + Me$_2$C=O, liq. NH$_3$	91

ALDEHYDES

$HC{\equiv}CCH{=}O$	$HC{\equiv}CCH_2OH + CrO_3, H_2O, H^+$	[240]
$RC{\equiv}CCH{=}O$ general methods	1. $RC{\equiv}CLi$ + DMF, THF or Et_2O, then H_2O, H^+	102
	2. $RC{\equiv}CCH(OEt)_2 + H_2O, H^+$	289, [3]
ortho-Ethynylbenzaldehyde	$PhC{\equiv}CH$ + 2 BuLi,*t*-BuOK, THF, then LiBr, DMF, then H_2O, H^+	213

AMINES

(order: primary > secondary > tert. amine; C≡C-N > C≡C-C-N; non-conj. > conjug. C≡C; terminal C≡C > non-terminal C≡C)

$HC{\equiv}CCH_2NH_2$	$HC{\equiv}CCH_2Br$ + liq. NH_3	214
$HC{\equiv}CCMe_2NH_2$	$HC{\equiv}CCMe_2Cl + 2\ NaNH_2$, liq. NH_3	277
	 + 2 $NaNH_2$, liq. NH_3	278
$RC{\equiv}CCH_2NH_2$	$RC{\equiv}CCH_2Br$ + hexamethylene tetramine, then NaI, then K_2CO_3	276
$HC{\equiv}CNMe_2$	$H_2C{=}C(SBu)NMe_2 + 2\ KNH_2$, HMPT, then $BrCH_2CH_2Br$	187
	 + 3 EtLi, Et_2O, then NH_4Cl, liq. NH_3	186
$MeC{\equiv}CNEt_2$	$HC{\equiv}CCH_2NEt_2$ + *t*-BuOK, DMSO	235
$RC{\equiv}CNR'_2$	$RC{\equiv}COEt + LiNR'_2, Et_2O$	189
$R_2NC{\equiv}CNR_2$ R = Me, Et	$ClCH{=}C(NR_2)_2 + KNH_2$, liq. NH_3	186
$PhC{\equiv}CNMe_2$	$ClC{\equiv}CPh + LiNMe_2, Et_2O$	191
	 + $LiNEt_2$, Et_2O	191
$H_2C{=}CHC{\equiv}CNR_2$ R = Me, Et	$MeOCH_2C{\equiv}CCH_2NR_2$ + *t*-BuOK, THF	[4]

$PhSC{\equiv}CNEt_2$	$PhSCH_2CF_3 + LiNEt_2, Et_2O$	[4]
$MeCH{=}CHC{\equiv}CNEt_2$	$H_2C{=}CHC{\equiv}CCH_2NEt_2$ + *t*-BuOK, DMSO	236
$MeC{\equiv}CC{\equiv}CNEt_2$	$HC{\equiv}CC{\equiv}CCH_2NEt_2$ + *t*-BuOK, HMPT	237
$HC{\equiv}CCH{=}CHNR_2$	$H_2C{=}CHC{\equiv}CNR_2 + KNH_2$, liq. NH_3	242
$HC{\equiv}CCH_2NMe_2$	$HC{\equiv}CCH_2Br + 2\ Me_2NH$, petr. ether	273
$HC{\equiv}CCH_2NR_2$ NR_2 = NEt_2, pyrrolidino, piperidino, morpholino	$HC{\equiv}CCH_2Br + 2\ R_2NH, Et_2O$	273
$HC{\equiv}CCH_2CH_2NEt_2$	$MeC{\equiv}CCH_2NEt_2 + KNH_2$, liq. NH_3	241
$HC{\equiv}CC{\equiv}CCH_2NEt_2$	$EtSCH{=}CHC{\equiv}CCH_2NEt_2 + KNH_2$, liq. NH_3	194
$H_2C{=}CHC{\equiv}CCH_2NEt_2$	$H_2C{=}CHC{\equiv}CH + Et_2NCH_2OH$, $Cu(OAc)_2$	211
$RC{\equiv}CCH_2NR'$ R and R' = alkyl	$R'_2NCH_2OH + RC{\equiv}CH$, $Cu(OAc)_2$	212
$MeC{\equiv}CCH_2NEt_2$	$LiC{\equiv}CCH_2NEt_2$ + MeI, liq. NH_3 + HMPT	42
$Et_2NCH_2C{\equiv}CCH_2NEt_2$	$BrCH_2C{\equiv}CCH_2Br + 4\ Et_2NH, Et_2O$	275
$MeOCH_2C{\equiv}CCH_2NR'_2$ R = Me, Et	$MeOCH_2C{\equiv}CH + R'_2NCH_2OH$, $Cu(OAc)_2$	212, [4]
$EtCH{=}CHC{\equiv}CCH_2NEt_2$	$EtCH{=}CHC{\equiv}CH + HOCH_2NEt_2$, $Cu(OAc)_2$	212
$EtC{\equiv}CC{\equiv}CCH_2NEt_2$	$EtC{\equiv}CBr + HC{\equiv}CCH_2NEt_2$ Cadiot-Chodkiewicz	213
$Et_2NCH_2(C{\equiv}C)_2CH_2NEt_2$	$Et_2NCH_2C{\equiv}CH + O_2$, pyridine, CuCl	221
$EtSCH{=}CHC{\equiv}CCH_2NEt_2$	$Et_2NCH_2OH + HC{\equiv}CCH{=}CHSEt$, $Cu(OAc)_2$	212

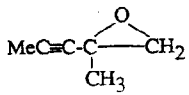
CARBOXAMIDES AND SULFUR ANALOGUES

$RC{\equiv}CC(=O)NH_2$	$RC{\equiv}CCOOCH_3 + NH_4OH, CH_3OH$	[3]
$RC{\equiv}CC(=O)NHPh$	$RC{\equiv}CLi + PhN{=}C{=}O$, THF	108
$RC{\equiv}CC(=O)NMe_2$	$RC{\equiv}CLi + Me_2NC(=O)Cl$, THF	107
$RC{\equiv}CC(=S)NHMe$	$RC{\equiv}CLi + MeN{=}C{=}S$	109

CARBOXYLIC ACIDS

$HC{\equiv}CCOOH$	$HC{\equiv}CCH_2OH + CrO_3, H_2O, H^+$	[241]
$RC{\equiv}CCOOH$ general method	$RC{\equiv}CLi + CO_2$, THF, then H_2O, H^+	100
$RC{\equiv}CCH_2COOH$ R = alkyl	$RCH_2C{\equiv}CCOOH + 2\ NaNH_2$, liq. NH_3	243
$HC{\equiv}CCH_2COOH$	$LiCH_2C{\equiv}CLi + CO_2$, then H^+, H_2O	[4]
$HC{\equiv}C(CH_2)_9COOH$	$H_2C{=}CH(CH_2)_9COOH + Br_2$, then $NaNH_2$, liq. NH_3, then H_2O, H^+	173

EPOXIDES

	$MeC{\equiv}CMgBr + ClCOMe$, THF, then H_2O then solid KOH, Et_2O	266

ESTERS

Sulfinates

$MeS(=O)OR$ general method	$ROH + MeS(=O)Cl + Et_3N, CH_2Cl_2$	257

Sulfonates

$ArylSO_2OR$;	ROH + Tosyl chloride + solid KOH, Et_2O	256
$MeSO_2OR$ general methods	$ROH + MeS(=O_2)Cl + Et_3N, CH_2Cl_2$	257

Acetates

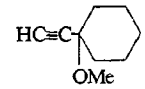
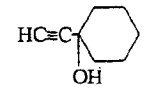
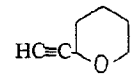
$MeC(=O)OR$ general method	$ROH + MeC(=O)Cl + PhNEt_2$ (+ Et_2O)	258

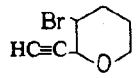
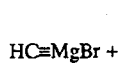
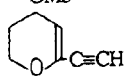
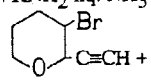
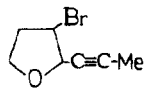
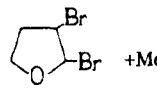
Acetylenic Carboxylates

$RC{\equiv}CCOOR'$ general method ($R \neq H$ or $-C{\equiv}C$)	$RC{\equiv}CLi + ClCOOR', Et_2O$	101

ETHERS

(order $C{\equiv}CO > C{=}C(C)_nO$; $HC{\equiv}C > RC{\equiv}C$; non-conj. > conj. $C{\equiv}C$)

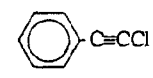
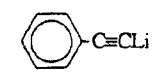
$HC{\equiv}COR$ R = Me, Et	$ClCH_2CH(OR)_2 + 3\ NaNH_2$, liq. NH_3	174
$RC{\equiv}COEt$ R = prim. alkyl	$LiC{\equiv}COEt + MeI$ or RBr, liq. NH_3	47,50,54
$Me_3SiC{\equiv}COEt$	$LiC{\equiv}COEt + Me_3SiCl$, THF	123
$H_2C{=}CHC{\equiv}COEt$	$EtOCH_2CH{=}C{=}CHOEt + EtLi, Et_2O$	[4]
$MeC{\equiv}CCH_2C{\equiv}COEt$	$MeC{\equiv}CCH_2OTs + BrMgC{\equiv}COEt$, THF, CuBr	227
$HC{\equiv}CCH_2OR$ R = Me, Et	$HC{\equiv}CCH_2OH + NaOH + Me_2SO_4, H_2O$	259
$HC{\equiv}CCH_2O$-*t*-Bu	$HC{\equiv}CCH_2OH$ + isobutene, H_2SO_4	266
$HC{\equiv}CCH_2OR$ R = CH(Me)OEt	$HC{\equiv}CCH_2OH + H_2C{=}CHOEt, H^+$	265
$HC{\equiv}CCH_2OCH{=}CH_2$	$CH_3CH{=}O + HCl + HC{\equiv}CCH_2OH$, then $PhNEt_2$	270
$HC{\equiv}CCMe_2OMe$	$HC{\equiv}CCMe_2OH + Me_2SO_4 + KOH$, DMSO	262
$HC{\equiv}CCH(Hex)OMe$	$HC{\equiv}CCH_2OMe + 2$ BuLi.*t*-BuOK, THF then HexBr	73
	 + BuLi, THF, then HMPT + MeI	263
	$HC{\equiv}CMgBr +$  Cl, THF	69

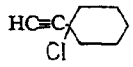
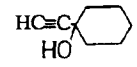
	 + HC≡MgBr, THF	70
$BrCH_2CH(OEt)C{\equiv}CH$	$HC{\equiv}CMgBr + BrCH_2CH(Br)OEt$, THF	70
$HC{\equiv}CCH_2OCH_2C{\equiv}CH$	$HC{\equiv}CCH_2OH + HC{\equiv}CCH_2Br + KOH$ (solid)	261
$HC{\equiv}CCH_2C{\equiv}CCH_2OR$ R = CH(Me)OEt	$HC{\equiv}CMgBr + BrMgC{\equiv}CCH_2OR$, THF, CuBr	225
$HC{\equiv}CCH{=}CHOEt$	$EtOCH_2C{\equiv}CCH_2OEt + 2\ NaNH_2$, liq. NH_3	192
$HC{\equiv}CCH{=}CHOR$ (R= OCH(Me)OEt)	$ROCH_2C{\equiv}CCH_2OR + 3\ NaNH_2$, liq. NH_3	[4]
$HC{\equiv}CC(OMe){=}CHR$ R= H, Me	$H_2C{=}C{=}C(OMe)CH(R)OMe + 2\ NaNH_2$, liq. NH_3	[4]
$HC{\equiv}CCH{=}C(Me)CH{=}CH$-OMe	$MeC{\equiv}CC(Me)(OR)CH_2CH(OMe)_2$ + 4 KNH_2 liq. NH_3 (R = CH(Me)OEt)	193
	 + *t*-BuOK, THF	206
	 +MeC≡CMgBr, THF	71
$ROCH_2C{\equiv}CCH_2OR$ R = Me, Et	$HOCH_2C{\equiv}CCH_2OH + NaOH + R_2SO_4$, H_2O	260
$EtOCH(Me)C{\equiv}CCH_2OMe$	$EtOCH(Cl)Me + LiC{\equiv}CCH_2OMe$, THF	[4]
t-$BuOCH_2C{\equiv}CCH_2O$-*t*-Bu	$HOCH_2C{\equiv}CCH_2OH$ + isobutene, H_2SO_4	[4]
$MeOCH_2C{\equiv}CCMe_2OMe$	$MeOCH_2C{\equiv}CLi$ + acetone, THF, then HMPT + MeI	[4]
$ROCH_2C{\equiv}CCH_2OR$ R = CH(Me)OEt	$HOCH_2C{\equiv}CCH_2OH + H_2C{=}CHOEt$, H^+	265, [4]
$MeC{\equiv}CCH_2OMe$	$LiC{\equiv}CCH_2OMe$ + MeI, liq. NH_3	48
$C_5H_{11}C{\equiv}CCH_2OEt$	$C_5H_{11}C{\equiv}CLi + ClCH_2OEt$, Et_2O, or THF	68
$MeOCH_2(C{\equiv}C)_2CH_2OMe$	$MeOCH_2C{\equiv}CH + O_2$, pyridine, CuCl	221

$H_2C{=}CHC{\equiv}CCH{=}CHOEt$	$MeCH{=}CHC{\equiv}CCH(OEt)_2$ + *t*-BuOK, DMSO	[4]
$R^1C{\equiv}CC(R^2)(R^3)OMe$ generally applicable	$R^1C{\equiv}CLi + R^2R^3C{=}O$, THF, then MeI, HMPT	264
$HC{\equiv}CCH_2OCH{=}CH_2$	$HC{\equiv}CCH_2OH + HCl + (CH_3CH{=}O)_3$, then $PhNEt_2$	270

HALOGEN COMPOUNDS

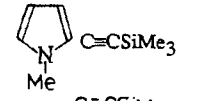
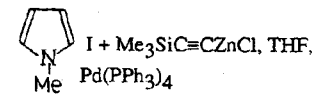
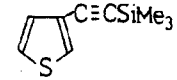
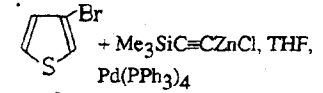
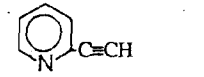
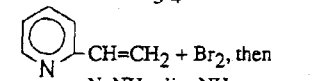
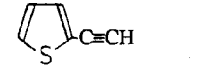
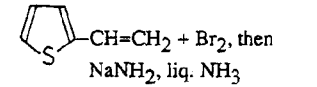
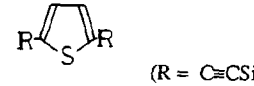
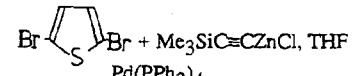
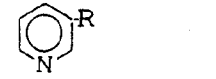
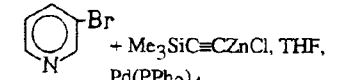
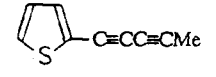
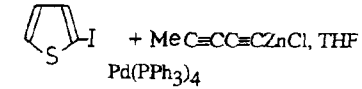
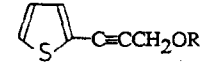
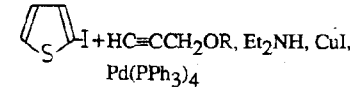
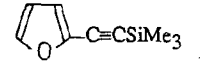
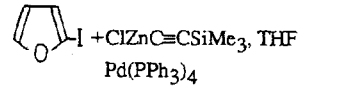
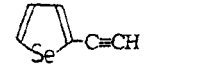
(order: Cl > Br > I; C≡CX > $C{\equiv}C(C)_nX$; HC≡C > RC≡C)

$BuC{\equiv}CCl$	$ClCH{=}CHCl + 2\ LiNH_2$, liq. NH_3, then BuBr	56
$PhC{\equiv}CCl$	1. $PhC{\equiv}CLi + PhSO_2Cl$, THF	147
	2. $PhC{\equiv}CLi + Cl_2$, Et_2O	153
	 + $PhSO_2Cl$, THF	147
$MeC{\equiv}CBr$	$BrCH{=}CHBr + 2\ LiNH_2$ + MeI, liq. NH_3	75
$RC{\equiv}CBr$ general method	1. $RC{\equiv}CLi + Br_2$, Et_2O (or THF)	149
$RC{\equiv}CBr$ R = aryl, >C=C<, -C≡C-	2. $RC{\equiv}CH$ + KOBr, H_2O	150
$RC{\equiv}CBr$ general method	3. $RC{\equiv}CLi + BrC{\equiv}N$, THF or Et_2O	156
$HOCH(Me)C{\equiv}CBr$	$HOCH(Me)C{\equiv}CH$ + KOBr, H_2O	150
$HOCMe_2C{\equiv}CBr$	$HOCMe_2C{\equiv}CH$ + KOBr, H_2O	150
$RC{\equiv}CI$ general method	$RC{\equiv}CLi$ (or Na) + I_2, liq. NH_3 or THF	152
$HC{\equiv}CCH(Me)Cl$	$HC{\equiv}CCH(OTs)Me$ + LiCl, DMSO	251
$HC{\equiv}CCMe_2Cl$	$HC{\equiv}CCMe_2OH + HCl$, NH_4Cl, CuCl, H_2O	252

	 + HCl, NH_4Cl, CuCl, H_2O	253
$HC{\equiv}CCHClPh$	$HC{\equiv}CCH(OH)Ph + SOCl_2$	[4]
$HC{\equiv}C(CH_2)_4Cl$	$LiC{\equiv}CCH_2Li + Br(CH_2)_3Cl$, THF	[4]
$RC{\equiv}CCH_2Cl$ R = Me, Bu	$RC{\equiv}CCH_2OMe + MeC(=O)Cl$	[3]
$ClCH_2C{\equiv}CCH_2Cl$	$HOCH_2C{\equiv}CCH_2OH + 2\ SOCl_2$, pyridine	254
$MeCH(Cl)C{\equiv}CCH_2Cl$	$MeCH(OH)C{\equiv}CCH_2Cl + SOCl_2$, pyridine	[4]
$ClCH_2C{\equiv}CCH_2OH$	$ClCH_2C{\equiv}CLi + (CH_2O)_n$, Et_2O	[4]
$ClCH_2C{\equiv}CCH(Me)OH$	$ClCH_2C{\equiv}CLi + MeCH{=}O$, Et_2O	82
$ClCH_2C{\equiv}CCOOMe$	$ClCH_2C{\equiv}CLi + ClCOOMe$, Et_2O	103
$ClCH_2C{\equiv}CSMe$	$ClCH_2C{\equiv}CLi + MeSC{\equiv}N$, Et_2O	[4]
$ClCH_2C{\equiv}CSiMe_3$	$ClCH_2C{\equiv}CLi + Me_3SiCl$, Et_2O + HMPT	122
$BrCH_2C{\equiv}CSiMe_3$	$BrCH_2C{\equiv}CLi + Me_3SiCl$, Et_2O + HMPT	122
$Br(CH_2)_4C{\equiv}CSiMe_3$	$Br(CH_2)_4C{\equiv}CLi + Me_3SiCl$, THF	123
$HC{\equiv}CCH{=}CHCH(Me)Cl$	$HC{\equiv}CCH(OH)CH{=}CHMe + HCl$, H_2O	252
$ClCH_2(C{\equiv}C)_2CH_2Cl$	$HOCH_2(C{\equiv}C)_2CH_2OH + SOCl_2$, pyridine	255
$MeC{\equiv}CC(Me)(OH)CH_2Cl$	$MeC{\equiv}CMgBr + ClCH_2COMe$, THF	[3]
$HC{\equiv}CCH_2Br$	$HC{\equiv}CCH_2OH + PBr_3$, Et_2O (pyridine)	247
$HC{\equiv}CCH(Me)Br$	$HC{\equiv}CCH(Me)OTs + LiBr$, DMSO	251
$HC{\equiv}CCMe_2Br$	$HC{\equiv}CCMe_2OH + PBr_3$	249
$HC{\equiv}CCH(Hex)Br$	$HC{\equiv}CCH(Hex)OTs + LiBr$, acetone	250
$HC{\equiv}CCH_2CH_2Br$	$HC{\equiv}CCH_2CH_2OTs + LiBr$, DMSO	250
$HC{\equiv}C(CH_2)_4Br$	$HC{\equiv}C(CH_2)_4OTs + LiBr$, DMSO	250
$RC{\equiv}CCH_2Br$ R = alkyl	$RC{\equiv}CCH_2OH + PBr_3$, Et_2O (pyridine)	248
$HC{\equiv}CCH{=}CHCH_2Br$	$HC{\equiv}CCH{=}CHCH_2OH + PBr_3$, Et_2O	248
$HC{\equiv}CCH{=}CHCH(Me)Br$	$HC{\equiv}CCH(OH)CH{=}CHMe + HBr$, H_2O	252
$BrCH_2C{\equiv}CCH_2Br$	$HOCH_2C{\equiv}CCH_2OH + PBr_3$, Et_2O	275
$HC{\equiv}CCH_2I$	$HC{\equiv}CCH_2Br$ + NaI, EtOH	[4]

$MeSC{\equiv}CCH_2I$	$LiCH_2C{\equiv}CSMe + I_2$, THF	[4]

HETEROAROMATIC COMPOUNDS

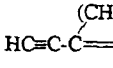
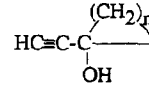
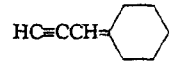
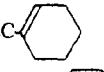
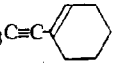
	 I + $Me_3SiC{\equiv}CZnCl$, THF, $Pd(PPh_3)_4$	215
	 + $Me_3SiC{\equiv}CZnCl$, THF, $Pd(PPh_3)_4$	216
	 $CH{=}CH_2 + Br_2$, then $NaNH_2$, liq. NH_3	177
	 $CH{=}CH_2 + Br_2$, then $NaNH_2$, liq. NH_3	[3]
 (R = $C{\equiv}CSiMe_3$)	 + $Me_3SiC{\equiv}CZnCl$, THF $Pd(PPh_3)_4$	216
	 + $Me_3SiC{\equiv}CZnCl$, THF, $Pd(PPh_3)_4$	216
	 + $MeC{\equiv}CC{\equiv}CZnCl$, THF $Pd(PPh_3)_4$	215
 R = CH(Me)OEt	 + $HC{\equiv}CCH_2OR$, Et_2NH, CuI, $Pd(PPh_3)_4$	217
	 + $ClZnC{\equiv}CSiMe_3$, THF $Pd(PPh_3)_4$	215
	$HC{\equiv}CC{\equiv}CC{\equiv}CH + Na_2Se$, MeOH	[4]

HYDROCARBONS

(order : terminal C≡C > non terminal C≡C; non-conj. C≡C > conj. C≡C

$HC{\equiv}CR$ R = Me, Et	$BrCH_2CHBrR$, solid KOH, phase transfer	165

$HC{\equiv}CR$	1. $HC{\equiv}CLi$ (Na) + RBr, liq. NH_3	52
R = prim. alkyl	2. $HC{\equiv}CLi$ + RBr, liq. NH_3 → DMSO	59
$HC{\equiv}CCH_2CH_2C{\equiv}CH$	$H_2C{=}CHCH_2CH_2CH{=}CH_2$ + 2 Br_2, then $NaNH_2$, liq. NH_3	170
$HC{\equiv}C(CH_2)_nC{\equiv}CH$	$HC{\equiv}CNa$ + $Br(CH_2)_nBr$, liq. NH_3	60
n = 4, 5, 6		
$HC{\equiv}CR$	Cl_2CHCH_2R + 3 $NaNH_2$, liq. NH_3	169,166
R = *i*-Pr, *c*-alkyl		
$HC{\equiv}C$-*t*-Bu, *i*-Pr	1. $BrCH_2CHBr$-*t*-Bu + *t*-BuOK, DMSO	167
	2. Cl_2CHCH_2-*t*-Bu or CH_3CCl_2-*t*-Bu + KOH (solid), phase transfer	166
$HC{\equiv}CCH_2$-*t*-Bu	1. $H_2C{=}C{=}CH$-*t*-Bu + EtLi.LiBr, Et_2O	244
	2. $CH_3C{\equiv}C$-*t*-Bu + KNH_2, liq. NH_3	239
$HC{\equiv}CCH_2$-*c*-alkyl	$H_2C{=}C{=}CHOCH_3$ + *c*-alkyl-MgBr, Et_2O CuBr	[4]
$HC{\equiv}CCH_2Ph$	$H_2C{=}C{=}CHOCH_3$ + Ph-MgBr, Et_2O, CuBr	[4]
$HC{\equiv}CCH_2CH_2Ph$	$LiCH_2C{\equiv}CLi$ + PhMgCl, THF	72
$HC{\equiv}CCH(CH_3)Ph$	$LiC{\equiv}CCH(Li)Ph$ + CH_3I, Et_2O or THF	[4]
$HC{\equiv}CCHBu_2$	BuCH=C=CCHOMe + BuMgBr, Et_2O, CuBr (catal.)	[4]
$HC{\equiv}CCH_2CH{=}CH_2$	$HC{\equiv}CMgBr$ + $H_2C{=}CHCH_2OTs$, THF, CuBr	227
$HC{\equiv}CCH_2C{\equiv}CH$	$HC{\equiv}CMgBr$ + $HC{\equiv}CCH_2OTs$, THF, CuBr	227
$HC{\equiv}CCH_2C{\equiv}CR$	$HC{\equiv}CCH_2OTs$ + $RC{\equiv}CMgBr$, THF, CuBr	227, [4]
R = Me, Bu, Pent		225
$MeC{\equiv}CMe$	$HC{\equiv}CEt$ + *t*-BuOK, DMSO	234
$MeC{\equiv}CHex$	$HC{\equiv}CCH_2Hex$ + *t*-BuOK, DMSO	234
$MeC{\equiv}C$-*t*-Bu	$LiC{\equiv}C$-*t*-Bu + MeI, liq. NH_3 + HMPT	42
$BuC{\equiv}CBu$	$LiC{\equiv}CH$ + $LiNH_2$ + 2 BuBr, liq. NH_3	56
Cyclooctyne	1-Bromocyclooctene + LDA, THF	183
$RC{\equiv}CCH_2CH{=}CH_2$	$RC{\equiv}CMgBr$ + $BrCH_2CH{=}CH_2$, THF, CuBr	225
$HC{\equiv}CC{\equiv}CH$	$ClCH_2C{\equiv}CCH_2Cl$ + KOH, H_2O, DMSO	179
$HC{\equiv}CC{\equiv}CMe$	$ClCH_2C{\equiv}CCH_2Cl$ + 3 $NaNH_2$ + MeI, liq. NH_3	46

$HC{\equiv}CC{\equiv}CR$	$ClCH_2C{\equiv}CCH_2Cl$ + 3 $NaNH_2$ + RBr, liq. NH_3 or liq. NH_3 + DMSO	51,53,60
R = Et, Pr, Bu, Hex		
$HC{\equiv}CC{\equiv}C$-*t*-Bu	*t*-$BuC{\equiv}CC{\equiv}CCMe_2OH$ + KOH, heat	290
$MeC{\equiv}CC{\equiv}CMe$	$ClCH_2C{\equiv}CCH_2Cl$ + 4 $NaNH_2$ + 2 MeI, liq. NH_3	47
$RC{\equiv}CC{\equiv}CR$	1. $RC{\equiv}CH$ + O_2, pyrid. (+ DBU) + CuBr	221
R = Et, Pr	2. $ClCH_2C{\equiv}CCH_2Cl$ + 4 $NaNH_2$ + RBr, NH_3	55
$HC{\equiv}CCH{=}CH_2$	$ClCH_2CH{=}CHCH_2Cl$ + solid or aq. KOH, phase-transfer	178
$HC{\equiv}CCH{=}CHR$	$HC{\equiv}CCH_2CH(OTs)R$ + KOH, H_2O	209
R = alkyl		
$HC{\equiv}CC(Me){=}CH_2$	$HC{\equiv}CCMe_2OH$ + *p*-tol.sulf.acid, Ac_2O	203
$HC{\equiv}C$- 	 + $POCl_3$, pyridine	203
	 + KNH_2, liq. NH_3	241
Z-$HC{\equiv}CCH{=}CH$-*c*-Hex	$CH_3C{\equiv}CCH{=}$  + KNH_2, liq. NH_3	241
$HC{\equiv}CC(R){=}CH_2$	$H_2C{=}C{=}C{=}CHOMe$ + $RMgBr$, Et_2O, CuBr	[4]
R = alkyl,*c*-C_6H_{11}		
$RC{\equiv}CCH{=}CH_2$	$ClCH_2CH{=}CHCH_2Cl$ + 3 $NaNH_2$ + RBr, liq. NH_3	52,53
R = Et, Pr, Bu		
$RC{\equiv}CCH{=}CH_2$	$RC{\equiv}CH$ + $BrCH{=}CH_2$, Et_2NH, Et_2O, CuI, $Pd(PPh_3)_4$	217
R = Hex		
$CH_3C{\equiv}C$- 	$LiC{\equiv}C$-  + MeI, liq. NH_3	44
$HC{\equiv}CCH{=}CHCH{=}CHR$	$HC{\equiv}CCH_2CH(OTs)CH{=}CHR$ + KOH, H_2O or Et_2O	209,206
R = H, Me		
$HC{\equiv}CPh$	$BrCH_2CHBrPh$ + NaOEt, EtOH	167
$MeC{\equiv}CPh$	$LiC{\equiv}CPh$ + MeI, liq. NH_3	44
$PhC{\equiv}CPh$	PhCHBrCHBr + NaOEt, EtOH	167
$EtC{\equiv}CC{\equiv}CPh$	$EtC{\equiv}CBr$ + $PhC{\equiv}CH$, Cadiot-Chodkiewicz	213

$HC{\equiv}CCH{=}CHPh$	$HC{\equiv}CCH_2CH(OTs)Ph + KOH, Et_2O$	206
$HC{\equiv}CCH{=}C{=}CH_2$	$HC{\equiv}CCH_2C{\equiv}CH + LiOPh$ (catal.), MeOH	[4]
$PhC{\equiv}CC{\equiv}CPh$	$PhC{\equiv}CH + O_2$, Pyridine, CuCl	221
$HC{\equiv}CC{\equiv}CC{\equiv}CH$	$ClCH_2(C{\equiv}C)_2CH_2Cl + t\text{-}BuOK$, THF	181
$t\text{-}Bu(C{\equiv}C)_4t\text{-}Bu$	$t\text{-}BuC{\equiv}CC{\equiv}CH + O_2$, Pyridine, CuCl	221
$HC{=}CC(CH_2c\text{-}Hex){=}CH_2$	$LiC{\equiv}CC(CH_2Li){=}CH_2 + c\text{-}HexBr$, THF	74

KETONES

$HC{\equiv}CCOR$ R = Me, Pr, Ph	$HC{\equiv}CCH(OH)R + CrO_3, H_2O$, acetone, H^+	281
$HC{\equiv}CCH_2COEt$	$HC{\equiv}CCH_2CH(OH)Et + CrO_3, H_2O$, acetone, H^+	[4]
$HC{\equiv}CCH_2COMe$	$H_2C{=}C{=}CHSnBu_3$ + MeC(=O)Cl	[4]
$RC{\equiv}CCOPh$ R = alkyl	$RC{\equiv}CLi + ZnCl_2$, $Pd(PPh_3)_4$, PhC(=O)Cl, THF	106
$RC{\equiv}CCOMe$ R = alkyl, >C=C<, 1-cyclohexenyl)	$RC{\equiv}CLi + MeC(=O)NMe_2$, THF or Et_2O, then H_2O, H^+	103
$RC{\equiv}CCOR'$ general method	$RC{\equiv}CLi + (R'CO)_2O$, Et_2O	104
$RC{\equiv}CCOC{\equiv}CR'$ general method	$RC{\equiv}CLi + ZnCl_2$, THF, $Pd(PPh_3)_4$ + R'C(=O)Cl	106
$RC{\equiv}CCOPh$ R = alkyl	$RC{\equiv}CLi + PhC(=O)NMe_2$, THF or Et_2O then H_2O, H^+	104
$RC{\equiv}CCOCH{=}CH_2$ R = alkyl, phenyl	$RC{\equiv}CLi + ZnCl_2$, THF, $Pd(PPh_3)_4$ + $H_2C{=}CHC(=O)Cl$	106
$RC{\equiv}CCOR'$ R = alkyl, phenyl; R' = alkyl	$RC{\equiv}CLi + ZnCl_2$, THF, then R'C(=O)Cl	105

NITRILES AND NITROALKYNES

$RC{\equiv}CC{\equiv}N$ general method ($R \neq H$)	1. $RC{\equiv}CLi + ClC{\equiv}N$, Et_2O	155
$RC{\equiv}CC{\equiv}N$ general method	2. $RC{\equiv}CBr + CuC{\equiv}N$, LiBr, THF	229
$HC{\equiv}CCH_2CH_2C{\equiv}N$	$HC{\equiv}CCH_2CH_2OTs + NaC{\equiv}N$, DMSO	279

$RC{\equiv}C(CH_2)_nC{\equiv}N$ general method, $n \geq 2$	$RC{\equiv}C(CH_2)_nOTs + KCN$, DMSO	279
$t\text{-}BuC{\equiv}CNO_2$	$t\text{-}BuC(I){=}CHNO_2$ + solid KOH, heat	184
$RC{\equiv}CCH_2C{\equiv}N$ R = alkyl	$RC{\equiv}CCH_2Br + CuCN$, LiBr, THF	280

SELENIDES AND TELLURIDES

$MeC{\equiv}CSeEt$	$MeCHBrCH_2Br + 3\ NaNH_2$, liq. NH_3 then Se, then EtBr	133
$EtC{\equiv}CSeCH_2Cl$	$EtC{\equiv}CLi$ + Se, THF, then $BrCH_2Cl$	135
$EtSeC{\equiv}CSeEt$	$HC{\equiv}CSeNa$ + EtBr, then NaOEt, liq. NH_3	134
$H_2C{=}CHC{\equiv}CSeMe$	$ClCH_2CH{=}CHCH_2Cl + 3\ NaNH_2$ + Se, then MeI, liq. NH_3	132
$H_2C{=}CHC{\equiv}CTeMe$	$ClCH_2CH{=}CHCH_2Cl + 3\ NaNH_2$ + Te, then MeI, liq. NH_3	132
$MeC{\equiv}CTeEt$	$MeCHBrCH_2Br + 3\ NaNH_2$ + Te, then EtBr, liq. NH_3	133
$HC{\equiv}CCH_2SeEt$	EtSeSeEt + 2 Li, liq. NH_3, then EtSeLi + $HC{\equiv}CCH_2Cl$, EtOH + H_2O	[4]

SILICON, TIN AND PHOSPHORUS COMPOUNDS

(for some Si-compounds see under heteroaromatic compounds)

$HC{\equiv}CSiMe_3$	$HC{\equiv}CMgBr + Me_3SiCl$, THF	116
$MeC{\equiv}CSiMe_3$	$MeC{\equiv}CLi + Me_3SiCl$, Et_2O	120
$Me_3SiC{\equiv}CSiMe_3$	$BrMgC{\equiv}CMgBr + 2\ Me_3SiCl$, THF	117
$EtOC{\equiv}CSiMe_3$	$EtOC{\equiv}CLi + Me_3SiCl$, THF	123
$HC{\equiv}CCH_2C{\equiv}CSiMe_3$	$HC{\equiv}CCH_2OTs + BrMgC{\equiv}CSiMe_3$, THF, CuBr	227
$Me_3SiC{\equiv}CCH{=}O$	$Me_3SiC{\equiv}CLi + DMF$, then H_2O, H^+	102
$ClCH_2C{\equiv}CSiMe_3$	$ClCH_2C{\equiv}CLi + Me_3SiCl$, Et_2O + HMPT	121

$BrCH_2C{\equiv}CSiMe_3$	$BrCH_2C{\equiv}CLi$ + Me_3SiCl, Et_2O + HMPT	122
$Br(CH_2)_4C{\equiv}CSiMe_3$	$Br(CH_2)_4C{\equiv}CLi$ + Me_3Si Cl	123
$HOCH_2C{\equiv}CSiMe_3$	$LiOCH_2C{\equiv}CLi$ + 2 Me_3SiCl, THF, then H_2O, H^+	[4]
$H_2C{=}CHC{\equiv}CSiMe_3$	$H_2C{=}CHC{\equiv}CLi$ + Me_3SiCl, THF or Et_2O	123
$HexC{\equiv}CC{\equiv}CSiMe_3$	$HexC{\equiv}CC{\equiv}CMgBr$ + Me_3SiCl, THF	124
$HC{\equiv}CC{\equiv}CSiMe_3$	$HC{\equiv}CC{\equiv}CLi$ + Me_3SiCl, THF or Et_2O	118
$Me_3SiC{\equiv}CC{\equiv}CSiMe_3$	$LiC{\equiv}CC{\equiv}CLi$ + 2 Me_3SiCl, THF or Et_2O	117
1-F-C_6H_4-3-$C{\equiv}CSiMe_3$	1-F-C_6H_4-4-Br + $Me_3C{\equiv}CZnCl$, THF, $Pd(PPh_3)_4$	216
1-Cl-C_6H_4-2-$C{\equiv}CSiMe_3$	1-Cl-C_6H_4-2-Br + $Me_3SiC{\equiv}CZnCl$, THF $Pd(PPh_3)_4$	216
1-NO_2-C_6H_4-4-$C{\equiv}CSiMe_3$	1-Br-C_6H_4-4-NO_2 + $HC{\equiv}CSiMe_3$, Et_2NH, CuI, $Pd(PPh_3)_4$	218
1-$Me_3SiC{\equiv}C$-*naphthalene*	1-Br-naphthalene + $Me_3SiC{\equiv}CZnCl$, THF $Pd(PPh_3)_4$	216
o-$(HC{\equiv}C)$-C_6H_4-$(SiMe_3)$	PhC≡CH + 2 BuLi.*t*-BuOK + 2 Me_3SiCl, THF, then KOH, MeOH	124
$Me_2C{=}C{=}CHC{\equiv}CSiMe_3$	$Me_2C{=}C{=}CHBr$ + $HC{\equiv}CSiMe_3$, Et_2NH, CuBr, $Pd(PPh_3)_4$	218
$HC{\equiv}CCH(Bu)SiMe_3$	$LiC{\equiv}CCH(Li)Bu$ + 1 Me_3SiCl, then H_2O	[4]
$HC{\equiv}CCH(Ph)SiMe_3$	$LiC{\equiv}CCH(Li)Ph$ + 1 Me_3SiCl, then H_2O	[4]
$HC{\equiv}CCH(SMe)SiMe_3$	$LiC{\equiv}CCH(Li)SMe$ + 1 Me_3SiCl, then H_2O	[4]
$HC{\equiv}CCH_2SiMe_3$	$H_2C{=}C{=}CHMgBr$ + Me_3SiCl, Et_2O	127
$HC{\equiv}CSnBu_3$	$HC{\equiv}CMgBr$ + Bu_3SnCl, THF	119
$HC{\equiv}CC{\equiv}CSnBu_3$	$LiC{\equiv}CC{\equiv}CH$ + Bu_3SnCl, THF	120
$HC{\equiv}CPBu_2$	$HC{\equiv}CMgBr$ + Bu_2PCl, THF	125
$(HC{\equiv}C)_2PPh$	$PhPCl_2$ + 2 $HC{\equiv}CMgBr$, THF	126
$(MeC{\equiv}C)_3P$	3 $MeC{\equiv}CMgBr$ + PCl_3, THF	127

SULFIDES

(order: $C{\equiv}CS > C{\equiv}C(C)_nS$; $HC{\equiv}C > RC{\equiv}C$; non-conj. $C{\equiv}C$ > conj. $C{\equiv}C$)

$HC{\equiv}CSR$ R = Me, Et	$BrCH_2CHBrSR$ + 3 $NaNH_2$, liq. NH_3	172
$(HC{\equiv}C)_2S$	$(ClCH{=}CH)_2S$ + 4 $NaNH_2$, liq. NH_3	[4]

$MeC{\equiv}CSR$ R = alkyl or Ph	$HC{\equiv}CCH_2SR$ + NaOEt, liq. NH_3 or EtOH	238
$RC{\equiv}CSR'$ general methods	1. $RC{\equiv}CLi$ (or Na) + S_8 + R'Br, liq. NH_3 2. $RC{\equiv}CLi$ + R'SSR', R'SC≡N or $R'SSO_2R'$ THF, Et_2O or liq. NH_3	132 130-132
$RC{\equiv}CSCH_2Cl$ generally applicable	$RC{\equiv}CSLi$ + $BrCH_2Cl$, THF	135
$ClCH_2C{\equiv}CSMe$	$ClCH_2C{\equiv}CLi$ + $MeSC{\equiv}N$ or $MeSSO_2Me$, Et_2O	132, [4]
$ICH_2C{\equiv}CSMe$	$LiCH_2C{\equiv}CSMe$ + I_2, THF	[4]
$(RC{\equiv}C)_2S$ R = alkyl, $SiMe_3$	$RC{\equiv}CLi$ + SCl_2 Et_2O	139
$H_2C{=}CHC{\equiv}CSR$ R = alkyl	1. $RSCH_2C{\equiv}CCH_2SR$ + *t*-BuOK, THF or liq. NH_3	[4]
$MeC{\equiv}CC{\equiv}CSMe$	$MeC{\equiv}CC{\equiv}CLi$ + $MeSSO_2Me$, liq. NH_3	130
$MeSC{\equiv}CSMe$	$HC{\equiv}CNa$ + $CH_3SC{\equiv}N$, liq. NH_3	130
$Et_2NC{\equiv}CSPh$	F_3CCH_2SPh + Et_2NLi, Et_2O	[4]
$HC{\equiv}CCH{=}CHSR$ R = Me, Et	$HC{\equiv}CC{\equiv}CH$ + RSH, NaOEt, EtOH	270
$EtSCH{=}CHC{\equiv}CCH_2NEt_2$	$EtSCH{=}CHC{\equiv}CH$ + Et_2NCH_2OH $Cu(OAc)_2$	211
$EtSCH{=}CHC{\equiv}CC{\equiv}C$-*t*-Bu	$EtSCH{=}CHC{\equiv}CH$ + *t*-Bu$C{\equiv}CBr$, Cadiot-Chodkiewicz	213
$HC{\equiv}CCH_2SR$ general method	$HC{\equiv}CCH_2Cl$ (or Br) + RSNa, EtOH or MeOH	267
$HC{\equiv}CCH_2SCH{=}CH_2$	$H_2C{=}CHSLi$ + $BrCH_2C{\equiv}CH$, liq. NH_3	271
$RSCH_2C{\equiv}CCH_2SR$	$ClCH_2C{\equiv}CCH_2SR$ + RSNa, EtOH	268

SULFUR COMPOUNDS (MISCELLANEOUS)

$HC{\equiv}CCH_2SC{\equiv}N$	$HC{\equiv}CCH_2Br$ + $KSC{\equiv}N$, H_2O	[4]
$HC{\equiv}CCH_2N{=}C{=}S$	$HC{\equiv}CCH_2NH_2$ + $Cl_2C{=}S$, KOH, H_2O CH_2Cl_2	278

MeC≡CSOMe	MeC≡CLi + MeS(=O)Cl, THF	139
MeC≡CSOEt	MeC≡CSEt + $NaIO_4$, H_2O, MeOH	282
$MeC{\equiv}CSO_2Et$	MeC≡CSEt + H_2O_2, MeCOOH	282
$(RC{\equiv}C)_2SO$ R = Me, Et	RC≡CLi + $SOCl_2$, Et_2O	139
$(MeC{\equiv}C)_2SO_2$	$(MeC{\equiv}C)_2S$ + H_2O_2, MeCOOH	282
t-BuC≡CS(=O)NHPh	*t*-BuC≡CLi + PhN=S=O, THF	110
MeC≡CSC≡N	MeC≡CSLi + ClC≡N, Et_2O	137
t-BuC≡CSC≡N	*t*-BuC≡CSLi + ClC≡N, Et_2O	137
$MeC{\equiv}CSSiMe_3$	MeC≡CSLi + Me_3SiCl, Et_2O	138
MeC≡CSSMe	MeC≡CSLi + $MeSSO_2Me$, THF	[4]
BuC≡CSC(=O)Me	BuC≡CSLi + MeC(=O)Br, Et_2O	136
BuC≡CSC(=O)OMe	BuC≡CSLi + ClCOOMe, Et_2O	136
$EtC(=S)SCH_2C{\equiv}CH$	EtMgBr + CS_2, then $HC{\equiv}CCH_2Br$, THF	[4]

THIOLS - Last and least...

$HC{\equiv}CCH_2SH$	$HC{\equiv}CCH_2Br$ + NaSH, H_2O	268
$MeC{\equiv}CCH_2SH$	$MeC{\equiv}CCH_2Br$ + NaSH, H_2O	268

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