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Preparative Polar Organometallic Chemistry 1

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Preparative Polar Organometallic Chemistry Volume 1

Foreword by Paul von Ragué Schleyer

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Foreword

Polar organometallic compounds are indispensable for the synthetic chemist. As this book shows, these almost ideal reagents are easy to prepare with high specificity under mild conditions and yet react quite readily with a great variety of substrates. Many compounds can be metallated directly at positions which would otherwise be difficult to substitute. Functional groups and heteroatoms already present in a molecule direct metallation to sites in their vicinity. The rules which govern polar organometallic chemistry often are not dominated by the usual π-delocalization and inductive effects; dipolar interactions, chelation, polarization, etc. often can be much more important. This affords novel synthetic opportunities. A good example is the development of a basically new type of aromatic substitution chemistry not based on positively charged intermediates.

Seebach's injunction, "Thinking of polar organometallic compounds as carbanions is an impoverishment rather than a simplification" (International Symposium, Chemistry of Carbanions, Durham 1984), stresses the need to consider the metal not only as an integral, but perhaps also as the key component of these reagents. Rather than wandering off as solvated cations and acting as uninvolved spectators, the metals, rather than the anion moieties, can initiate and govern the subsequent reactions. To the founders of this field, e.g. Grignard, Ziegler, Gilman, Wittig, and their followers, the metal was critical. The title of Schlosser's book, "Polare Organometalle", certainly was apt. If stabilized, carbanions certainly may be free, but the majority of reagents used synthetically are based on weak acids. That ion pairs or ion clusters are the reactive intermediates, must be appreciated in order to understand this chemistry. Thus, the accelerating effects of donor solvents, polydentate ligands, and crown ethers is better attributed, in most instances, to the lowering of the degree of aggregation rather than to the separation of cation from anion.

The complexity of this chemistry, which we are only now beginning to understand from a detailed mechanistic viewpoint, is part of its richness. Many reagents, typically based on lithium, the other alkali metals, or magnesium are available, sometimes in combination. These reagents may vary greatly in their effectiveness. The choice of solvents, ligands, and reaction conditions also can be critical. Success may depend on the design of the experiment, but the literature is not easily searched. How much better it would be to seek the guidance of experts. This book provides the examples and the advice one needs.

Laboratory work is Lambert Brandsma's passion. His techniques, developed over three decades, are not only remarkable in their simplicity, but also in their effectiveness. Brandsma and his associate, Hermann Verkruijsse, learn more about the course of a reaction by use of a simple thermometer than most other chemists with the full array of spectroscopic equipment.

This series of books are remarkable in documenting the practical knowledge accumulated through actual personal experience. Each reaction and procedure has benefited from the critical perspective of the authors. Indeed, “Why run a reaction for a day when it’s over in two minutes?” We learn not only how to prepare a given compound but, more important, how, in general, polar organometallic reactions can be carried out most effectively.

Erlangen, December, 1986

Paul von Ragué Schleyer

Preface

The application of organometallic reagents in organic synthesis has a long and impressive history. During the past ten to fifteen years the significance of the main group organometallics, in particular of organoalkali and Grignard reagents, has been augmented by the phenomenal rise of (organo) transition metal compounds as intermediates in stoichiometric and catalytic processes. The extensive literature concerning polar organometallic compounds has been summarized in several review articles and books dealing with various synthetic and more theoretical aspects.

Nevertheless, the design of appropriate reaction conditions for a particular synthesis, based on the vast amount of data, remains difficult. Many of the published procedures are product-directed, which means that the reaction conditions applied do not always reflect the reactivities of starting compounds and intermediates. Very low concentrations, in some cases, may be a necessary requirement for obtaining satisfactory yields, but they are often the natural consequence of working with small quantities of starting compounds. For someone who is not familiar with this particular field, but who intends to perform a reaction on a larger scale, this may lead to an uneconomic use of solvents. Some procedures do not mention seemingly minor but critical experimental details, either because the authors do not realize that they could be essential or because the editors and referees of the particular journal may regard detailed descriptions unnecessary or undesirable.

The present series, the first volume of which deals with polar organometallic intermediates derived from sp^2-compounds, is intended to be a laboratory manual for chemistry students at all higher educational levels and for research workers in industry and universities. The books are a continuation of our series of manuals in the field of acetylenes and allenes.

A large number of experimental procedures show how polar organometallic intermediates of the broad spectrum of organic compounds can be generated and how these can be functionalized with various electrophilic reagents. All procedures (on the 0.05–0.10 molar scale) have bee preparatively checked in the laboratory of the authors. The reaction conditions recommended reflect reactivities of starting compounds and intermediates directly. This may save the user a considerable amount of time.

The books also contain several variants of known synthetic methods and a number of practical tips, which have proved their usefulness in the experience of the authors. Also the indexes guide the user in the selection of the most suitable conditions for a new metallation-functionalization experiment.

We are indebted to Dr. A. J. Lawson (Managing Director of the Beilstein Institut, Frankfurt am Main, FRG) for valuable advice in preparing the manuscript.

Financial support and gifts of chemical from AKZO Chemie, Deventer, DSM, Geleen, Dyosynth BV, Oss, Océ-Andeno, Venlo and Shell, Amsterdam are gratefully acknowledged.

Utrecht, December 1986

L. Brandsma
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Appendix

Introduction to Volume 1, and Instructions for the Use of this Book and its Indexes

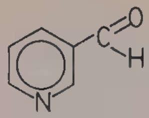
The first part of this series deals with the preparation and reactivity of sp^2-polar organometallic intermediates. Although particularly the prefix sp^2 may be subject to criticism, we propose this definition for metal compounds in which one can imagine the replacement of an sp^2-hydrogen atom in an olefinic, allenic, cumulenic, aromatic or heteroaromatic compound by a metal atom. During the preparation of this volume we have frequently consulted the reviews by Gilman and Morton [4]; Mallan and Bebb [5]; Gschwend and Rodriguez [1] and the books of Schlosser [3] and Wakefield [2]. We had to make some selection from the vast number of metallation and functionalization reactions reported in literature. Much relevant polar organometallic chemistry has been carried out on the basis of relatively cheap commercially available substrates, e.g. furan, thiophene, a number of benzene derivatives and ethyl vinyl ether. Satisfactory procedures have been developed for starting compounds, e.g. 1,3-thiazole derivatives, 1-methylcyclopropene and alkyl vinyl sulfides. These are also included in this volume. Many of the procedures in our book are a stage in the development of more ideal concepts and have been preceded by less satisfactory experiments or complete failures. We found it useful to describe these attempts also, as far as they seem rational.

Experimental information for synthetic problems in the field of sp^2-polar organometallic chemistry can be obtained most efficiently *via* the Indexes and Chap. II. In many cases, however, this searching procedure does not give a complete solution, so that one has to look for procedures or combinations of procedures that give the best approximation. We shall illustrate the searching procedure with a few examples. In all cases one should read Chap. II before carrying out the derivatization reaction!

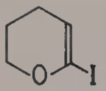
1. 2-Hexylthiophene

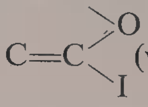
a) Index I gives the basic reagents, which may be used to metallate thiophene in the 2-position.

b) Look into Index II under the part of Chap. V (heteroaromatic compounds) and notice that the book contains a procedure in which 2-lithiothiophene is alkylated with **butyl** bromide. It will be clear that the procedure will also apply in the case of the synthesis of 2-hexylthiophene.
General information about alkylations may be obtained from Chap. II, while the introduction to the procedure for 2-butylthiophene (Exp. 3 of Chap. V) gives more specific details.

2. 

a) Look into Index I for the structural formula of pyridine: apparently the book contains only procedures for the 2- and 4-metallation.
b) Consult after this "disappointing" experience Index II: under Chap. V one will notice that the required 3-lithiopyridine can be obtained by reaction of 3-bromopyridine with butyllithium in THF. However, the last column gives only two examples of functionalization, viz, deuteration and methylthiolation.
c) After this incomplete answer one should look into Index III under the heading "Formylations with DMF". There are two procedures which seem good models, namely the reaction of 2-lithiated thiazoles with DMF in THF: thiazole and pyridine derivatives have a number of common properties. Application of the procedure for the formylation of 2-lithiated thiazoles (Exp. 19 of Chap. V, including notes) gives the best guarantee for a successful formylation of 3-lithiopyridine.

3. 

a) Index I shows that the α-metallation of 2,3-dihydropyran is feasible using the couple BuLi · *t*-BuOK in THF.
b) As 2,3-dihydropyran is a hetero-substituted olefine, one has to look under the part of Chap. IV of Index II. Since the iodination of the metallated ether is not mentioned in the last column, one has to look into:
c) Index III under "Halogenations". The procedures for 2-iodofuran and iodonorbornadiene (Ref [77]) seem to be good approximations. However, consulting these procedures reveals that it is the lithio derivative which is reacted with iodine. This means that the α-potassiated dihydropyran has to be transformed into the lithium compound. In the introduction to the procedure for the α-metallation of dihydropyran it is mentioned that this can be done by addition of anhydrous LiBr. Since one has to read Chap. II prior to carrying out the iodination, one will undoubtedly notice the K/Li exchange under the heading "Exchange between counter ions". In the generalized equation for the halogenations in Chap. II the metal is indicated to be either Li or MgX.
d) In view of the structure system  $C{=}C\begin{matrix}\diagup O \\ \diagdown I\end{matrix}$ (water-sensitive), special conditions for the work-up might be necessary. It should be pointed out that this book in general will not give an answer on problems concerning the stability of compounds in relation to the work-up.

Chapter I
Organometallic Reagents, Solvents and Laboratory Equipment

1. Strongly Basic Reagents used in Organic Synthesis

Most pK values of sp^2-hydrogen atoms in the various types of organic compounds lie in the range of 30–40 [8]. With the exception of some heterocyclic compounds (e.g. 1,3-thiazole, 1-methylimidazole, polyfluorobenzenes, dimethylformamide and its sulfur analogue) the kinetic acidity of sp^2-hydrogens in organic compounds is much lower than that of the ethynyl sp-hydrogen in terminal acetylenes. As a result of the available basic reagents, **alkyllithiums** are most frequently used for deprotonation. The same holds if the organometallic intermediate is to be generated via halogen-lithium exchange from a bromo or iodo derivative [8, 10].

Though for some deprotonations **lithium dialkylamides** are sufficiently strong, one may prefer to use alkyllithium in particular cases, for example when a functionalization with an amine-sensitive reagent is carried out (CH_3I, ClCOOR, etc.): this may react competitively with the dialkylamine formed from the reagent during deprotonation of the substrate. There are other reactions in this volume in which lithium dialkylamides are the base of choice. Butyllithium is unsuitable, if an sp^2-hydrogen atom has to be removed from a substrate containing sp^2-linked bromine, since bromine-lithium exchange may compete with deprotonation. The desired reaction can be performed with lithium diisopropylamide (LDA) which has little ("thermodynamic") tendency to replace bromine [11]. Furthermore, for the abstraction of the acyl-protons in dimethylformamide and -thioformamide, LDA is preferred over butyllithium. Lithium amides have been successfully applied to protect formyl groups; they give adducts $RCH(NR_2)(OLi)$ [12–15].

Alkali amides MNH_2 are weaker bases than lithium dialkylamides. In this book their application as deprotonating agents is confined to a few cases: cyclopropenes, for example, are easily deprotonated by potassium amide in liquid ammonia at low temperature [16].

The basic reagent for most reactions proceeding via (polar) organometallic intermediates is ***n*-butyllithium** (Compare Ref. [232]). It is commercially available, mostly as a dilute (e.g. 1.5 mol/l) solution in hexane, and can be stored at room temperature for an unlimited period if kept in a well-closed bottle under nitrogen or argon. The price even for purpose in the laboratory is relatively low, particularly if it is purchased in larger amounts (cylinders, containing 25 or more litres)[1], and most research chemists therefore will not spend time by preparing the reagent. If desired, however, this can be done in three ways. A sodium-containing impurity (1–2 %) in

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[1] Butyllithium was supplied by Chemetall GmbH, Frankfurt am Main, FRG, the European producer of lithium compounds, Grignard reagents, alcoxides, etc.

the lithium is required for the preparation [17]. *n*-Butyllithium in hexane or pentane can be made by stirring chipped lithium (flattened with a hammer to a thickness of about 1 mm and subsequently cut directly into the solvent) with *n*-butyl chloride in one of these solvents. The reaction is carried out conveniently at 20–35 °C and if the scale is modest (of the order of 0.5 molar), all the halide can be added at once. Pieces of broken glass added to the mixture serve to continuously scratch the lithium chloride from the metal (in the absence of the glass the reaction is much slower due to coating of the metal surface with salt). Secondly, a solution of butyllithium in Et_2O can be obtained by controlled addition of *n*-butyl chloride to lithium chips in Et_2O [18]. The reaction proceeds much more easily (at 15–20 °C) than in pentane or hexane, and addition of glass is not necessary. The yields in both cases are high since "Würtz-coupling" to octane and dehydrohalogenation occur to a slight extent only. A solution of *n*-butyllithium in diethyl ether can also be prepared at -20 to -25 °C by dropwise addition of butyl bromide to a mixture of chipped lithium and ether. Under favourable conditions yields may be as high as 95 % (based on C_4H_9Br). The lower temperatures are necessary to suppress formation of octane. One advantage in this preparation is that the lithium bromide remains in solution, so that after the reaction only the excess of lithium has to be filtered off. Small amounts of octane formed in this preparation and butanol, formed by the entrance of traces of oxygen may give rise to difficulties in the purification of volatile products in syntheses with this butyllithium. For this reason one might prefer to prepare ethyllithium from ethyl bromide and lithium. This can be done in a similar way; about 30 % more ether should be used since the solubility of EtLi · LiBr at low temperatures is less than that of BuLi · LiBr. The solutions of EtLi · LiBr and BuLi · LiBr can be kept unchanged for at least two weeks when stored at -20 °C under inert gas.

The considerably higher prices of *sec*- and *tert*-butyllithium may indicate that these reagents (also solutions in volatile alkanes) are more difficult ot prepare than *n*-BuLi. We observed that *t*-butyl chloride does react with chipped lithium in hexane at room temperature, but the solution obtained did not contain *t*-butyllithium. We assume therefore that any *t*-BuLi is destroyed immediately by reaction (dehydrohalogenation) with the chloride. With freshly prepared, finely divided lithium it seems to be possible to prepare *t*-BuLi in diethyl ether at low (~ -40 °C) temperatures [213]. Most research chemists, however, will prefer to purchase an alkane solution of *t*-butyllithium (in spite of the relatively high price), because the procedure of making a lithium dispersion (in paraffin oil), followed by replacing the dispersion solvent by alkane or diethyl ether and adding *t*-butyl chloride is very laborious. Furthermore, an ethereal solution of this reagent can be stored for a very limited period only even at very low temperatures.[2]

For most syntheses *sec*- or *tert*-butyllithium can be replaced by the very reactive combination of ***n*-butyllithium** and **potassium *t*-butoxide in THF** [236, 239]. This is a clear solution which can be prepared by mixing solutions of *t*-BuOK in THF and *n*-BuLi in hexane at < -90 °C. The specific advantage of the BuLi · *t*-BuOK-THF combination is the possibility of carrying out deprotonations that give thermolabile metallic intermediates. Effectively, the reagent can be considered as an

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[2] We are indebted to Dr. J.H. Wieringa for informing us about his experiences in preparing *t*-BuLi.

equimolar mixture of butylpotassium and lithium *tert*-butoxide [238], compare [237]. Deprotonation with this reagent yields a potassium derivative which, however, can be easily transformed into the lithio compound by addition of a THF solution of anhydrous lithium bromide [241].

Although the reagent **BuLi · TMEDA in hexane** is kinetically less effective than BuLi · *t*-BuOK in deprotonations, it has the advantage of being applicable at higher temperatures, since it is stable. Several deprotonations with BuLi · TMEDA have been carried out at temperatures in the region +40 to +70 °C (see e.g. Ref. [20]).

Another strongly basic system is obtained when an apolar solvent, such as pentane or hexane, is mixed with equimolar quantities of *t*-BuOK, BuLi and TMEDA. In contrast to the original mixture BuLi · *t*-BuOK [161], this base-"cocktail" has a good solubility (above −40 °C) in the apolar solvents [21, 22]. A similar system can be made on the basis of sodium *t*-butoxide [22]. The advantage of these cocktails is that rapid deprotonations can be carried out in an inert solvent at temperatures up to 0 °C (at higher temperatures the TMEDA is attacked) under practically homogeneous conditions. After completion of the deprotonation the required solvent for the functionalization reaction may be added.

A solution of **BuLi · TMEDA** is not stable in THF, since this solvent is readily attacked at room temperature by the chelation complex, leading to formation of lithium ethenolate and ethene. Butyllithium reacts with THF even in the absence of TMEDA: after a few hours at 40 °C, all butyllithium has reacted (at 1-molar concentrations) [23]. The BuLi · *t*-BuOK complex metallates THF "preparatively" at −70 °C within 75 min [9]. At about −40 °C the 1-potassiated THF undergoes a rapid cycloelimination to ethene and potassium ethenolate.

Methyllithium and phenyllithium are considerably less effective deprotonating bases than the alkyllithiums already mentioned, and their use as deprotonating reagents is therefore limited. Ethereal solutions of $CH_3Li \cdot LiBr$, $CH_3Li \cdot LiI$ and PhLi · LiBr can be prepared from the corresponding halides and lithium in a way similar to that of the other organolithium reagents.

Transformation of secondary amines R_1R_2NH into the corresponding lithium amides is usually carried out with BuLi in Et_2O or THF. This reaction is very rapid, even with sterically hindered amines having pK values as high as 37. The pK values of the aliphatic and cycloaliphatic secondary amines increase with increasing bulkiness of the group R [25, 30]. One exception is bis(trimethylsilyl)amine $(Me_3Si)_2NH$, with pK 29.5 [25]. Most substituted lithium amides have a good solubility in diethyl ether and THF. The solvents are not readily attacked by these bases.

Of the non-substituted **alkali amides**, lithium and sodium amide are commercially available. In many cases, however, the bases are prepared from the alkali metals in liquid ammonia, which is often also used as the solvent for the subsequent reaction [6, 7]. A small amount of ferric nitrate or chloride is necessary for the conversion of the metals into the amides. The actual catalyst is zero-valent iron, which is formed as a black or grey colloidal solution. In contrast to the other alkali amides, potassium amide is soluble in liquid ammonia and therefore it is kinetically more active. Deprotonations of compounds having pK values near that of ammonia are more complete with potassium amide than with the insoluble sodium or lithium amide [26]. If desired, lithium or sodium amide can be isolated in a "dry" state by simply evaporating the ammonia by warming the reaction flask in a water bath at 40 to 50 °C. The remaining solid can be scratched from the glass by means of a curved spatula after which the last traces of adhering ammonia can be removed by evacuation. The solids thus obtained are presumably more reactive than the commercial powders. They must be stored under nitrogen in well-closed bottles.

2. Solvents and some Reagents: Their Analysis, Purification and Storage

Whereas before 1960 most syntheses with organolithiums were carried out in diethyl ether, the use of **tetrahydrofuran** (THF) has increased enormously during the last 25 years. In part this is the consequence of the fact that butyllithium, one of the most important starting reagents, has become commercially available as a solution in hexane: in the earlier investigations alkyllithium solutions were always prepared in diethyl ether, THF giving unsatisfactory results ("Würtz-coupling"). In many of the metallation and derivatization reactions THF gives better, and in some cases other results than in diethyl ether. The same holds for Grignard preparations. The THF purchased from the supplier sometimes contains peroxides and traces of water. The peroxides can be easily detected by shaking the solvent with an aqueous solution of alkali iodide. The intensity of the developed brown colour gives a rough impression of the peroxide content. Of course it is also possible to use special test strips. Small amounts of water are less easily detectable. One may roughly determine the amount of peroxides plus water by adding, from a burette, a red solution of triphenylmethyllithium in THF and hexane (obtained by allowing equimolar amounts of triphenylmethane and butyllithium in THF-hexane to stand for 1 hour at 20 °C) to a sample of the THF [9]. Prior to this analysis, the THF sample is flushed with dry nitrogen in order to replace dissolved oxygen. Water and peroxides can be removed in one combined operation by shaking the solvent with freshly machine-powdered KOH (~100 g/2 l) and subsequently distilling the filtered solvent from $LiAlH_4$ (~1 g/l). The solvent is best stored in brown flasks under nitrogen.

Diethyl ether can be purified by a similar procedure. For most purposes the distillation can be omitted.

Liquid ammonia is less favoured as a solvent than THF or Et_2O. Many chemists believe that reactions in ammonia have to be carried out in a specially adapted reaction vessel, provided with a dry-ice condenser.

In order to remove the water, the ammonia is distilled from sodium and condensed in the reaction flask. For reactions on a preparative scale (0.1 mol or more) this drying procedure may be time-consuming, since quantities of 200 ml or more are required. It should be stressed, however, that in these cases this procedure is not necessary if the water content is 0.1 to 0.2 % (which is normal for a good quality of ammonia). The water can be "neutralised" with small pieces of sodium, added to the stirred liquid. The amount of metal necessary to give a persisting blue colour gives a good impression of the water content. The required volume of ammonia can be obtained by allowing the liquid to flow from the cylinder through a plastic tube into the flask. Large cylinders often contain a dip tube which reaches nearly the bottom. The liquid ammonia is obtained by turning on the tap while the cylinder is standing upright. Since the plastic tube connected with the cylinder may contain moisture, at least 100 ml of liquid should be allowed to flow through the tube into the hood before the end of the plastic tube is placed into the flask. If no dip tube is present the cylinder is placed upside down in the manner indicated in A.I. Vogel, Textbook of Practical Organic Chemistry, 4th ed., p. 98.

Ammonia has a relatively high heat of evaporation (1370 kJ/kg or 934.7 kJ/l) and therefore many reactions, carried out at the boiling point (-33 °C) can take place in normal round-bottomed flasks without a reflux condenser. The evaporation may be reduced by surrounding the reaction flask with cotton wool.

Hexamethylphosphoric triamide $(Me_2N)_3P{=}O$ (HMPT, in English often abbreviated as HMPA) is a rather expensive solvent. However, in most cases a small amount as co-solvent is sufficient to obtain the desired acceleration of the reaction [27] (either a deprotonation or a functionalization with an alkyl halide or an epoxide). The commercial product often contains water and other impurities and purification is therefore necessary. This may be carried out by dissolving commercial *t*-BuOK (free from complexed *t*-BuOH) in the liquid (10 to 15 g/l) and subsequently distilling at a low pressure (0.5 mm Hg or lower, so that the solution need not be strongly heated. (b.p. ca. 50 °C/0.5 mm Hg). The distillate, which may contain a small amount of *t*-BuOH, is redistilled at water pump pressure (b.p. ca. 110 °C/15 mm Hg). HMPT is a cancer-suspect compound, and only persons who have the reputation of being careful workers should be allowed to work with it. Strongly basic reagents, notably butyllithium, react with HMPT [28]: at temperatures above -20 °C $(Me_2N)_2P{=}O$ and Me_2NLi are formed. Deprotonations with these very strong bases in the presence of HMPT therefore have to be carried out at very low temperatures.

Dimethylsulfoxide (DMSO) is sometimes referred to as an aprotic solvent, because weakly basic anions, e.g. $^{\ominus}CN$, $CH_3{-}CO\overset{\ominus}{C}H{-}COCH_3$, $RS^{\ominus}$ and $PhO^{\ominus}$ are not solvated by hydrogen-bridging in DMSO [29]. With its pK value of 31 (MSAD-scale, [8]) it is certainly more acidic than HMPT. Acetylenic anions $RCH_2C{\equiv}C^{\ominus}$ (the pK of alkylacetylenes on the MSAD-scale is about 25) have a limited kinetic stability, and upon heating protonation occurs leading to the 2-alkynes $R{-}C{\equiv}C{-}CH_3$ [9, 71]. This means that the DMSO protons are exchanged relatively easily, and the consequence is that in the generation and functionalization of the more strongly basic sp^2-“anions” DMSO cannot be applied as a solvent or co-solvent. It may be purified by a similar procedure as applied in the case of HMPT.

Amines. Although reagents with a high purity and a low water content are commercially available, a drying procedure may be necessary, especially for reactions on a very small scale or when the reagents have been stored for a long time and the bottle has been opened several times. Trace amounts of water in *tertiary* amines (pyridine, TMEDA, triethylamine) can be detected by putting 1 ml in a thoroughly dry reagent tube under dry nitrogen and subsequently adding 0.5 ml of trimethylchlorosilane [9]. Even in the case of minute amounts of water a precipitate of the amine · HCl is formed.

Pyridine, triethylamine and also secondary amines can be dried by shaking with freshly machine-powdered KOH (100–200 g for each litre) and subsequently distilling the decanted liquid. Perfectly dry TMEDA can be obtained by distillation in a partial vacuum (about 100 mm Hg) from $LiAlH_4$ [9].

The best way to obtain dry benzene, dichloromethane, chloroform, carbon tetrachloride and a number of reagents that form azeotrops with water, such as thiophene, is to distill the compounds until clear liquid flows through the condenser. After collection of about 10% of the starting amount, the condenser should be cleaned and the distillation continued to ensure that no more turbid liquid is formed in the condenser. The remaining liquid in the distillation flask is perfectly dry.

Abbrevations

The following abbreviations are used in this volume for some solvents and reagents.

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

3. Laboratory Equipment and some General Remarks Concerning Performance of the Procedures

The reaction vessel (Fig. 1) for most procedures in this volume is a round-bottomed flask with three vertical necks, fitted with a mechanical stirrer on the middle neck (a glass rod of no less than 5 mm diameter with a blade, and connected to a stirring motor)[3]. On the other necks are placed a dropping funnel, combined with a gas-inlet, connected to a supply for inert gas, and a thermometer combined with a gas-outlet. Deviations from or variants on this equipment are indicated in the descriptions of the respective procedures. Prior to charging the reaction flask and dropping funnel with solvents and/or reagents, the air in the apparatus is purged

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[3] The denotation "efficient stirring" means, that the reaction mixture in the flask is rotating in such a way that the reagents are immediately distributed over the whole volume of the reaction mixture. Vigorous stirring means: stirring at a high rate, causing a fast rotation of the reaction mixture with much turbulence: this may be necessary when introduced gases have to be absorbed efficiently or when the viscosity of the reaction mixture has increased considerably by formation of a thick suspension.

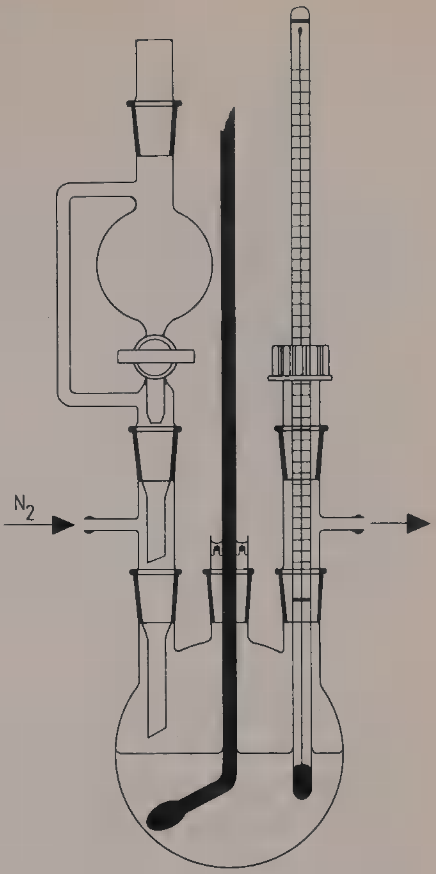

Fig. 1

with inert gas. This may be done by keeping the end of an inlet tube connected to the supply of inert gas on the bottom of the flask and dropping funnel, while vigorously intruducing the gas. Alternatively one could also consider evacuating the apparatus and subsequently admitting the inert gas. During the reaction, a slow stream of inert gas is led through the flask. If sudden strong cooling is necessary, the intensity of the flow should be increased accordingly.

Instead of continuously introducing inert gas one may connect a balloon filled with gas (1 to 1.5 litre) to the flask. Of course, all connections should then be gas-tight so that during cooling no air can leak into the flask.

Some organometallic intermediates (e.g. carbenoids, *ortho*-metallated halo-aromatics or hetero-aromatics) are highly unstable and in spite of sufficient cooling, partial decomposition (brown or black colour) may occur when the reaction mixture is swept, or splashes onto the upper part of the flask, which is less strongly cooled. This can be avoided by adjusting the rate of stirring: vigorous agitation of the reaction mixture is mostly unnecessary after the reagent has been introduced and the exothermic reaction has ceased. Decomposition may be further limited by placing the greater part of the reaction flask in the cooling vessel and covering the upper part with cotton wool. If liquid nitrogen is used care should be taken that the flask is not in continuous contact with the liquid nitrogen: occasional cooling for a few seconds, combined with a good isolation of the upper part of the flask, will often be sufficient.

Solutions of basic organometallic reagents such as *n*-butyllithium can be stored in an Erlenmeyer flask provided with a device for the introduction of inert gas while

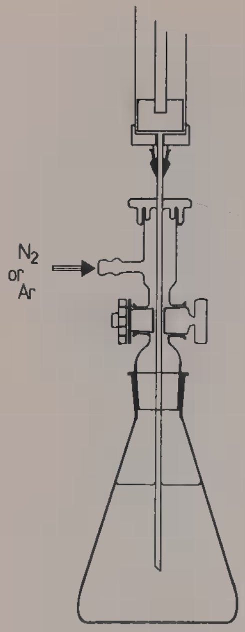

Fig. 2

drawing part of the solution by means of a syringe. The device is closed by a rubber septum. Prior to drawing the solution, the end of the injection needle is placed in the upper part, the upper tap is opened and nitrogen or argon is supplied. The plunger is slowly drawn upward, so that inert gas is sucked into the reservoir. Subsequently the needle is withdrawn and the plunger pushed downward. This operation is repeated once or twice, then the lower tap is opened so that the needle can be stuck through the hole and the end placed into the solution. The desired volume is sucked into the reservoir by slowly moving the plunger upward, while the inert gas is still being introduced. The same flask can be used to store other organolithium solutions. In the case of *n*-alkyllithium in hexane or pentane the flask can be kept at room temperature, solutions of *n*-alkyllithium or phenyllithium in diethyl ether, containing complexed lithium salts, must be stored in the refrigerator (−20 °C). If the concentration does not exceed 1 mol/l, all reagent remains in solution during storage at this temperature, so that warming to room temperature is not necessary. Particularly in the case of ethereal reagents it is advisable to periodically determine the titer of the solutions. This may be done according to the procedures described in Refs. [31–34].

Many Grignard solutions in Et_2O or THF may be stored at room temperature in the same sort of flask. Most solutions remain homogeneous at reagent concentrations of about 1 mol/l, otherwise some warming (30–40 °C) may be applied to effect dissolution of the salts.

4. Safety, Handling and Methods of Disposal

4.1 Introduction

Strongly basic reagents such as alkyllithium and alkali amides have the reputation of being dangerous compounds that have to be handled with the greatest possible respect. Traces of oxygen are said to cause fire hazards, while painful burns are predicted if these strong bases come into contact with the skin. Indeed solutions of *tert*-butyllithium (commercially available as a solution in pentane) are extremely flammable, and also concentrated solutions of *n*-butyllithium may ignite upon contact with air. Addition of water to dry sodamide or (notably) potassium amide (left after evaporating the solvent ammonia) gives rise to an extremely vigorous reaction which sometimes proceeds explosively. If solutions of alkali amides in liquid ammonia or solutions of organolithium are spilled on the skin[4], the skin may be affected in a way similar to that caused by aqueous hydroxide if it is not washed off with water immediately. The specific conditions (inert atmosphere in the reaction flask, carefully dried solvents and glassware) and precautionary measures required for syntheses with these strong bases makes them less suitable for introduction in preliminary courses which are often followed by large groups of students.

We wish to point out, however, that the dangers involved in working with these reagents in the laboratory are not exceptionally great and probably less so than during syntheses with lithium aluminum hydride. The spilling of a dilute solution of ethyl- or butyllithium in diethyl ether or hexane (concentration up to 2 mol/l) is not likely to result in a fire in most cases, and burns on the skin can largely be prevented by immediately washing with plenty of water. Working with strongly basic reagents is not the prerogative of a select group of skillful academic research chemists. The penalty for not maintaining a completely inert atmosphere or anhydrous conditions during a synthesis with a strong base is in most cases only a low yield or an impure product. The student who, after a few experiments, has acquired sufficient experimental skill has gained access to a very important and rich field of chemistry. There is no reason to exclude strong bases from advanced practical laboratory courses. The information about handling, safety and precautionary measures, and disposal of mixtures given in this section is mainly intended for working on a laboratory scale.[5] Alkali metals and a few other reagents, often used for the preparation of very strong bases and purification of solvents, are included.

4.2 Organoalkali Reagents

Butyllithium is commercially available as a solution in hexane in concentrations varying from 15 to 90 %. The dilute 15 % solution (1.5 mol/l) is most frequently used for syntheses on a laboratory scale. It is delivered in steel containers (containing up

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[4] It is advisable to wear smooth-fitting protective disposable gloves while working with alkali metals and strongly basic reagents.

[5] With special equipment *n*-butyllithium can be handled without problems on a technical scale; information is supplied by Chemetall GmbH, Reuterweg 14, D-6000 Frankfurt am Main, FRG.

to more than 100 l) equipped with a dip tube and a connection for inert gas, and in glass bottles provided with a self-sealing rubber septum closed with a screw cap. The solution is removed from the bottle in the following way. After filling the chamber of the syringe with the volume of inert gas equal to or slightly more than the required volume of the solution, the needle is inserted through the septum and the plunger is pushed downwards.[6] Then the end of the needle is placed into the solution and the plunger is retracted until the required volume of solution has been pushed (by the excesspressure) into the syringe. The needle is then withdrawn from the bottle while carefully fixating the plunger with the hand. In order to prevent part of the solution from flowing out of the needle, the syringe is held upside down after withdrawal from the bottle. The solution is immediately introduced (by pushing the plunger downwards) into the reaction flask or dropping funnel, which has been previously filled with inert gas. During this operation, the end of the needle is directed away from face and body and any other persons in the near vicinity (unexperienced or nervous persons should not carry out this operation for the first time without supervision!). The septum on the storage flask is covered with parafilm. The bottle with butyllithium solution should not be stored in the refrigerator or in a cold place: air may leak through the septum.

If much synthetic work is to be carried out regularly with butyllithium, it may be economical to purchase a cylinder containing several liters of butyllithium. The solution is transferred into a number of dry 0.5 to 1 litre round-bottomed or conical flasks. It is advisable to empty the container in one operation, and to carry out this operation with two persons. For a large container (27 l) this takes 1.5 to 2 hours.

The required number of dry flasks and well-greased (silicon grease should be used) stoppers should be put in the hood. To avoid turbulence in the upper part of the flasks during filling, the ventilation is switched off. The air in the flasks should be completely replaced by nitrogen or (preferably) argon, after which the stopper is placed in the flask. If round-bottomed flasks are used, this may be done by successive evacuation and admission of inert gas. In the case of conical flasks the end of the inlet tube is kept on the bottom of the flask and a vigorous stream of inert gas is introduced during a 1–2 min period (conical flasks may implode during evacuation!). The container is connected to the cylinder containing inert gas by a *brand-new* plastic tube which has previously been filled with inert gas. Provided that sufficient excesspressure is present in the container, the solution will flow through the plastic tube into the flask which should be maximally filled to 90%. During filling, the pressure is gradually released, so that the flow will stop in time. Directly after filling, the flask is closed with the stopper which is sealed with parafilm. The other flasks are then filled without delay.[7] In order to minimize the entry of air during filling, a moderate flow of inert gas may be introduced into the upper part of the flask. When a flask is needed, the stopper is replaced by the adapter as shown in Fig. 2. For the storage of LiBr-containing ethereal solutions of alkyllithium prepared from alkyl halide and lithium *vide infra*.

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[6] T. Durst in "Comprehensive Carbanion Chemistry"; E. Buncel, T. Durst (Ed) Elsevier, 1984, p. 239.

[7] In view of the possibility of spillage, protective gloves should be worn.

Cleaning and Maintenance of the Syringe

The syringe should be cleaned within half an hour after use. After removal of the plunger, the parts are rinsed successively with water and acetone (or ethanol). After blowing air through the needle, the separate parts are dried for a few hours at 100–120 °C (a quicker way is to use a fohn). In order to prevent the plunger from sticking, it should be greased regularly: a grease based on teflon is recommended.

Transfer of Organolithium Solutions to the Reaction Vessel

The reaction flask and equipment used for a synthesis with organometallic reagents should be dry. This may be done by keeping the parts at a temperature of 100–120 °C for some hours or overnight. A quicker and also satisfactory way is to first rinse the glassware with acetone, followed by blowing with a vigorous stream of air to remove the acetone vapours, and finally by blowing with hot air (using a fohn) for several minutes. After cooling to room temperature, the apparatus (see Fig. 1) is constructed.

In the next stage, the air in the apparatus is replaced by inert gas. The most economical way to do this is to evacuate the apparatus (water pump) after having made the glass-joints "gas-tight" with grease. Inert gas is then admitted. This evacuation-admitting-inert-gas operation is repeated once. Alternatively a vigorous flow of (dry) inert gas may be blown through the apparatus for a few minutes (keeping the inlet tube of the bottom of the flask and the dropping funnel). Solvents and reagents are then placed into the flask or dropping funnel, while the thermometer outlet combination is temporarily removed and a moderate flow of inert gas is introduced *via* the inlet. Solids (e.g. *t*-BuOK or chipped lithium) are added by means of a special funnel. A weak to moderate flow of inert gas is maintained throughout the experiment. During the cooling-down period, the flow should be increased, It is more economic, however, to close the inlet and to connect the outlet with a balloon, containing 1–1.5 l of inert gas (after having replaced the air in the apparatus). In this case it is essential that the stirrer and all the glass joints are "gas-tight", so that during the cooling process no air can leak into the flask.

Disposal of Residues of Organolithium Reagents

If by some cause the quality of a solution of an organolithium reagent has deteriorated, it may be desirable to dispose of the solution. This can be done in a safe way by cautiously pouring the solution onto a large amount of crushed ice in a beaker (half-filled) while introducing nitrogen (we have even done this operation without the use of inert gas). The empty flask is subsequently rinsed with water. Smaller amounts of organolithium solutions may be added by means of a syringe. The organolithium solutions should never be deactivated by applying the addition in reverse order (i.e. adding water or ice to the solution). We have no experience with *tert*-butyllithium; but a safe way of disposal could be the addition of an equal volume of THF to the cooled solution and subsequently allowing the temperature to gradually rise to 20 °C (the THF reacts with *t*-BuLi to give ethene and lithium ethenolate $H_2C{=}CHOLi$).

Lithium aluminium hydride is often used for drying solvents such as THF or Et_2O. When most of the solvent has been distilled off, the solvent remaining in the distillation flask will still contain $LiAlH_4$. Disposal may be carried out by pouring this solution onto finely crushed powdered carbon dioxide in a beaker, rinsing the flask with a small amount of THF in Et_2O and adding this also to the dry ice. Another way is to add an excess of ethyl acetate with cooling to the residue after diluting with 100 or 200 ml of Et_2O. After termination, ice water is added cautiously.

Storage and Disposal of Sodium- and Potassium tert-*butoxide*

Alkali- *tert*-butoxide, in particular the potassium compound, is frequently used in this book, in combination with *n*-butyllithium. In many cases the 1 : 1 molar mixture of *n*-BuLi and *t*-BuOK can be used instead of the dangerous and (much more) expensive *tert*-butyllithium. To maintain a good quality, the powder should be stored under indert gas in flasks which are closed by rubber stoppers. Glass stoppers should not be used, as there is the possibility that they may become stuck due to alkali residues. Disposal of bad-quality material can best be carried out by cautiously adding it (in small portions) to a sufficient amount of 96 % ethanol followed by water.

4.3 Alkali Metals

Storage

The best way to store alkali metals is, in our opinion, to keep them under dry paraffin oil in a flask closed by a rubber stopper (as a glass stopper can get stuck). An atmosphere of inert gas above the oil will give an additional protection against oxidation. The storage under protective liquid involves the necessity of rinsing the metal by dipping in pentane or diethyl ether in order to avoid contamination of reaction products, i.e. residues of light-petrol or paraffin oil adhering to the metal. Particularly in the case of potassium this cleaning operation should be done with the utmost care due to the flammability of the material.

Weighing and Introducing Metals into the Reaction Flask

Lithium can be weighed and handled without any danger. It is usually delivered in cylindrical sticks of 1 to 1.5 cm in diameter. After complete removal of the protective liquid with a tissue, the required amount of metal is cut off and subsequently flattened with a hammer on a clean surface (e.g. iron block) to a thickness of a few mm. Using scissors, the flattened piece is then cut into chips. If a solution of alkyl- or aryllithium is to be prepared, the chips are cut as small as possible (e.g. 10 × 3 × 2 mm). For the preparation of lithium amide in liquid ammonia the size may be considerably larger. In both cases the metal is directly cut into the liquid. The uncoated cutting surface facilitates dissolution.

If the quality of sodium is good (no crusts of oxide and hydroxide) the weighing operation is relatively simple. The required amount of material is introduced into a conical flask filled with nitrogen, after removing the adhering liquid with a dry tissue or cloth and dipping the lumps in dry diethyl ether (kept in a beaker). The flask is then closed with a stopper, and the lumps are removed, one at a time, from the flask with the aid of tweezers and cut directly into the flask containing the liquid ammonia (in 1–2 g pieces). Some pieces may fall outside the flask by accident, therefore the bottom of the hood should be made dry prior to cutting the metal!

Lumps of potassium are sometimes covered by a rather thick crust of oxide and hydroxide or peroxide (yellow). The safest, and most simple way, is to carry out the operations of cleaning the metal, weighing, and, introduction into the reaction flask as follows. A beaker and two conical flasks (the size depending on the amount of metal to be weighed) are filled with dry paraffin oil (200–300 ml), dry diethyl ether or pentane (200–300 ml) and inert gas, respectively. The flasks are closed with rubber stoppers. The flask with inert gas (preferably argon!) is placed on the scale. A piece (5–15 g) of metal is picked up by means of tweezers from the storage flask and the crust is cut off. During this operation the metal is held in one hand (wearing gloves) above the beaker containing the paraffin oil. The piece of metal is then dipped into the ether or pentane and then put directly into the flask standing on the scale. Other pieces of metal are treated in the same way, until the flask contains the amount required. The metal is then introduced into the reaction flask in the same way as in the case of sodium. If relatively small amounts (up to 20 g) of metal have to be cleaned and cut, much less diethyl ether or pentane is needed for rinsing off the protective liquid. While cutting, care should be taken that no water is present in the direct neighborhood. Unexperienced persons should not attempt to carry out this operation without supervision.

Storage and Disposal of Alkali Metal Residues

Crusts and small pieces cut off from sodium and potassium lumps during the weighing procedure should be collected and stored under protective liquid in separate flasks closed by a rubber stopper. Limited amounts of sodium residue (up to 30 g) can be destroyed in the following way. The residue is filtered off on a plug of glass wool that is placed in a funnel. The filtrate can be used again for storage purposes. The plug with the residues of sodium is put in a beaker containing 96 % ethanol (100 ml for each 10 g). The mixture is allowed to stand until the solid has disappeared. In some cases the dissolution may be accelerated by gradually adding a 1 : 1 mixture of ethanol and water after the bulk of the residues has disappeared. One should **never** try to destroy potassium residues with ethanol as this is likely to result in an explosion or fire. The best way is to filter off the residues on glass wool and to bury the plug containing the residues under sand on a piece of waste ground. The following way of disposal (carried out twice by us) of potassium residues may be considered. The glass wool and the chips of potassium are separated and spread on the bottom of a pan with a diameter of 15 to 20 cm and a height of ~20 cm. Subsequently, the metal and the plug of glass wool are covered with a layer of dry sand about 5 cm thick (the kind of sand used for extinguishing). After stirring vigorously, (necessary to scratch the protective oil from the metal) an additional layer of 15 cm of sand is put into the pan. Water is then cautiously poured on the sand until the sand surface is covered with a few mm of water. Care should be taken that during this addition the sand surface remains as flat as possible. The potassium remains in the lower part of the pan. Very small particles of metal may occasionally be swept to the surface with the bubbles of hydrogen and ignite. We believe that it is possible to destroy potassium residues weighing up to 50 g in this way. One should wait at least 5 h before spreading the contents of the pan outside. The filtered protective liquid is returned in the storage flask and used again for residues.

Diethyl ether or pentane which has been used for the purpose of rinsing off the protective liquid from the metal, may contain very small pieces of metal and disposal should be carried out with the utmost care. In the case of sodium, addition of a 70:30 mixture of ethanol and water (or methanol) to the ether or pentane will presumably be effective. For potassium we are reluctant to recommend the use of ethanol. Although one might object against the following unsophisticated way of disposal, we have found it suits our purpose well. Pour out the ether or pentane outside on a stone surface, and rinse the flask or beaker (as it could still contain minute particles of metal) with water (after the residue of the solvent has completely evaporated!). One might also consider pouring the solvents slowly onto the stone surface of the thoroughly dried and well-ventilated hood. Tissues which have been used for removing protective liquid from the lumps of metal may also contain small particles of metal. They should **never** be thrown in the waste container! In the case of sodium one should put them in a beaker and add plenty of water. Tissues containing potassium can be burned outside, or covered with ice water in a beaker. Sodium is often used (chips or wire) for the removal of traces of water from organic solvents. After some time, the metal is covered with a thick white crust of hydroxide. This may make it difficult to estimate the amount of metal present in the flask. One should, therefore, never add ethanol to the metal residue. The greater part of the wire or lumps should first be removed from the flask (by holding the flask upside down above a beaker and shaking it or picking it with a pair of tweezers) The remaining small amount of metal in the flask is subsequently dissolved in a sufficient amount of 96 % ethanol, the bulk is destroyed in small quantities in the usual way.

Lithium residues (if there are any) can be disposed by means of a 70:30 mixture of ethanol and water.

4.4 Alkali Metal Amides

Although lithium and sodium amide are commercially available, the suspensions prepared in liquid ammonia are much more reactive, and most reactions with these bases are carried out in this solvent. Lithium and sodium amide can be obtained in a "dry" state by completely evaporating the ammonia, the last traces in a water-pump vacuum. The powders obtained are very reactive and must be stored under nitrogen (or argon) in well-closed bottles with rubber stoppers. Potassium amide is not commercially available and we have never attempted to obtain it free from ammonia as we feel it to be a hazardous operation. Contact of the "dry" amides with water should be avoided. If, by accident, the ammonia has evaporated, no water or alcohol should be added to the remaining solid, since this may cause an extremely vigorous (sometimes even explosive) reaction. Liquid ammonia should be added first, followed by 96 % ethanol or powdered NH_4Cl (which is added dropwise or portion wise to excess). During the preparation of alkali amides in liquid ammonia a mirror of alkali metal is formed in the upper part of the flask or in the necks. Since any unconverted alkali metal may give rise to fire hazards during the aqueous work up of the reaction product, one should take care that all metal deposits stuck to the glass are converted into alkali amide. After the bulk of the dissolved metal has been converted, the suspension is stirred very vigorously (manual swirling is in some cases more effective). Subsequently the equipment is removed temporarily and liquid ammonia is allowed to flow from the plastic tube connected to the cylinder along the inner side of the necks. If during the preparation of alkali amides part of the suspension or solution frothes out of the flask, it may be desirable (since one does not know exactly how much has remained in the flask) to destroy the amide (in the case of the preparation of KNH_2 the chance of frothing is very small). A 20–50 % excess of powdered ammonium chloride is then added in small portions and the ammonia is allowed to evaporate, after which water is added. This method can also be applied when the ammonia still contains dissolved alkali metal.

5. Experimental Procedures

5.1 *n*-Butyllithium in Diethyl Ether

$$C_4H_9Br + 2Li \xrightarrow[-20\,°C]{Et_2O} C_4H_9Li \cdot LiBr$$

Apparatus: Fig. 1, 2 l

Scale: 1 molar
Lithium (18 g, 2.57 mol, Note 1) is flattened with a hammer to 1.5 mm thickness and subsequently cut into the flask (chips of 2 × 10 × 1.5 mm) containing 800 ml Et_2O. The ether is cooled to −25° and the air purged with inert gas (2 l/min during 1–2 min). From the dropping funnel, containing 150.7 g, 1.1 mol, 10 g butyl bromide is added in one portion. After a few minutes a turbidity (detachment of the Li_3N coating) appears and a distinct rise of the temperature is observed. When, after about 10 min, the reaction has subsided, the remainder of the bromide is added dropwise over 1 h, while keeping the temperature of the mixture between −15 and −20 °C. The black coating disappears almost entirely from the metal which has a bright silver-like colour. After the addition is complete, stirring (at ca. −15 °C) is continued for an additional hour. The temperature is then allowed to rise to 0° and

the glow on the metal gradually disappears. In some experiments the "ball" of lithium chips, which has previously formed, disintegrates. The solution is then poured into the storage flask (Fig. 2), which previously has been filled with inert gas (it is not necessary to filter off the lithium chips). During this transfer operation a fast stream (2 to 3 l/min) inert gas is passed through the reaction flask to protect the solution against attack by oxygen. Diethyl ether is added to bring the solution to a volume of 1 litre. After gentle shaking or swirling (homogenization), the titer is determined: this is usually close to 1 molar (corresponding to a yield of ca. 90 %).

EtLi · LiBr, PhLi · LiBr and MeLi · LiBr are prepared in exactly the same way. MeLi · LiI can be obtained in a slightly lower yield (~80 %) from CH_3I and Li at ca. −10 °C. *n*-Butyllithium can also be prepared from lithium chips and butyl chloride in Et_2O, by a procedure analogous to that of BuLi · LiBr. The reaction is conveniently carried out at temperatures around +20 °C. The lithium chloride does not form a soluble complex with BuLi, but precipitates, so that the supernatant solution contains little salt. After decanting the clear solution through glass-wool (to remove the excess of lithium), the salt is rinsed 3 to 5 times with small amounts of Et_2O. These ethereal solutions are decanted and added to the main solution. Yields of at least 80 % are obtained.

Notes

1. Lithium containing 1–2 % of sodium must be used. Analytically pure lithium gives lower yields.
2. The remaining lithium is immediately destroyed by adding 150 ml of ethanol (containing about 30 % of water).

5.2 *n*-Butyllithium · TMEDA (in Hexane)

Apparatus: Fig. 1, 500 ml

Scale: 0.10 molar
A solution of 0.105 mol of butyllithium in 75 ml of hexane is placed in the flask. Dry TMEDA (12.18 g, 0.105 mol) is added over 1 min with stirring at a moderate rate. The temperature usually rises by 15–20 °C and cooling is not necessary. A clear solution is formed. If the reaction is to be carried out in the presence of Et_2O or THF as a cosolvent, the obtained hexane solution of BuLi · TMEDA is cooled to below −20 °C and the desired volume of Et_2O or THF is gradually added with cooling. There is no point in carrying out reactions with BuLi · TMEDA in hexane-THF at temperatures higher than −10 °C, since the THF is rapidly attacked.

5.3 Butyllithium, Complexed with Potassium *tert*-Butoxide in THF

Apparatus: Fig. 1, 500 ml

Scale: 0.10 molar
A solution of 0.105 mol of butyllithium in 75 ml hexane is added to the flask by means of a syringe. The solution is brought to a temperature of −100 °C (occasional cooling with liquid nitrogen) and a solution of 0.105 mol (11.9 g) of

t-BuOK in 80 ml of THF is added dropwise with moderate rate of stirring (Note 1). During this addition, which takes about 10 minutes, the internal temperature is maintained closely around −100 °C. The complex is a clear solution having the same light-yellow colour as the solution of butyllithium in hexane. It can – and should – be used directly after its preparation. When the solution is kept for 2 h at −65 °C and diethyl disulfide is added subsequently, (2-ethylthio)tetrahydrofuran, (b.p. 56°/14 mmHg, n_D^{20} 1.4838), is obtained in ~70 % yield. Above −40 °C the α-potassiated tetrahydrofuran undergoes a rapid cycloelimination with formation of ethene and potassium ethenolate ($H_2C{=}CH{-}OK$).

Notes

1. In the case of vigorous stirring the solution is swept up to the upper part of the flask, where the glass is less cooled, so that reaction with the THF may occur.

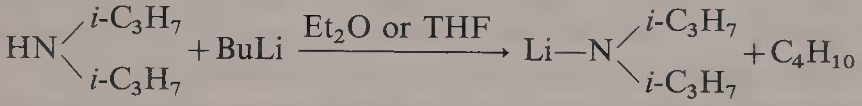
5.4 Butyllithium, Complexed with Sodium- or Potassium *t*-Butoxide and TMEDA in Hexane or Pentane

Apparatus: Fig. 1, 500 ml

Scale: 0.10 molar

0.10 Mol (9.6 or 11.3 g) of powdered sodium or potassium *t*-butoxide and 50 ml of hexane or pentane are placed into the flask. The mixture is cooled to −70 °C and a solution of 0.10 mol of butyllithium in 70 ml of hexane is added over a few seconds with efficient stirring. The suspension is then cooled to −40 °C and 0.10 mol of TMEDA is added in one portion. In the case of sodium *tert*-butoxide a homogeneous solution is formed, the addition of TMEDA to the BuLi-potassium *tert*-butoxide mixture results in a fine suspension. The mixtures are kept below −30 °C since at 0 °C or higher the TMEDA is attacked by the base.

5.5 Lithium Diisopropylamide (LDA)



$$HN(i\text{-}C_3H_7)_2 + BuLi \xrightarrow{Et_2O \text{ or } THF} Li{-}N(i\text{-}C_3H_7)_2 + C_4H_{10}$$

Apparatus: Fig. 1, 500 ml

Scale: 0.05 molar

A solution of 0.055 mol (Note 1) of butyllithium in hexane (38 ml) is added (using a syringe) to a flask containing 40 ml of Et_2O or THF and cooled to below 0 °C. Subsequently a mixture of 0.055 mol (5.5 g) of diisopropylamine and 20 ml of THF or Et_2O is added dropwise over a few minutes. Temperature control during this addition is not essential; however,in the metallation reaction, which is usually carried out with the lithium dialkylamide at low temperatures, the solution may be cooled to 0 °C or lower. The formation of LDA is very fast, even in the temperature range −20 to −60 °C, so that the solution obtained can be used for further syntheses after only a few minutes.

Other secondary amines (piperidine, morpholine, dicyclohexylamine) can be converted into the lithium amides in a similar way. Most lithium dialkylamides are solutions, if prepared as described above (concentrations ~0.5 mol/l), but upon cooling to very low temperatures (−70 °C) they may become suspensions. Lithium dimethylamide is only slightly soluble in Et_2O, even at room temperature.

Notes

1. The slight excess is to compensate for losses due to traces of moisture and oxygen.

5.6. Lithium Amide in Liquid Ammonia [6]

$$Li + NH_3 \xrightarrow[-33\ ^\circ C]{\text{liq. } NH_3} LiNH_2\downarrow + 1/2\ H_2\uparrow$$

Apparatus: 2 l round-bottomed flask (three vertical necks), equipped with a mechanical stirrer, a gas-outlet (curved glass tube, 5 mm internal diameter, with glass joint). A stopper is placed on the third neck.

Scale: 1 molar

The flask is charged with about 1 litre of liquid ammonia. This is done by placing the end of a plastic tube (about 10 mm internal diameter), connected to the ammonia cylinder, in the flask and cautiously turning on the tap of the cylinder (Note 1 and page 7). This operation takes 2 to 3 min. Stirring is started and ferric nitrate (ca. 400 mg, Note 2) is added. One gram of lithium is directly cut into the flask in 4 to 6 pieces (Note 3) causing vigorous evolution of ammonia vapour (due to the exothermic dissolution of the metal and its conversion into the amide). The stopper is therefore not yet placed on the flask. As soon as the blue color of the dissolved metal has disappeared and a white to greyish (Note 4) suspension has formed, an additional 2 g of lithium is cut in (Note 5). The remainder of the 1.0 mol of metal is introduced in the same way. In order to prevent penetration of moisture during the conversion of the lithium, a loose plug of cotton wool is placed on the third neck. The conversion of the total amount of lithium requires about 30 min. When it is completed, the cotton wool is replaced by the stopper (or dropping funnel if a further conversion is to be carried out). The amide prepared in this way is a white, (or light-grey) rather thick suspension, which settles out (after stopping the stirrer) very slowly. If desired the amount of ammonia for 1 mol of $LiNH_2$ can be reduced to about 600 ml. In that case, however, the conversion of the last portion of metal may take longer and careful observation is necessary to ensure that no small pieces of unconverted metal are present in the thick suspension.

Notes

1. The plastic tube may contain some moisture. It is therefore advisable to rinse the tube a few seconds with the stream of liquid ammonia, before the end of the tube is placed into the reaction flask.

2. If considerably less is added, the conversion of the lithium is slow and may take longer than 1 hour; on the other hand, in the case of much more ferric nitrate the aqueous work-up may be difficult due to the formation of a thick gel of ferric hydroxide.
3. If pre-cut lithium is introduced, the conversion may be slower, because the surface of the metal is coated with oxide and nitride. During cutting a red to blue glow appears on the surface of the metal, due to adsorption of ammonia vapour.
4. The actual catalyst, zero-valent iron, is partly adsorbed on the amide.
5. Severe frothing, resulting in loss of part of the suspension, may occur if all metal is added in a few minutes.

General Note for the Preparation of Alkali Amides

A good quality of ammonia, containing not more than 0.1 to 0.2 % of water, is used. The quality should be checked before the catalyst is added. This may be done by adding a small piece of metal (0.05 g of Li, 0.2 g of Na or K) to the stirred liquid. If the solution remains blue after 5 min, the quality is good, if the colour disappears, an additional piece is introduced. This operation is repeated until the blue colour persists.

5.7 Sodamide in Liquid Ammonia [6]

$$\mathrm{Na} + \mathrm{NH_3} \xrightarrow[-33\ ^\circ\mathrm{C}]{\text{liq. NH}_3} \mathrm{NaNH_2}\downarrow + 1/2\ \mathrm{H_2}\uparrow$$

Apparatus: 2 l round-bottomed flask (vertical necks), equipped with a mechanical stirrer, a stopper and a vent (curved glass tube, 5 mm internal diameter, with a glass joint).

Scale: 1 molar
About 1 l of liquid ammonia (see Exp. 6) is placed in the flask and ca. 400 mg of ferric nitrate is added with stirring. After a few seconds 3 g of the 1 mol of sodium are added in 0.5 g pieces (Note 1). Normally the blue color disappears after 10 min and a grey to black solution is formed. The remainder of the sodium is then introduced and in most cases the conversion is complete after 30 min. The greyish suspension which has formed, settles out soon after stirring has stopped leaving a supernatant solution which is grey to black. Some unconverted sodium in the upper part of the flask may be washed down by vigorous stirring for a short time.

For some reactions "dry" sodamide is required. This can be prepared by placing the flask in a water bath at 35–40 °C after the conversion has completed. During this operation the outer necks are open. When the stream of ammonia has become faint, the stirrer is replaced with a stopper. A stopper and an outlet are placed on the other necks and the flask is evacuated by means of water aspirator, first without external heating. When the pressure has dropped below 100 mm Hg, the flask is warmed for an additional 15 min at ca. 35 °C. Nitrogen is then admitted and the solid is scratched from the glass using a curved spatula. Then the flask is evacuated again, and warmed at 40 °C for 30 min. The grey powder (partly small lumps) is transferred into a storage flask and the lumps broken by pressing with a glass rod. The flask is filled with nitrogen or (preferably) argon and closed with a well-greased glass stopper or rubber stopper.

Notes: (consult also the procedures for $LiNH_2$!)

1. After removing the paraffin oil or light petrol from the sodium (by dipping the lumps into diethyl ether, or by means of a tissue) the required amount is weighed and then cut into 0.5 g pieces, which are kept under ether. If oxide crusts are on the metal, these should be removed with a knife.

5.8 Potassium Amide in Liquid Ammonia [6]

$$K + NH_3 \xrightarrow[-33\,^{\circ}C]{\text{liq. } NH_3} KNH_2 + 1/2\ H_2\uparrow$$

Apparatus: 2 l round-bottomed, one-necked flask (without stirrer) and 2 l round-bottomed three-necked flask, equipped with a funnel containing a plug of glass wool.

Scale: 1 molar
About 750 ml of liquid ammonia is placed in the flask (see Exp. 6) and ferric nitrate (ca. 100 mg, Note 1) is introduced with manual swirling. Subsequently 1 mol of potassium, cut in pieces of about 1 g (Note 2), is introduced as quickly as possible (Note 3). A rubber stopper with a hole of ~5 mm diameter is placed on the flask. The conversion of the potassium usually takes about 15 min, forming a grey solution. This solution has to be freed from small particles (1–2 mm^3) of potassium covered with a crust of oxide (Note 4). This can be done in the following way. A loose plug of glass wool is placed into a funnel and is kept in place by means of a glass rod. The funnel is put on the middle neck of the reaction flask (2 l) with the other necks open. The solution of potassium amide is then cautiously poured (some splashing may occur until the glass of the funnel has cooled to the temperature of the ammonia) on the glass wool. This operation takes about 2 minutes. The small pieces of potassium are collected on the glass wool (Note 5). After this operation the flask is equipped with the stirrer, etc.

Notes

1. The required amount of ferric nitrate is considerably less than that necessary for the preparation of the other alkali amides, possibly because potassium amide is soluble, and thus the zero-valent iron is not inactivated by adsorption.
2. Before cutting, the lumps of potassium (10–20 g each) are freed from paraffin oil by means of a tissue. To compensate for some loss due to the presence of thin oxide crusts, 41 g instead of 1 mol is weighed, then immediately cut and the pieces put into a beaker containing 100–150 ml of dry diethyl ether. Potassium which has been stored for a very long time may contain a thick crust of oxide.

This can be removed by means of scissors. It is advisable to carry out this operation before removal of the paraffin oil: this protects the metal against oxidation. After the introduction of the potassium into the ammonia, the diethyl ether containing minute pieces of metal, has to be removed: in our opinion the safest way is to pour the ether away on a piece of waste ground. Addition of *t*-butylalcohol to the ether does not give sufficient guarantee that the potassium is destroyed, since the potassium particles may be covered by *t*-butoxide; when the ether is poured into the waste container, the particles may react with the other material in the container, causing fire hazards.

3. No frothing will occur in contrast to the preparation of lithium amide: the heat of dissolution of potassium (to K^+ and e^-) is less than that of lithium.
4. If these particles are not removed, fire hazards will most probably occur during the aqueous work-up and extraction with ether of the products formed in the following reaction.
5. The safest way to destroy these potassium particles is to throw the plug into a beaker, containing water (!). The flask in which the potassium amide has been prepared may contain minute particles of potassium. These should be also destroyed by quickly rinsing the flask with plenty of water (!) immediately after it has been poured empty. (Compare also Section I-4.)

Chapter II
Reactivity of Polar Organometallic Intermediates

1. Introduction

Conversions via polar organometallic intermediates are among the most frequently applied procedures in organic synthesis. Since chemists usually strive to attain satisfactory yields of products with the highest possible purity, considerable effort must be expended in finding the most favorable reaction conditions. This may be done by varying concentrations, temperature or other conditions systematically. A much easier and often applied procedure is to mix the reactants in high dilution (on the order of 0.1 mol per litre or less) at a low temperature, and then either allow the temperature to rise slowly, or maintaining the low temperature for a long period. Indeed, some reactions give good results only when carried out in a relatively large amount of solvent at very low temperatures (e.g. the generation of *o*-Li—C_6H_4—Br and of *o*-Li—C_6H_4—NO_2 from BuLi and 1,2-dibromobenzene [35] or 1-bromo-2-nitrobenzene [36], respectively. In most cases, however, synthetic operations can be performed successfully at more practical and economical concentrations of 0.5 to 1 mol/l or higher. Then heating effects are often significant and routine observations with a thermometer can serve as a probe of the course of the reaction (more reliable than the appearance of a thin precipitate or a colour change); the selection of the most favorable temperature range is thus facilitated. Some conversions do not give problems, since they generally are fast, even at low temperatures (e.g. carboxylations of RLi with CO_2, coupling with carbonyl compounds, reactions with disulfides and trialkylchlorosilane). Selections of reaction conditions, such as solvent and counter ion, can, in principle, be derived from analogous reactions described in the literature. However, this often requires an extensive, and complicated literature search.

It is the aim of this chapter to provide some guidance in the selection of reaction conditions. Useful data are given about the scope, characteristics, typical conditions and trends for various derivatization reactions with sp^2-polar organometallic intermediates. This information is based on a critical consideration of relevant literature and on our own experimental experience.

2. General Remarks About Reactivity

Edwards and Pearson [37] have proposed qualitative relationships between the reactivity of nucleophiles and their basicity and polarisability. Anions, such as cyanide, thiolate, sulfide and iodide were used to obtain quantitative reactivity data, mainly from rate measurements in aqueous solution. The reactivity of these species was concluded to be largely determined by basicity and polarisability, their relative importance depending on the type of reaction. For nucleophilic attack on carbon (the familiar S_N2 reaction with alkylating agents), polarisability was concluded to be more important than basicity, whereas the reactivity towards acyl carbon seemed to parallel mainly basicity. The HSAB-principle [38] evolved from these considerations is now often used to explain the outcome of reactions with nucleophiles [39, 40] particularly those with mesomeric or "ambident" structures.

The HSAB-principle may be criticized as being too "opportunistic": the qualitative "hard" and "soft" assignments for reacting centers are used to explain rather small regio preferences, which reflect energy differences of only a few tenths of a Kcal/mol. However, the HSAB-principle is soundly based [41]. Basicity and polarisability may be used (with care) to predict qualitatively relative reactivities of a series of nucleophilic species.

The sp^2-organometallic reagents, to which this volume is devoted, are derived from derivatives RH with pK values roughly in the range between 25 and 40. Compounds such as $ClCH{=}CHCl$ and $HC({=}S)NMe_2$ are probably the most acidic, while the pK values of benzene and simple alkenes lie in the upper part of the range [8]. With the exception of allenic ($C{=}C{=}C^{\ominus}$) and cumulenic ($C{=}C{=}C{=}C^{\ominus}$) anions, all derived species have their charge localized on one sp^2 carbon atom. Polarisabilities of the organometallic centers in this group of species will be comparable. Hence, one would expect the (thermodynamic) basicities of the organometallic intermediates to determine their reactivity toward "electrophilic" reagents, provided that the solvent, counter-ion, aggregation state, and concentration are the same. We have made a number of comparisons, some in the form of competition experiments, with a series of sp^2-polar organometallic intermediates, and have observed reactivities of species varying significantly with basicity. These observations will be discussed in more detail below as well as in Chaps. III–VI.

3. Alkylation Reactions

3.1 Reactivity of the Various Types of Alkylating Agents

The most familiar reaction in organic chemistry, usually called alkylation, involves nucleophilic attack on saturated aliphatic (or alicyclic) carbon. The alkylation agents (most with halogen as a leaving group) may be subdivided as follows:

a) Primary alkyl halides.
b) Secondary alkyl halides (e.g. $i\text{-}C_3H_7Br$, $c\text{-}C_6H_{11}Br$).
c) Tertiary alkyl halides.
d) Allyl halides (e.g. $H_2C{=}CHCH_2Br$).
e) Propargyl halides (e.g. $HC{\equiv}CCH_2Br$).
f) Benzyl halides (e.g. $PhCH_2Cl$).
g) 1-Haloethers (e.g. $ClCH_2OCH_3$).
h) 1,2-Dihaloethers (e.g. $BrCH_2CH(Br)OC_2H_5$).
i) α-Halonitriles (e.g. $BrCH_2C{\equiv}N$) and α-haloesters (e.g. $BrCH_2COOC_2H_5$).

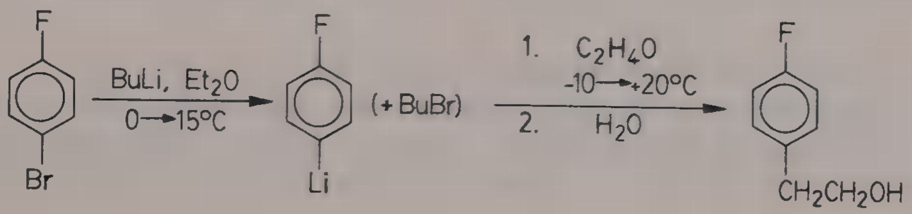
j) Haloacetals (e.g. $BrCH_2CH(OC_2H_5)_2$.
k) Epoxides (e.g. epoxyethane).

Instead of halogen one could consider another leaving group, such as sulfate or sulfonate.

In this volume, it suffices to illustrate alkylation reactions with a few representative examples. Some alkylations are not expected to give satisfactory results and have not been carried out, e.g. reactions with cycloalkyl halides or with *t*-alkyl halides where 1,2-eliminations predominate. Neither did we investigate alkylations with $XCH_2C{\equiv}N$ and XCH_2COOR' ($X=$halogen), as an extremely rapid subsequent reactions of RM with the cyano and ester groups should take place.

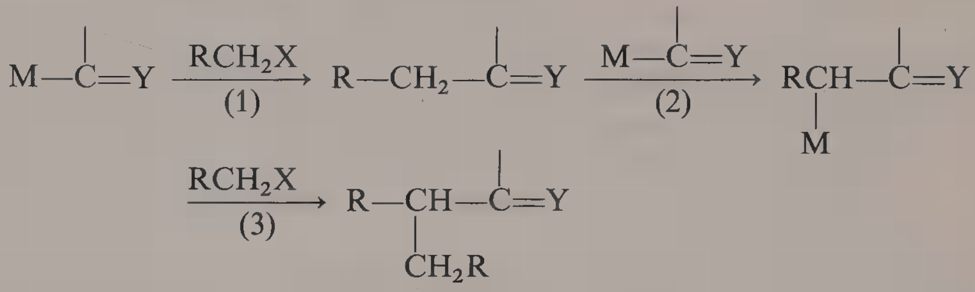
Compared to other types of "electrophilic" reactions, alkylations are generally slow (some very reactive reagents, e.g. $Et_3O^{\oplus}BF_4^{\ominus}$, are exceptions). Derivatization with unstable polar organometallic intermediates (e.g. $MC(=S)NMe_2$, 2-thiazolyl-M, *o*-M—C_6H_4—F, $MC(Cl)=CHCl$) have to be carried out at low temperatures, in some cases even at −100 °C or lower. The most common solvents have moderate polarities (e.g. THF and Et_2O). However, alkyl halides (with the exception of a few very reactive reagents) and epoxides do not react under these conditions with organometallic intermediates where the negative charge is localized on sp^2-carbon. Addition of a relatively small amount of HMPT may increase the rates of alkylation considerably [27]. An additional rate enhancement may be achieved by replacing lithium by potassium; this can be done simply by adding an equivalent amount of *t*-BuOK [161]. The best guarantee for an acceptably high alkylation rate at low temperatures is to use potassium as counter ion, iodide as the leaving group and HMPT as a co-solvent. A less favourable consequence of enhancing the polarity (K instead of Li, HMPT as co-solvent) is, that the rate of the competing dehydrohalogenation increases as well, particularly when RM is a strong base (in a thermodynamic sense).

Hydroxyalkylations with epoxides are also promoted by increasing the polarity, but to a lesser extent than alkylations with alkyl bromides; on the other hand, nucleophilic attack on epoxides may be assisted by Lewis acids, such as $Li^{\oplus}$ and $^{\oplus}MgX$. This is shown by comparision of the results of competition experiments using 2-thienyllithium as the nucleophile and THF as the solvent [9]. When equal amounts of oxirane and butyl bromide were allowed to compete at 20 °C for 2-thienyllithium, the predominant product was 2-thienyl-CH_2CH_2OH. However, if about 20% of HMPT was present, mainly 2-butylthiophene was isolated. If an organolithium intermediate, generated from RBr and BuLi, is to be hydroxyalkylated, one can take advantage of this effect. In Et_2O, the butyl bromide concomitantly formed by halogen-lithium exchange, does not seriously compete with oxirane. A significant example is the following synthesis of *p*-F—C_6H_4—CH_2CH_2OH in high yield (compare Chap. VI, Exp. 4):



In THF, the preference of the aryllithium intermediate for oxirane is somewhat less pronounced.

Alkylation of intermediates containing the M—C=Y systems (Y=N or O) may give di-substituted products [42]:



$$\mathrm{M{-}\overset{|}{C}{=}Y} \xrightarrow[(1)]{\mathrm{RCH_2X}} \mathrm{R{-}CH_2{-}\overset{|}{C}{=}Y} \xrightarrow[(2)]{\mathrm{M{-}\overset{|}{C}{=}Y}} \mathrm{R\underset{\substack{|\\ \mathrm{M}}}{C}H{-}\overset{|}{C}{=}Y} \xrightarrow[(3)]{\mathrm{RCH_2X}} \mathrm{R{-}\underset{\substack{|\\ \mathrm{CH_2R}}}{CH}{-}\overset{|}{C}{=}Y}$$

This situation may arise when the rates of the Reactions (1) and (2) in the above sequence are comparable. Examples are 2-metallated thiazole, imidazole, pyridine and metallated formamides. Yields of the mono-alkylation products are low, except in the case of CH_3I and other reactive alkyl halides (where Reaction (1) is fast).

While successful couplings with α-haloacetals are rare (elimination of HBr and/or alcohol usually is the main reaction), satisfactory yields of alkylation products have been obtained from the reactions of 2-furyllithium and of 2-thienyllithium with $BrCH_2CH(OEt)_2$ in THF [43]. This haloacetal is less reactive than simple primary alkyl bromides. Addition of HMPT, in order to give higher rates of conversion, had an adverse effect due to promotion of the elimination reaction [9]. With phenyllithium, which is more strongly basic than the heteroaryllithiums, elimination predominated, even in the absence of HMPT [9].

Reactions of organolithium or Grignard reagents with 1-chloroethers in THF or Et_2O often proceed very smoothly at low temperatures. Yields are generally excellent, e.g.:

$$\mathrm{RM + ClCH_2OCH_3 \rightarrow RCH_2OCH_3 + MCl\ (M = Li\ or\ MgX)}$$

The ease of the halogen displacement is attributed to mesomeric stabilization of the transition state, which has some S_N1 character. Neither addition of HMPT nor replacement of Li by K is necessary; both could even have an adverse effect, since the chloroether could be deprotonated to the carbenoid ClCH(M)OR (the $RCH_2CH(Cl)OR$ homologues also could undergo 1,2-elimination of HCl under more polar conditions).

As expected, the 1-halogen atom in 1,2-dihaloethers is most easily displaced: reactions with Grignard compounds give much better results than with the corresponding lithium derivatives [9], e.g.:

$$\mathrm{PhMgBr + BrCH_2CH(Br){-}OC_2H_5 \xrightarrow[-10\,^{\circ}C]{THF} BrCH_2CH(Ph){-}OC_2H_5}$$

Alkylations with benzyl bromide proceed more smoothly than those with aliphatic alkyl halides [2]. As the polarity of RM and of the solvent, or the basicity of RM increases, two types of side reactions may become serious. Halogen-metal-exchange may take place if the basicity of RM is similar to that of $PhCH_2M$ and subsequent benzylation gives bibenzyl:

$$\mathrm{RM + PhCH_2Br \rightarrow RBr + PhCH_2M}$$

$$\mathrm{PhCH_2M + PhCH_2Br \rightarrow PhCH_2CH_2Ph + MBr}$$

Replacement of Li by K in RM gives a species with higher kinetic basicity capable of abstracting a benzylic proton. The resulting carbenoid intermediate is benzylated and the coupling product loses hydrogen halide to give stilbene:

$$\mathrm{RM + PhCH_2Br \rightarrow RH + PhCH(M)Br}$$

$$\mathrm{PhCH(M)Br + PhCH_2Br \rightarrow PhCH(Br)CH_2Ph \xrightarrow{RM} PhCH{=}CHPh}$$

Only 2-thienyllithium and 2-furyllithium give good yields of the coupling products with benzyl bromide, the more strongly basic phenyllithium gives mainly bibenzyl. Replacement of Li by K gives rise to the additional formation of stilbene [9]. Analogous reactions are to be anticipated with allylations and propargylations using allyl halides and propargyl halides, respectively.

Alkylation with **secondary** alkyl halides, e.g. *i*-propyl bromide, is very often accompanied by elimination of HX. It might be expected that this side-reaction be more serious as the basicity of the nucleophilic species increases, however experimental facts indicate otherwise. For example, alkali acetylides $\mathrm{RC{\equiv}CM}$ give poor yields of $\mathrm{RC{\equiv}C{-}}i\text{-}\mathrm{C_3H_7}$ [9] whereas the more strongly basic metallated allenic sulfides, $\mathrm{RCH{=}C{=}C(M)SR'}$ give $\mathrm{RCH{=}C{=}C(}i\text{-}\mathrm{C_3H_7)SR'}$ in good yields [44]. Other examples also indicate that "softness" (good polarisability) is important in obtaining good yields in secondary alkyl halide alkylations. A small counter ion ($\mathrm{Li^+}$) seems to be better than a large one ($\mathrm{K^+}$). We expect poor yields of secondary alkyl derivatives and sluggish conversions in all reactions of RM that have the negative charge localized on a single carbon (no resonance stabilization).

3.2 Possible Influence of Thermodynamic Basicity and Polarisability

More strongly basic polar organometallic intermediates should exhibit increased rates of alkylation. Polarisability effects, also may be significant, e.g. for allenic $\mathrm{C{=}C{=}C^{\ominus}}$ and cumulenic anions $\mathrm{C{=}C{=}C{=}C^{\ominus}}$. A few examples strongly suggest that basicity is important [9]. They can be used to help in determining temperature ranges for alkylation reactions under similar conditions with species having intermediate basicities. The reaction of butyl bromide with 2-thienyllithium or with 2-furyllithium in a THF-hexane mixture (concentration about 0.7 mol/l) proceeds at a convenient rate indicated by an observable heating effect) at 20 to 30 °C. With the much more strongly basic phenyllithium, the best temperature range is −10 to 0 °C. In competition experiments, butyl bromide appears to react exclusively with phenyllithium. The same preference is observed when Li is replaced by K, or when 20 vol. % of HMPT are added. Lithium acetylides $\mathrm{RC{\equiv}CLi}$, being much weaker bases than 2-furyllithium and 2-thienyllithium, react slower with butyl bromide in THF, even at reflux temperature [9]. In such cases, HMPT (or DMSO) allows the reaction to be carried out at temperatures, that may be at least by 50° lower.

Although no pK values of allenic sulfides $RCH{=}C{=}CHSR'$ are known, other experimental data indicate the basicity of the lithiated compounds $RCH{=}C{=}C(Li)SR'$ to be somewhat lower than that of 2-thienyllithium. Competition experiments with butyl bromide in THF or in a THF-HMPT mixture showed the metallated allenic sulfide to be much more reactive than 2-thienyllithium [9]. This difference might be due to the higher polarisability of the allenyl system.

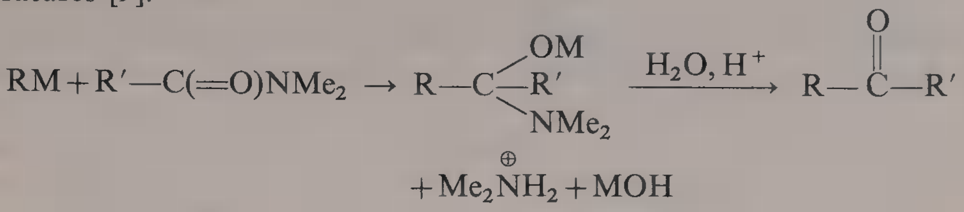
Other differences (though less dramatic and less relevant for synthetic experiments) have been observed in competitions (for butyl bromide) between metallated ($M = Li$ or K) unsaturated oxygen compounds and their sulfur analogues. Thus 2-thienyl-M, $H_2C{=}C(M)SEt$ and $H_2C{=}C{=}C(M)SCH_3$ appeared to be more reactive towards butyl bromide in THF or in THF-HMPT mixtures than the oxygen analogues [9]. Since the basicities of the sulfur compounds are undoubtedly lower than those of the oxygen analogues, polarisability may be responsible for the higher reactivity of the metallated sulfur compounds.

3.3. Reactivity of Some *Ortho*-Lithiated Benzene Derivatives

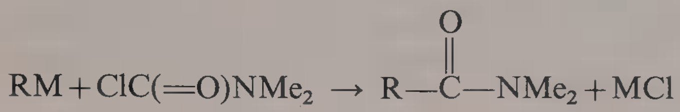
We observed that certain *ortho*-lithiated benzene derivatives $o\text{-}Li{-}C_6H_4{-}OCH_3$, $o\text{-}Li{-}C_6H_4{-}NMe_2$, $o\text{-}Li{-}C_6H_4{-}CF_3$, $o\text{-}Li{-}C_6H_4{-}CH_2OLi$ and $2\text{-}Li{-}C_6H_3{-}1,3\text{-}(OCH_3)_2$ were alkylated in THF more slowly than phenyllithium and many of their *meta*- or *para*-isomers. In fact the rates of the reactions of these *o*-lithio derivatives with butyl bromide were comparable to that of 2-thienyllithium which is a weaker base. $o\text{-}Li{-}C_6H_4{-}S{-}t\text{-}C_4H_9$ and $o\text{-}Li{-}C_6H_4{-}CH_3$ showed the same high reactivity as PhLi. Measurements of the enthalpy of protolysis revealed that $o\text{-}Li{-}C_6H_4{-}OCH_3$ is more stable (by $Li\ldots OCH_3$ interaction?) than the *para* isomer by about 12.5 (in TMEDA) to 33.5 (in dibutyl ether) kJ/mol [45]. The difference is least in TMEDA, because of the strong complexation to lithium; an intermediate value may be expected in THF. This stabilizing effect is probably responsible for the lower reactivity of *o*-lithioanisole in alkylations. Even stronger internal stabilization perhaps due to double bridging is expected to be present in *ortho*-lithiated benzyl alcohol [84].

4. Acylation Reactions

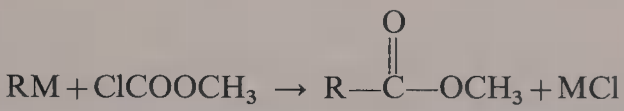
The acylations with N,N-dimethylformamide, N,N-dimethylbenzamide, dimethylcarbamoyl chloride and methyl chloroformate, discussed in this section are illustrated by experimental procedures. The derivatization reactions shown below, generally give the best results with lithium derivatives in THF or Et_2O and in most cases proceed smoothly at −60 °C or lower. Grignard compounds require higher temperatures [9].



$$\mathrm{RM}+\mathrm{R'{-}C({=}O)NMe_2} \rightarrow \mathrm{R{-}C}\begin{smallmatrix}\mathrm{OM}\\ \mathrm{R'}\\ \mathrm{NMe_2}\end{smallmatrix} \xrightarrow{\mathrm{H_2O,\,H^+}} \mathrm{R{-}}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}R'} + \mathrm{Me_2\overset{\oplus}{N}H_2} + \mathrm{MOH}$$



$$\mathrm{RM}+\mathrm{ClC({=}O)NMe_2} \rightarrow \mathrm{R{-}}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}NMe_2}+\mathrm{MCl}$$



$$\mathrm{RM}+\mathrm{ClCOOCH_3} \rightarrow \mathrm{R{-}}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}OCH_3}+\mathrm{MCl}$$

A number of side and consecutive reactions are possible; these are expected to become more important with increasing thermodynamic and kinetic basicity of RM.

Reactions with dimethylformamide

Good results have been obtained from many reactions of organolithium compounds with DMF. Potassium derivatives seem to be suitable as well; phenylpotassium and DMF gave benzaldehyde in an excellent yield [9].

The work-up in some formylation reactions may be essential for good yields. If an α,β-unsaturated aldehyde is to be prepared, the dimethylamine liberated during hydrolysis may add in a conjugate type of reaction to the C=C—CH=O system, unless the amine is deactivated by protonation. In practical terms, the reaction mixture has to be added cautiously to a well-stirred aqueous solution of an excess of mineral acid. If the volume of the reaction mixture is limited, this is most efficiently performed by means of a syringe. Syntheses with other acid amides such as $\mathrm{CH_3C({=}O)NMe_2}$ and $\mathrm{PhC({=}O)NMe_2}$ are carried out similarly to DMF. The following side reactions may reduce the yield:

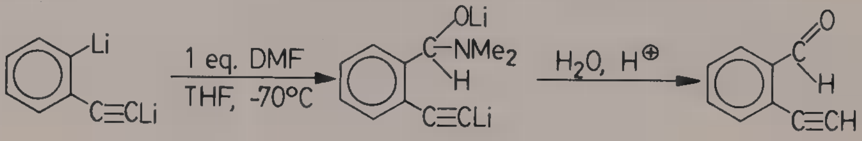
$$\mathrm{CH_3C({=}O)NMe_2}+\mathrm{RM} \rightarrow \mathrm{M{-}CH_2{-}C({=}O)NMe_2} \quad (\alpha\text{-metallation})$$

$$\mathrm{C{=}C{-}C({=}O)NMe_2}+\mathrm{Me_2NH} \rightarrow \mathrm{Me_2N{-}C{-}C{-}C({=}O)NMe_2}$$
(conjugate addition)

$$\mathrm{Ph{-}C({=}O)NMe_2}+\mathrm{RM} \rightarrow o\text{-}\mathrm{M{-}C_6H_4{-}C({=}O)NMe_2}+\mathrm{RH}$$
(*o*-metallation)

Whereas reactions with dimethylacetamide often give poor yields, those with dimethylbenzamide generally are quite successful. An important side reaction, deprotonation of the reagent by RM, may be favoured by high kinetic basicity of RM (e.g. M = K) or the presence of a strongly polar solvent, such as HMPT.

The thermodynamic basicity of RM is likely to determine the reactivity in these acylations. Since most polar organometallic intermediates react smoothly even at very low temperatures, this relationship may have little relevance synthetically. However, the less basic lithium acetylides, RC≡CLi, do not react easily at very low temperatures. This difference in reactivity between acetylides and more strongly basic RLi has been exploited in the synthesis of *o*-ethynylbenzaldehyde [46]:



Carbamoylations
N,N-disubstituted acid amides $RC(=O)NR'_2$ can be prepared from acid halides (or anhydrides) and an amine R'_2NH. This may often require the preparation of carboxylic acids and of the corresponding acid halides. One may prefer, however, a simple route, involving conversion of the cheap, commercially available (carcinogenous) dimethylcarbamoyl chloride with an organometallic derivative [47]:

$$RM + Cl{-}C(=O)NMe_2 \rightarrow R{-}C(=O)NMe_2 + MCl$$

Lithiated aromatic and hetero-aromatic compounds gave satisfactory results in THF, when the solution of RLi was added at a low temperature to an excess of carbamoyl chloride. However, with $H_2C{=}C(Li)SCH_3$ the result was poor [9]. The following guide lines are based on our experiments:

1. Reactions of RLi with $ClC(=O)NMe_2$ in the THF can be carried out successfully if R = aryl or heteroaryl provided that the addition is inverse (RLi is added).
2. With the more strongly basic aryllithium compounds, the tendency of further reaction to symmetrical ketones is increased:

$$RC(=O)NMe_2 + RLi \rightarrow R_2C(OLi)NMe_2 \xrightarrow{H_2O} R_2C{=}O$$

Reactions with chloroformic esters
Direct introduction of an ester function can be achieved by reacting an organolithium derivative with a chloroformic ester (e.g. $ClCOOCH_3$) in THF or in Et_2O [47]:

$$RLi + ClCOOCH_3 \rightarrow R{-}COOCH_3 + LiCl$$

Yield-reducing processes are analogous to those in other acylations; the extent to which they take place depends upon the (thermodynamic) basicity of RM and the structure of R:

$$RCOOCH_3 + RLi \rightarrow R_2C{=}O \xrightarrow{RLi} R_3C{-}OLi$$

$$>C{=}\overset{|}{C}{-}COOCH_3 + RLi \rightarrow R{-}C{-}C{=}C(OLi)OCH_3$$

(conjugate addition of RLi)

Such side reactions can be avoided by inverse addition using a large excess of the chloroformate. We have described some very successful reactions with lithium acetylides [6, 7]. Addition of solutions of 2-furyllithium and of 2-thienyllithium to a large excess of methyl chloroformate also gave good results, but a low yield of methyl benzoate was obtained with the stronger base phenyllithium [9].

The poor result with the reaction of methyl chloroformate and 2-lithiothiazole [9] indicates that the direct introduction of ester groups cannot be applied to $\mathrm{Li{-}\overset{|}{C}{=}N{-}}$ systems. The obvious reason is that the excess of chloroformate reacts to form an ammonium salt $\mathrm{{=}N^{\oplus}{-}COOCH_3 \ldots Cl^{\ominus}}$.

5. Carboxylation

Perhaps carboxylation is the most frequently applied reaction with polar organometallic derivatives. Yields are mostly excellent and purification can be carried out conveniently via the water-soluble alkali metal salts, and subsequently, in many cases, by crystallization:

$$\mathrm{RM + CO_2 \xrightarrow{THF\ or\ Et_2O} RCOOM \xrightarrow{H_2O,\ H^+} RCOOH}$$

The reaction with alkali metal derivatives is extremely fast, even at very low temperatures. The usual procedure involves addition of the organometallic intermediate to a large excess of powdered carbon dioxide, in some cases covered with the organic solvent. Although the application of its inverse addition procedure minimizes the risk of further reaction of RM with the carboxylate, rapid introduction of gaseous CO_2 may be more practical: it is difficult to maintain anhydrous conditions during the production of powdered "dry ice". Excellent yields of acetylenic acids, $\mathrm{RC{\equiv}C{-}COOH}$, have been obtained by introducing gaseous CO_2 into THF solutions of acetylides [6, 7]. Carboxylation of 2-thienyllithium and of 2-furyllithium in this manner also gave good results, but the carboxylation of phenyllithium appeared to be much more successful when a solution of phenyllithium was added to a mixture of THF and a large excess of (dissolved) CO_2. The same is true for the preparation of allenic acids, $\mathrm{RCH{=}C{=}CHCOOH}$, from $\mathrm{RCH{=}C{=}CHLi}$ and CO_2 [7, 9]. This experience allows to draw the following conclusion:

Carboxylic acids can be obtained in good to excellent yields by rapidly introducing CO_2 at low temperatures into THF solutions of RLi, unless RLi is too strongly basic (i.e. aryllithiums, formation of $\mathrm{R_2C(OLi)_2}$) or unless the acid to be prepared contains a $\mathrm{{>}C{=}\overset{|}{C}{-}COOH}$ structure which is prone to conjugate addition or unless the product contains an easily abstractable proton. In the case of Grignard compounds, oily or viscous precipitates are sometimes formed giving rise to incomplete conversion. For the same reason THF is preferred as a solvent to Et_2O.

6. Additions to Carbonyl Compounds

The addition of a polar organometallic derivative to an aldehyde or ketone can be represented by the following general scheme:

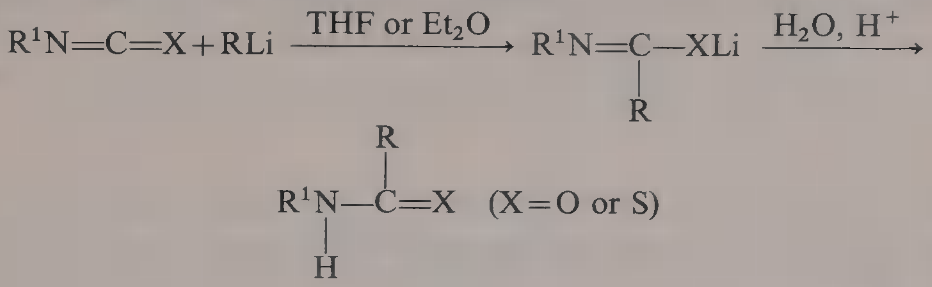
$$\mathrm{RM + R^1R^2C{=}O \rightarrow RR^1R^2C{-}OM\ (M{=}Li,\ Na,\ K,\ MgX)}$$

The most common side reaction is the abstraction of a proton in the α-position to the carbonyl group by RM to form an enolate; its extent depends upon the counter ion, the polarity of the solvent, and the structure of the carbonyl compound. Although strongly polar conditions tend to promote formation of enolates [210, 214], yields of the products are not always poor. A number of couplings of lithium- and sodium acetylides, RC≡CM, with enolizable ketones have been carried out successfully in liquid ammonia [6]. Good yields have also been obtained in the reaction of α-lithiated allenic sulfides with enolizable ketones in the same solvent [48]. Generally, the best chance for satisfactory additions of organometallic compounds to enolizable ketones is to carry out the reactions with lithium or Grignard compounds in THF. When HMPT is present [210], or when potassium derivatives are used [214], yields are considerably lower or may even approach zero. However, the potassium derivative $H_2C{=}C(K)OEt$ could be coupled with benzaldehyde to give the expected carbinol in an excellent yield [9]. This result suggests that hydroxyalkylations of other potassium compounds with non-enolizable aldehydes or ketones may also be successful. Additions of organometallic intermediates to aldehydes and to ketones are usually extremely fast, even at temperatures far below 0 °C, so that reaction times of 1 hour or longer, mentioned in some papers, are irrational. Grignard compounds react somewhat less easily, so that in most cases, the additions should be carried out at higher temperatures (−30 to 0 °C) for 10 to 30 minutes, at concentrations of 0.5 to 1 mol/l.

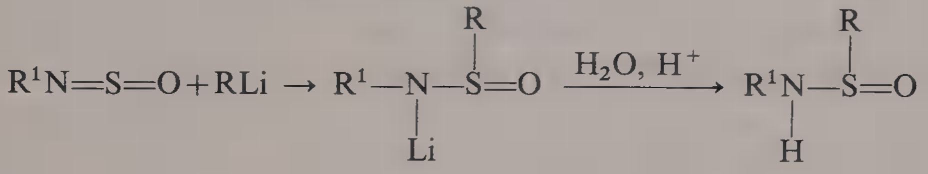
Hydroxymethylation of organometallic intermediates can be achieved with dry, powdered paraformaldehyde [49], using THF or Et_2O as a solvent. Grignard as well as lithium reagents have been used, and the reported yields are generally good. The reaction normally proceeds at 10 to 30 °C and takes 1–2 hours, irrespective of the base strength of RM. The rate-limiting process presumably is the depolymerization of the chain $O{-}CH_2{-}O{-}CH_2{-}O{-}$ which may be assisted to some extent via coordination with $Li^{\oplus}$ or $^{\oplus}MgX$. 2-Thienylpotassium (in THF) and paraformaldehyde reacted smoothly at 10 to 20 °C to give 2-thienylmethanol in excellent yield [9].

7. Additions to Heterocumulenes

Heterocumulenes such as $R^1N{=}C{=}O$, $R^1N{=}C{=}S$ and $R^1N{=}S{=}O$ react smoothly with polar organometallic intermediates [50]. Although in many procedures the counter ion is $Li^{\oplus}$, other alkali metal ions or $^{\oplus}MgX$ might also be applicable. The addition of the potassium derivative $H_2C{=}C(K)SCH_3$ to $CH_3N{=}C{=}S$ was found to proceed quite satisfactorily [9]. The yields of the acid amides or thioamides are generally excellent.



$$R^1N{=}C{=}X + RLi \xrightarrow{\text{THF or Et}_2\text{O}} R^1N{=}\underset{\substack{|\\ R}}{C}{-}XLi \xrightarrow{H_2O,\ H^+} R^1\underset{\substack{|\\ H}}{N}{-}\overset{\substack{R\\ |}}{C}{=}X \quad (X{=}O \text{ or } S)$$

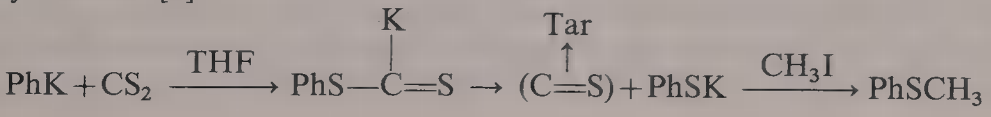


$$R^1N{=}S{=}O + RLi \rightarrow R^1{-}\underset{\substack{|\\ Li}}{N}{-}\overset{\substack{R\\ |}}{S}{=}O \xrightarrow{H_2O,\ H^+} R^1\underset{\substack{|\\ H}}{N}{-}\overset{\substack{R\\ |}}{S}{=}O$$

The rate of RLi additions to methyl isothiocyanate seems to be strongly dependent upon the basicity of RLi [9]. Whereas phenyllithium reacts rapidly at −90 °C, the addition of the much more weakly basic 2-thiazolyllithium (pK of 1,3-thiazole is about 29) has to be carried out at −30 to −50 °C and the reaction with lithium acetylides $RC{\equiv}CLi$ (pK acetylenes is 26 or lower) requires 0 to 20 °C (all reactions were carried out at the same 0.5 to 1 mol/l concentrations). These temperatures indicate the conditions for other organolithium compounds and also the chance of success for other reactions. A rough estimation of the pK values of RH has to be made first, taking into account stabilizing effects of substituents. Side reactions have not yet been observed in the conversions of isothiocyanates with lithium compounds.

Reactions with carbon disulfide

The weak polarization of the heterocumulene CS_2 and the polarisability of the $C{=}S$ bond leads to the expectation that the nature of the attacking nucleophile (substituents in R as well as the counter ion) and the solvent might influence the course of the reaction. A systematic, extensive study of the reactions of polar organometallic reagents with carbon disulfide or other thiocarbonyl compounds is lacking, but the results of more or less incidental reports [51, 52] prove that nucleophiles can attack both carbon (carbophilic attack) and sulfur (thiophilic attack). The available experimental data does not allow the outcome of reactions between CS_2 and all possible RM under different conditions to be predicted. Polarisable anions may have a preference for carbophilic attack [200], while intermediates in which the negative charge is localized on carbon, can attack either at carbon or at sulfur. A large alkali metal ion (K^+) and a high basicity seem to favour thiophilic attack: PhLi or 2-thienyl-Li and carbon disulfide gave considerable amounts of benzenethiolate (together with tarry material), isolated as the methyl sulfides [9]:



$$PhK + CS_2 \xrightarrow{THF} PhS{-}\overset{\substack{K\\ |}}{C}{=}S \rightarrow (\overset{\substack{Tar\\ \uparrow}}{C}{=}S) + PhSK \xrightarrow{CH_3I} PhSCH_3$$

With the less basic 2-thienyllithium, mainly the dithioester, 2-thienyl-C(S)SCH$_3$ (resulting from carbophilic attack and subsequent methylation), was obtained. 2-Furyllithium also mainly gave the dithioester. By using the Grignard derivatives, the pure dithioesters were obtained in excellent yields [55]:

$$\mathrm{RMgBr} \xrightarrow[\mathrm{THF}]{\mathrm{CS_2}} \mathrm{RC(S)SMg} \xrightarrow{\mathrm{CH_3I}} \mathrm{RC(S)SCH_3}$$

Catalytic or equivalent amounts of copper(I)bromide, added to the solutions of the lithium compounds, appeared to promote carbophilic attack as well [56].

The reactions of non-aromatic organolithium compounds with CS$_2$ afforded high-boiling unidentified products. In these cases a very fast subsequent conjugate addition of RLi to the primary product might have taken place [9]:

$$\mathrm{C{=}C{-}Li} \xrightarrow{\mathrm{CS_2}} \mathrm{C{=}C{-}C(S)SLi} \xrightarrow{\mathrm{C{=}C{-}Li}} \mathrm{C{=}C{-}C{-}C{=}C(SLi)_2}$$

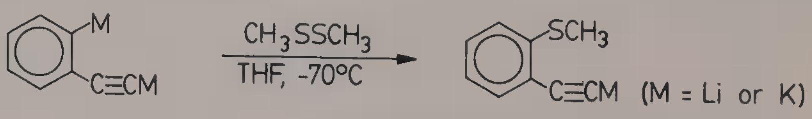
8. Reactions with Sulfenylating Reagents

An R^{1}S group can be introduced by reaction of an organometallic derivative with a disulfide, thiosulfonate or thiocyanate [2, 230]:

$$\mathrm{RM} + \mathrm{R^1SX} \rightarrow \mathrm{RSR^1} + \mathrm{MX}$$

$$(\mathrm{X} = \mathrm{R^1S{-}},\ \mathrm{R^1SO_2}\ \text{or}\ {-}\mathrm{C{\equiv}N};\ \mathrm{M} = \mathrm{Li, Na, K, MgY})$$

With regard to the solvent and the counter ion, such sulfenylations are among the least demanding functionalization reactions. The conversions are generally extremely fast, even below -60 °C though Grignard reagents may require higher temperatures. Di-(*t*-butyl)disulfide is less reactive but organoalkali compounds with a higher basicity than that of acetylides RC≡CM (which reacts sluggishly below 0 °C [9]) will presumably give satisfactory results under suitable conditions. The ease with which sulfenylations proceed seems to depend upon the basicity of RM. Thus, addition of one equivalent of CH$_3$SSCH$_3$ to dimetallated phenylacetylene results in a specific thiomethylation of the more basic center [57]:



Yields of the sulfenylation products are generally excellent (except in the case of arylthiocyanates [58] which may undergo attack on the nitrile carbon) irrespective the fact if disulfides, thiosulfonates or thiocyanates are employed [59]. In some cases the thiolate, $RS^{\ominus}$, produced can react with the sulfenylation product though the chance of a further reaction is minimal when thiosulfonates or thiocyanates are used. In general, the yield of a quench reaction with a sulfenylating reagent can be considered to be a reliable quantitative measure for the success of the preceding metallation (for an exception see the reaction of $H_2C{=}CHK$ with PhSSPh, Chap. III, Exp. 24 and Ref. [21]).

9. Reactions with Elemental Sulfur, Selenium and Tellurium

The reaction of a polar organometallic compound with elemental sulfur, selenium or tellurium gives a thiolate, selenolate or tellurolate, respectively [60, 61]; in many syntheses, however, further reactions are carried out with the intermediary "chalcogenates", e.g. alkylations:

$$\begin{tikzcd} RM + \text{“Y”} \arrow[r] & RYM \arrow[r, "H^+, H_2O"] \arrow[d, "R'X"] & RYH \\ & RYR' \quad (X = \text{halogen};\ Y = S, Se \text{ or } Te) & \end{tikzcd}$$

Very good yields have been obtained from chalcogenations with lithiated aromatics or hetero-aromatics or with the Grignard derivatives, but acetylides $RC{\equiv}CM$ [6] and vinyllithium compounds ($C{=}CLi$) [9] give also reasonable results. Most of the reactions with organometallic compounds have been carried out in Et_2O and THF; in particular, those with sulfur and selenium proceed smoothly at -10 to -60 °C but tellurolations require somewhat higher temperatures. Although the considerations of Edwards and Pearson suggest that thermodynamic basicity should be a very important factor in determining the reactivity of polar organometallic intermediates towards sulfur (and thus also Se and Te), there are no very large differences in the rates of reaction. The slight solubility and low rate of dissolution of these elements in organic solvents might be the limiting factor; in liquid ammonia at -33 °C the conversions with $RC{\equiv}CM$ are very fast [6]. Lithium acetylides, being weaker bases, react in THF much less easily than do aryllithiums. This observation has led to efficient one-pot syntheses of benzo(b)thiophene and the Se and Te analogues [46].

Thiolations with elemental sulfur are normally carried out with lithium compounds; in the reaction of acetylides $RC{\equiv}CM$ in liquid ammonia with sulfur, the sodium compounds give the same (good) results as lithium compounds [6]. Whereas thiolation of 2-thienyllithium and phenyllithium in THF gives good results, the potassium compounds appeared to react sluggishly, giving dark-brown, heterogeneous reaction mixtures. Subsequent reaction with methyl iodide gave low yields of the corresponding thioethers. Similar differences have been observed in reactions with selenium and tellurium [9]. A possible explanation might be that some intermediate poly-chalcogenate $R(X)_nK$ is slightly soluble, so that further attack by RK is very slow.

10. Reactions with Sulfur Dichloride

Although the reaction of organometallic intermediates with sulfur dichloride seems an obvious method for the preparation of symmetrical sulfides, it has not been applied very often [59]:

$$2\,RM + SCl_2 \xrightarrow{\text{THF or } Et_2O} R_2S + 2\,MCl$$

We prepared di(1-alkynyl)sulfides, $(RC{\equiv}C)_2S$, in excellent yields by adding sulfur dichloride at very low temperatures to solutions of alkynyllithiums in Et_2O [7]. Grignard derivatives gave poor results. In Chap. V and VI the successful preparation of di(thienyl)sulfides, di(furyl)sulfide and a di(aryl)sulfide are described, using THF as a solvent. All these reactions are extremely rapid and must be carried out at −80 °C or lower in order to prevent the attack of SCl_2 on the product.

11. Trimethylsilylation

Most conversions of organolithium, -sodium or -potassium compounds with trimethylchlorosilane can be carried out at temperatures below 0 °C; yields are often almost quantitative. The reaction is not very demanding with respect to the nature of the organic solvent. Trimethylsilylation of Grignard compounds require significantly higher temperatures [9].

12. Introduction of Chlorine, Bromine and Iodine

Halogenation reactions with organometallic intermediates may be represented by the following general scheme [62]:

$$RM + X{-}Y \rightarrow RX + MY \quad X = Cl, Br, \text{ or } I \quad M = Li, MgHalg.$$

$$XY = X_2 \text{ or “halogen source”}$$

The reaction of iodine with lithium compounds proceeds rapidly, generally below −40 °C. The reaction of most Grignard derivatives with elemental iodine can be carried out conveniently at temperatures around 0 °C. Many chemists are intimidated by the aggressive nature of chlorine gas (attack of the organic solvent; considerable chance of further reaction with the chlorination product) and therefore resort to chlorine donors, such as N-chlorosuccinimide (NCS) or hexachloroethane [196] which “give off” their chlorine under mild conditions:

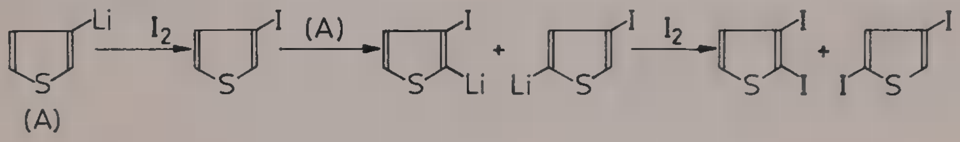
$$\text{M-Succinimide} + RCl \xleftarrow{\text{N-Chlorosuccinimide}} RM \xrightarrow{C_2Cl_6}$$

$$RCl + MCl + Cl_2C{=}CCl_2$$

There is some chance of side reactions with these chlorination reagents, particularly when RM is strongly basic and the temperature is not kept sufficiently low; the organometallic intermediate can also attack the metallated succinimide resulting from the desired reaction. While 2-thienyllithium reacted rather smoothly at about +20 °C with tetrachlorethene to 2-chlorothiophene, chlorination with hexachloroethane proceeded at considerably lower temperatures. Hence, it should be possible to avoid the subsequent reaction with tetrachloroethene by working at low temperatures [9].

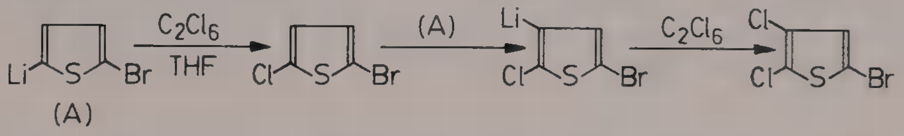
In many cases bromination can be carried out successfully with elemental bromine. If the use of free bromine is not desirable, one can choose reagents such as N-bromosuccinimide (NBS), hexabromoethane, cyanogen bromide (BrCN), and $(CH_3)_2C(Br)C(Br)(CH_3)_2$. An illustrative example is the bromination of *o*-Li—C_6H_4—CH_2NMe_2 with the latter reagent [197]. The presence of the dimethylamino group does not allow the use of free bromine. Halogenations with the elements may also give poor results when the organometallic intermediate has been generated with BuLi · TMEDA or with LDA since amines react vigorously with bromine. Iodine also reacts with TMEDA, but if the reaction of iodine with the intermediate RM is sufficiently fast at low temperature, these side reactions are unimportant.

Halogenations of lithiated hetero-aromatic compounds may give less satisfactory results because of subsequent reactions, e.g. in the iodination of 3-lithiothiophene [9]:



Addition of iodine to a solution of 3-lithiothiophene in THF gave the expected 3-iodothiophene in a moderate yield together with two isomeric di-iodo compounds. We presume that 3-lithiothiophene lithiates 3-iodothiophene at the 2- and 5-positions respectively; further reaction with iodine gives the di-iodo compounds. These yield-reducing side reactions could be suppressed completely by conversion of 3-lithiothiophene into the less reactive Grignard compound by addition of $MgBr_2$.

The chlorination of 2-bromo-5-lithiothiophene with hexachloroethane gave some bromo-dichlorothiophene [9]:



Such di-halogenations are not likely to occur with benzene derivatives, since protons, *ortho* to the halogen introduced, are much less acidic than those in the hetero-aromatic compounds.

13. Protonation and Deuteration

Protonation of organometallic intermediates by addition of water or alcohol usually is a trivial reaction of little synthetic interest. However, delocalized anionic intermediates may give different protonation products. Thus, protolysis of cumulenic systems may give acetylenes as well as cumulenes. If only one insomer is formed, the protonation may be synthetically useful:

$$RCH_2C{\equiv}C{-}SR' \xrightarrow[\text{liq. } NH_3]{NaNH_2} \overbrace{RCH{\cdots}C{\cdots}C}^{\ominus}{-}SR'\ Na^{\oplus} \xrightarrow{H_2O}$$

$$RCH{=}C{=}CHSR'$$

$$H_2C{=}CH{-}C{\equiv}C{-}NMe_2 \xrightarrow[\text{THF}]{BuLi\cdot t\text{-}BuOK} H_2C{=}\overbrace{C{\cdots}C{\cdots}C}^{\ominus}{-}NMe_2 \quad K^{\oplus}$$

$$\xrightarrow{t\text{-}BuOH} H_2C{=}C{=}C{=}CHNMe_2$$

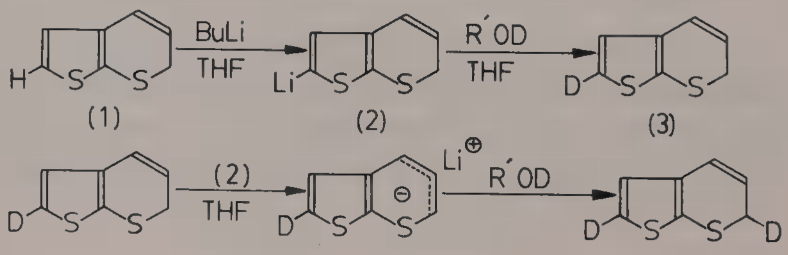
Such cumulenic derivatives cannot be obtained by isomerization of acetylenic precursors under catalytic conditions, since they are thermodynamically less stable than the acetylenes. Special conditions for the protonation of metallated acetylenic sulfides and metallated enyne amines are described in Refs. [7] and [106] and in Chap. IV, Exp. 19.

Deuteration can generally be carried out by reaction of D_2O or a deuterio-alcohol (e.g. CH_3OD or t-BuOD) with the organometallic intermediate.

$$RM + R'OD \xrightarrow{\text{THF or } Et_2O} RD + R'OM \quad (R' = H,\ CH_3 \text{ or } t\text{-}C_4H_9)$$

The high price of the deuteration reagents requires their economical use. However, stoichiometric amounts often give incomplete conversions. Although deuterations are extremely fast, the hydroxide or alkoxide R'OM form complexes with R'OD from which D is less readily available. Therefore, at least 100% excess of R'OD should be used. If the deuteration has to be carried out at low temperatures, D_2O, if added to the reaction mixture, solidifies, so that complete deuteration may not be achieved; hence, use of a deuterio-alcohol (THF or Et_2O solution) is preferred.

Complications may arise when the normal addition procedure is followed with deuteration reagents. Suppose that thienothiopyran is to be deuterated (in the thiophene ring)



Despite very efficient stirring during the addition of R′OD to **2**, not all molecules of **2** will be deuterated at the same time. Deprotonation of **3** by **2** leads to the formation of some di-deuterated compound **5**. More polar conditions (K^+ as a counter ion; HMPT as a co-solvent) are likely to favour such processes. These can be minimized by inverse addition: a solution of the organometallic compound is added to an excess of R′OD in the organic solvent (for an example see Chap. V, Exp. 44).

14. Exchange Between Counter Ions

In a number of derivatization reactions it is advisable to replace the original counter ion by another one. As mentioned in Sects. II-6 and II-9, organolithium compounds give much better results than potassium compounds in reactions with enolizable carbonyl compounds and with sulfur, selenium and tellurium. On the other hand, alkylations with alkyl halides and with oxiranes proceed more smoothly with the potassium intermediates. Although HMPT may be used as a co-solvent, simple replacement of lithium by potassium may give similar results; combination of the counter ion and solvent effects may be even better. The replacements $Li^+ \rightarrow K^+$ and $K^+ \rightarrow Li^+$ are generally fast reactions in a wide temperature range (compare e.g. [161, 241]):

$$\mathrm{RK + LiBr \xrightarrow{THF} RLi + KBr\downarrow}$$

$$\mathrm{RLi} + t\text{-}\mathrm{BuOK} \xrightarrow{\mathrm{THF}} \mathrm{RK} \cdot t\text{-}\mathrm{BuOLi}$$

Grignard reagents may be preferred over lithium or potassium compounds, for example, in reactions with CS_2 (see Sect. II-7), in iodinations (see Sect. II-12) or in perester syntheses (see Chap. V, Exp. 32). In some cases replacement by MgX causes a change in the regiochemistry. For example, $H_2C{=}C{=}C(MgBr){-}O{-}t\text{-}Bu$ and acetone give mainly $(CH_3)_2C(OH)CH_2C{\equiv}C{-}O{-}t\text{-}Bu$, whereas the sole product from the 1-lithiated allenic ether is the allenyl ether carbinol [9]. The exchange can be effected most simply by addition of anhydrous $MgBr_2$ (from 1,2-dibromoethane and Mg in Et_2O):

$$\mathrm{RM + MgBr_2 \cdot Et_2O \xrightarrow{THF} RMgBr + MBr} \quad (\mathrm{M = Li, K})$$

Zinc derivatives can be obtained by a similar procedure:

$$\mathrm{RM + ZnX_2 \xrightarrow{THF\ or\ Et_2O} RZnX + MX} \quad (\mathrm{R = Li, K; X = halogen})$$

Since it is extremely difficult to remove traces of water from commercial zinc salts, it is desirable to prepare the salts in Et_2O. $ZnCl_2$ and $ZnBr_2$ are obtained by reacting clean zinc (e.g. powder, successively treated with aqueous HCl or HBr, absolute ethanol, dry Et_2O and subsequently dried in vacuo) with gaseous HCl and HBr. Zinc iodide can be made from clean zinc and iodine in Et_2O.

Although syntheses via copper compounds are beyond the scope of this book, some directions for the transformation of lithium or Grignard reagents into copper intermediates may be useful. Copper(I)halides are added to solutions of RLi or RMgX: reaction with one equivalent of CuX gives "RCu", 0.5 equivalent of CuX yields "R_2CuLi" or "$R_2CuMgBr$". The best solvent for such transformations seems to be THF (however, Et_2O also may be satisfactory):

$$\mathrm{RM + CuX \rightarrow RCu + MX}$$

$$\mathrm{2\,RM + CuX \rightarrow R_2CuM + MX} \quad (\mathrm{M{=}Li\ or\ MgX;\ X{=}Cl,\ Br\ or\ I})$$

Addition of solid copper halide often gives incomplete conversion (covering of CuX particles by RCu or R_2CuM), for this reason it is advisable to add CuX in a solubilized form, e.g. as the complex $CuX \cdot LiX$ in THF (obtained by simple mixing of the required amounts of CuX and LiX in THF) or as the $CuX \cdot Me_2S$ complex. A disadvantage of the latter variation is that the volatile Me_2S, liberated during the work-up, may give rise to complaints because of the stench.

Chapter III
Metallated Olefinic and Allenic Hydrocarbons

1. Deprotonation by Strongly Basic Reagents

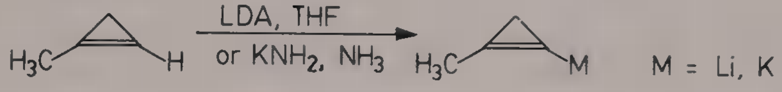
Although some studies dealing with the vinylic metallation of ethene homologues by alkyl sodium have been reported [63, 64], this direct metallation is not interesting from a synthetic point of view, because allylic deprotonation occurs to a considerable extent [65]. Interaction between *t*-butylethene (ten-fold excess) and BuLi · TMEDA in hexane at reflux temperature, followed by quenching with dimethyl disulfide, resulted in a low yield of the expected vinylic sulfide (only the *E*-isomer was isolated) [9]:

$$\mathrm{Me_3C{-}CH{=}CH_2} \xrightarrow[\text{hexane, reflux}]{\mathrm{BuLi\cdot TMEDA}} \mathrm{Me_3C{-}CH{=}CH{-}Li} \xrightarrow{\mathrm{CH_3SSCH_3}}$$

$$(E)\mathrm{Me_3C{-}CH{=}CH{-}SCH_3}$$

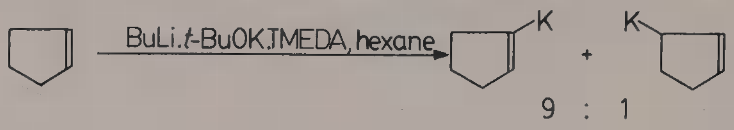
We succeeded in generating vinylpotassium by passing ethene through a solution of BuLi · *t*-BuOK · TMEDA in hexane at −20 °C (21). Derivatization reactions with diphenyl disulfide or benzaldehyde (after addition of THF and lithium bromide) gave the expected derivatives in excellent yields.

Vinylic hydrogen atoms in strained ring systems have an increased acidity [65]. Cyclopropenes can be smoothly metallated with alkyllithium [66] (in the case of the unsubstituted hydrocarbon, addition across the double bond occurs), lithium dialkylamides in THF [9], or with alkali amides in liquid ammonia [16]. Whereas reaction of propene with strong bases results in the exclusive formation of the allylic derivative, the kinetically preferred process with 1-methylcyclopropene is vinylic deprotonation:

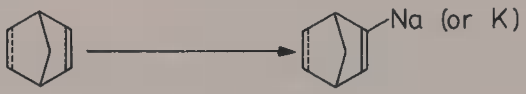


Unfortunately, cyclopropenes are not readily available, and several of them are very unstable. These factors may explain why not much research has been carried out with these olefins.

The thermodynamic acidity, and kinetic preference for vinylic deprotonation decrease with increasing size of the ring, and in the case of cyclohexene allylic deprotonation predominates [65]. Reaction of cylopentene (two-fold excess) and BuLi · *t*-BuOK · TMEDA in hexane at −20 °C gives the vinylic and allylic potassium compounds in a ratio of about 9:1 [64a]. Subsequent addition of dimethyl disulfide affords the corresponding mixture of sulfides in a high yield.



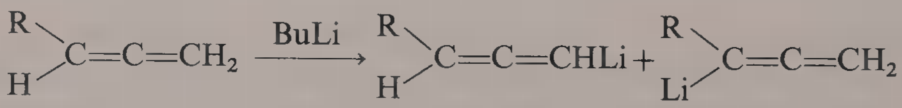
Deprotonation of cyclobutene under similar conditions therefore may be expected to result in almost exclusive formation of the vinylic metal intermediate [198]. It is clear from these results that the vinylic hydrogen atoms in three-, four-, and five-membered cycloalkenes are more acidic than those in ethene and its homologues. Other examples of strained olefins are norbornene and norbornadiene [67]. If present in excess, these hydrocarbons can be successfully converted into the sodium or potassium compounds at low temperatures, using the systems BuLi · *t*-BuONa (or K) in THF [77, 198] or BuLi · *t*-BuOK · TMEDA in hexane [21]. Previous attempts carried out with less effective base-solvent combinations at considerably higher temperatures, gave poor results [68, 69].



One might expect hydrocarbons, such as styrene, 1,3-butadiene and 1,3-enynes $R{-}C{\equiv}C{-}CH{=}CH_2$ to be deprotonated relatively easily under suitable conditions. However, these deprotonations which would provide synthetically useful intermediates, have not yet been realized, polymerization or conjugate addition being the only processes observed. Lithium vinylacetylide $Li{-}C{\equiv}C{-}CH{=}CH_2$ undergoes a very smooth addition of butyllithium across the double bond, initiating the formation of polymeric material [9]. Double deprotonation to $KC{\equiv}C{-}C(K){=}CH_2$ has been achieved with BuLi · *t*-BuOK in THF at very low temperatures [9]. Quenching with trimethylchlorosilane gives the corresponding disilyl derivative in a reasonable yield.

Allenic Hydrocarbons

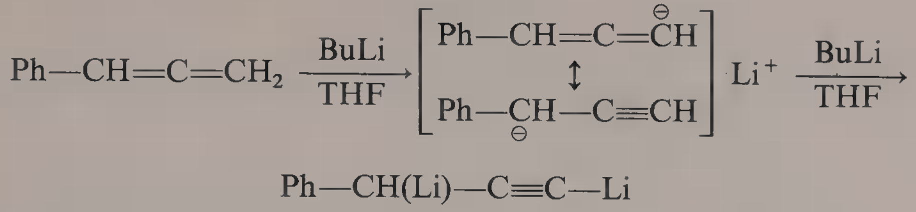
Depending upon the nature of the substituents, allenic hydrocarbons undergo either predominant or exclusive deprotonation at the terminal carbon atom. This reaction can be conveniently carried out with BuLi in THF at temperatures in the region of −70 °C (in the case of allene and monoalkylallenes) or at ca. −30 °C (in the case of di- and trialkylallenes). The deprotonation of methylallene with BuLi in THF gives $CH_3CH{=}C{=}CHLi$ and $CH_3C(Li){=}C{=}CH_2$ in a ratio of about 8:1, respectively, with longer alkyl chains the ratio increases. *t*-Butylallene is deprotonated exclusively at the terminal carbon atom [7].



$$\mathrm{(R)(H)C{=}C{=}CH_2 \xrightarrow{BuLi} (R)(H)C{=}C{=}CHLi + (R)(Li)C{=}C{=}CH_2}$$

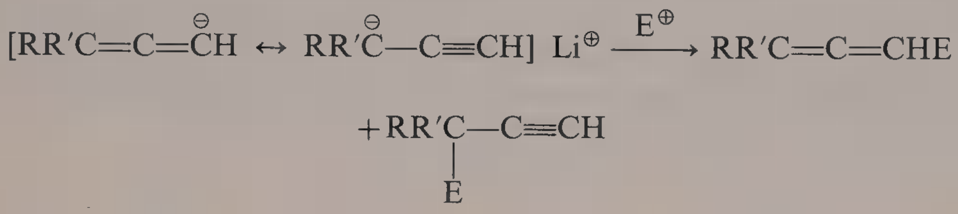
(R = H or alkyl)

In the case of phenylallene the first lithiation is immediately followed by the removal of a second proton:



$$\mathrm{Ph{-}CH{=}C{=}CH_2} \xrightarrow[\text{THF}]{\text{BuLi}} \left[\begin{array}{c}\mathrm{Ph{-}CH{=}C{=}\overset{\ominus}{C}H}\\ \updownarrow \\ \mathrm{Ph{-}\underset{\ominus}{C}H{-}C{\equiv}CH}\end{array}\right]\mathrm{Li^+} \xrightarrow[\text{THF}]{\text{BuLi}} \mathrm{Ph{-}CH(Li){-}C{\equiv}C{-}Li}$$

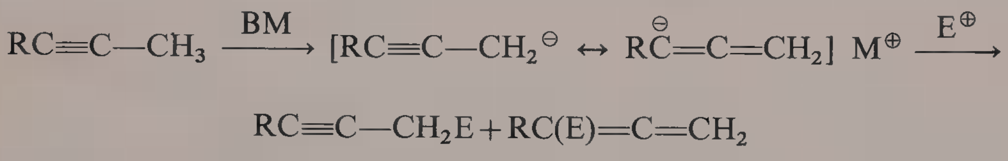
In principle, the reaction of terminally lithiated allenes with electrophilic reagents may give both the allenic and the acetylenic derivative:



$$[\mathrm{RR'C{=}C{=}\overset{\ominus}{C}H} \leftrightarrow \mathrm{RR'\overset{\ominus}{C}{-}C{\equiv}CH}]\,\mathrm{Li^{\oplus}} \xrightarrow{\mathrm{E^{\oplus}}} \mathrm{RR'C{=}C{=}CHE} + \mathrm{RR'\underset{\displaystyle E}{\underset{|}{C}}{-}C{\equiv}CH}$$

The ratio strongly depends upon the nature of the substituents and the electrophilic reagent: alkylation of the various lithiated allenes with alkyl halides, for example, gives only the corresponding allenes, but $(CH_3)_2C{=}C{=}CHLi$ and carbon disulfide give $(CH_3)_2C(CSSCH_3){-}C{\equiv}CH$ as the sole product (after methylation with methyl iodide) [197]. Whereas 1-lithio-*t*-butylallene and Me_3SiCl give the allene exclusively, silylation of lithiopropadiene leads to predominant formation of propargyl trimethylsilane [9].

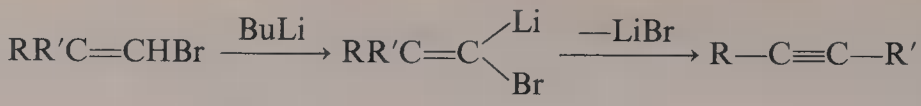
3-Metallated allenes can be obtained from 2-alkynes and BuLi · *t*-BuOK in tetrahydrofuran at ca. −60 °C [70] or at 0 to 30 °C using BuLi in THF or Et_2O [71] (compare also Ref. [212]). Subsequent interaction with electrophilic reagents also gives two products [9]. The trimethylsilylation is exceptional in that the acetylenic derivative Alkyl$-C{\equiv}C{-}CH_2SiMe_3$ is produced cleanly. The present state of knowledge does not permit prediction of the product ratio of a given functionalization reaction on a rational basis (compare Refs. [71, 199]).



$$\mathrm{RC{\equiv}C{-}CH_3} \xrightarrow{\text{BM}} [\mathrm{RC{\equiv}C{-}CH_2^{\ominus}} \leftrightarrow \mathrm{R\overset{\ominus}{C}{=}C{=}CH_2}]\,\mathrm{M^{\oplus}} \xrightarrow{\mathrm{E^{\oplus}}} \mathrm{RC{\equiv}C{-}CH_2E + RC(E){=}C{=}CH_2}$$

2. Halogen-Lithium and Tin-Lithium Exchange

Whereas in the aromatic and hetero-aromatic series halogen-lithium exchange is a useful reaction, it is much less important for the generation of vinylic lithium compounds. The desired bromine-lithium exchange is often accompanied by dehydrohalogenation reactions [9], e.g.:



$$RR'C{=}CHBr \xrightarrow{BuLi} RR'C{=}C\begin{smallmatrix}Li\\Br\end{smallmatrix} \xrightarrow{-LiBr} R{-}C{\equiv}C{-}R'$$

Using *tert*-butyllithium at very low temperatures, the side reactions can be largely avoided [234].

$$RCH{=}CHBr + 2\ t\text{-}BuLi \rightarrow RCH{=}CH{-}Li + (CH_3)_2C{=}CH_2 + (CH_3)_3CH$$

In a few cases, interesting synthetic intermediates can be successfully prepared by bromine-lithium exchange under mild conditions [202], (compare also Ref. [233]).

$$(Z)BrCH{=}CH{-}OEt \xrightarrow{RLi} (Z)LiCH{=}CH{-}OEt$$

Iodine is replaced more easily than bromine, but unfortunately, vinylic iodides are in general not readily available.

Tin-lithium exchange has been also used as a method for generating vinylic lithio derivatives [73, 206]:

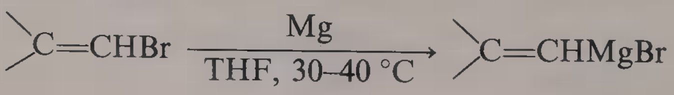
$$(Z)Bu_3Sn{-}CH{=}CH{-}OEt \xrightarrow{BuLi} Bu_4Sn + (Z)LiCH{=}CH{-}OEt$$

$$(H_2C{=}CH)_4Sn \xrightarrow[Et_2O]{4\ PhLi} Ph_4Sn\downarrow + 4\ H_2C{=}CH{-}Li$$

The concomitant formation of tetraalkyltin may give rise to problems during the purification of less volatile products: chromatographic purification will then be necessary, making this method less suitable for syntheses on a larger scale.

3. Direct Preparation from Halogen Compounds and Metal

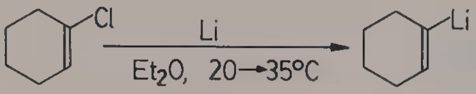
In some cases, the preparation of solutions of alkenyllithium or Grignard compounds is synthetically attractive. Vinyl bromide, for example, can be converted in THF with magnesium into vinylmagnesium bromide with excellent results [74]. This Grignard solution can be used for the preparation of a number of derivatives, e.g. $H_2C{=}CH{-}SiMe_3$ and $(H_2C{=}CH)_4Sn$. Other aliphatic alkenylmagnesium bromides may be obtained in a similar way.



$$\rangle C{=}CHBr \xrightarrow[THF,\ 30\text{–}40\ °C]{Mg} \rangle C{=}CHMgBr$$

Direct preparation of alkenyllithium solutions in general cannot be carried out in a simple manner [75]. Vinyllithium has been obtained as a solution in THF by reacting vinyl chloride with finely divided lithium at low temperatures. This form of lithium is necessary to attain an acceptable rate of conversion. At higher temperatures (in the region of +20 °C) the vinyllithium may dehydrohalogenate vinyl halide. In view of the laborious procedure for preparing a lithium dispersion (melting the metal in paraffin oil under argon, followed by high-speed stirring or vibrating, and replacing the oil by THF after repeated rinsing) many chemists will be hesitant to prepare vinyllithium by this method.

Solutions of cycloalkenyllithium can be obtained with excellent results from the readily available chlorocycloalkenes and chipped lithium at temperatures between 20 and 35 °C. Elimination of HCl does not occur at all. Pieces of broken glass are added to scratch the salt from the metal surface ([9], compare also Ref. [76]):



4. Experimental Procedures

All temperatures are internal, unless indicated otherwise.

4.1 Vinylmagnesium Bromide

$$H_2C{=}CH{-}Br + Mg \xrightarrow[35\text{–}40\ ^\circ C]{THF} H_2C{=}CH{-}MgBr$$

Scale: 1 molar

Apparatus: Chap. I, Fig. 1, 21

Procedure
Well-dried magnesium turnings (1.5 mol, 36 g) are covered with 100 ml of THF and 4 ml of 1,2-dibromoethane is added with stirring. After the exothermic reaction has ceased, the THF is cooled to 35 °C. A mixture of 1.1 mol (118 g) of vinyl bromide and 250 ml of THF is added dropwise over a period of 2.5 h, while keeping the temperature of the dark-grey solution between 35 and 40 °C (Note 1). After the addition, stirring and heating at 40 °C are continued for another hour. The warm solution is transferred (under a blanket of inert gas) into a calibrated flask of 1 l (compare Fig. 2), which previously has been filled with inert gas. The excess magnesium is rinsed twice with 30 ml portions of THF, the rinsings being added to the solution in the flask. A small amount of THF is added to bring the volume to 500 ml (35–40 °C) (Note 1), after which the flask is shaken for homogenization. The

yield, as derived from the results of the conversions described in Exps. 2–4, is at least 90 %, and thus the solution contains about 1.0 mol of vinylmagnesium bromide.

$(CH_3)_2C{=}CHBr$ (Exp. 21) and magnesium reacted (at 35–40 °C) to give the Grignard derivative in yields of at least 80 %. A good purity of the bromo compound seemed to be essential.

Notes

1. At lower temperatures salt will crystallize out, causing the conversion to proceed less smoothly. During storage (at room temperature) great quantities of salt precipitate. Before using part of the solution, the flask should be warmed (with swirling) until the salt has dissolved.

4.2 Trimethylsilylethene

$$H_2C{=}CH{-}MgBr + Me_3SiCl \xrightarrow[40\ \rightarrow\ 70\ ^\circ C]{THF} H_2C{=}CH{-}SiMe_3 + BrMgCl$$

Scale: 0.9 molar.

Apparatus: Chap. I, Fig. 1, 2 l; in the last stage of the reaction, the thermometer-outlet combination is replaced with a reflux condenser.

Procedure

A solution of 1.0 mol of vinylmagnesium bromide (see Exp. 1) in about 500 ml of THF is warmed to 40 °C. Trimethylchlorosilane (0.9 mol, 100 g) is added over 15 min causing the temperature to rise gradually to 60° or higher. A reflux condenser is then placed on the flask and the temperature is allowed to rise further to 70 °C. After the temperature has dropped to 60 °C, the mixture is heated for an additional hour at this temperature, then it is cooled to room temperature. A mixture of 100 ml of concentrated hydrochloric acid and 400 ml of water is added with vigorous stirring and cooling in ice water over 15 min. After the hydrolysis, the mixture is cooled to −5 °C, and subsequently transferred into a 2 l separating funnel and the layers are separated carefully. In order to remove the THF, the organic layer is "extracted" 10 times with 200 ml portions of cold (−5 °C) 3 N hydrochloric acid and subsequently twice with 50 ml portions of water. At this point, NMR spectroscopy showed that practically all THF had disappeared. After drying over $MgSO_4$, the liquid is distilled through a 40 cm Vigreux column to give pure trimethylsilylethene (b.p. 55 °C/760 mm, n_D^{20} 1.3927) in 90 % yield. Extraction of the combined twelve aqueous layers with two 50 ml portions of light petrol (b.p. at least 170 °C), followed by washing the extracts with 4 N HCl (5 times), water (twice), drying over $MgSO_4$ and distillative separation of the product from the extraction solvent (in a vacuum of 10–20 mmHg, collecting the volatile product in an effectively cooled receiver, and subsequently redistillation of the contents of the receiver, at normal pressure) gives an additional 3–6 % yield.

4.3 Tetravinyltin

$$4\ H_2C{=}CH{-}MgBr + SnCl_4 \xrightarrow[40\ ^\circ C]{THF} (H_2C{=}CH)_4Sn + 4\ BrMgCl$$

Scale: 0.1 molar ($SnCl_4$).

Apparatus: Chap. I, Fig. 1, 1 l.

Procedure

A solution of 0.5 mol of vinylmagnesium bromide (see Exp. 1) in ca. 250 ml of THF is warmed to 30 °C (partial dissolution of the salt) and a mixture of 0.10 mol (26 g) of tin tetrachloride and 30 ml of benzene is added dropwise over 15 min, while keeping the temperature of the mixture close to 40 °C. The insoluble $SnCl_4 \cdot THF$ complex, which is initially formed, dissolves rapidly. After the addition, stirring at 40 °C is continued for another half hour, then the solution is cooled to room temperature and the mixture is poured into a cold (0 °C) solution of 100 g of ammonium chloride in 500 ml of water. After separation, the aqueous layer is extracted three times with small portions of pentane. The combined organic solutions are dried over $MgSO_4$, and subsequently the greater part of the solvents is distilled off at normal pressure through a 40 cm Vigreux column, keeping the bath temperature below 100 °C. Careful distillation of the remaining liquid gives tetravinyltin, b.p. 45 °C/12 mm, n_D^{20} 1.5007, in 92 % yield.

4.4 Reaction of Alkenylmagnesium Bromide with Benzaldehyde

$$H_2C{=}CH{-}MgBr + PhCH{=}O \xrightarrow[-10\ \rightarrow\ +20\ ^\circ C]{THF}$$

$$H_2C{=}CH{-}CH(OMgBr)Ph \xrightarrow{H_2O} H_2C{=}CH{-}CH(OH)Ph$$

Scale: 0.2 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

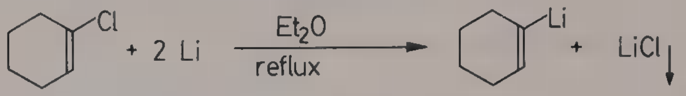
Procedure

A solution of 0.23 mol of vinylmagnesium bromide in 100 ml of THF (see Exp. 1) is diluted with 50 ml of THF. The solution is cooled to −10 °C, and 0.20 mol (21.2 g) of freshly distilled benzaldehyde is added dropwise over 15 min. After the addition is complete the temperature is allowed to rise to +20 °C. After an additional 15 min a solution of 25 g of ammonium chloride in 120 ml of water is added with vigorous stirring and cooling in ice water. After separation of the layers and extraction of the aqueous layer (twice) with Et_2O, the combined solutions are dried over $MgSO_4$ and subsequently concentrated in *vacuo*. Distillation of the remaining liquid through a

30 cm Vigreux column gives the carbinol, b.p. 100 °C/12 mm, n_D^{18} 1.5344, in 88 % yield.

In a similar way $(CH_3)_2C{=}CH{-}MgBr$ (see Exp. 1) and benzaldehyde give $(CH_3)_2C{=}CH{-}CH(OH)Ph$, b.p. ca. 80 °C/0.1 mm, n_D^{19} 1.5333, in more than 80 % yield.

4.5 Cyclohexenyl- and Cycloheptenyllithium



Scale: 0.5 molar.

Apparatus: Chap. I, Fig. 1, 1 l; at a later stage of the reaction, the thermometer-outlet combination is replaced with a reflux condenser.

Introduction

The original literature [76] describes the preparation of these useful reagents from the corresponding chlorocycloalkenes and lithium in Et_2O in yields of about 60 %. After dropwise addition of the chlorocycloalkene the mixture was stirred for several hours. Although no further experimental details are mentioned, we assume that the reaction with lithium was carried out at room temperature. The authors obtained a grey to blue solution. We have often observed this color in lithiations with pure lithium. If the metal contains 1–2 % of sodium, it reacts more easily, and yields are significantly higher than with pure metal. In the procedure described below, the use of sodium-containing lithium is prescribed. To guarantee a smooth lithiation, it seems necessary that the coating of lithium chloride be continuously removed from the surface of metal. The start of the reaction is often visible from the appearance of a turbidity, which may be explained by partial detachment of oxide and nitride from the surface of the metal. The temperature then slowly rises, but after some time (1–2 h) the reaction seems to stop and the metal surface has again become dull. This inactivation is most probably due to lithium chloride being deposited on the metal, which even occurs under argon. We have succeeded in re-starting the conversion by adding sharp pieces of broken glass. Another experimental detail should be noted, it seems trivial, but we believe it to be essential for a successful lithiation. Because of the fact that lithium has a lower density than Et_2O, the desired contact between the metal chips and the pieces of glass will not take place if stirring is carried out too vigorously. The lithium will rotate on the surface of the ether and the glass in a small circle on the bottom of the flask. A satisfactory contact can be established if the blade of the stirrer is placed close to the bottom of the flask, and stirring is carried out at a relatively low rate. With these conditions the lithium and the glass will rotate in a vortex which nearly reaches the bottom of the flask and the salt is continuously scratched from the metal. During the preparation of solutions of CH_3Li and higher-alkyllithiums from RBr or of PhLi from bromobenzene activation is not necessary, because lithium bromide forms a soluble complex with RLi or PhLi. We did not succeed in preparing vinyllithium from vinyl bromide and chipped lithium in a manner analogous to that described for the cycloalkenyllithiums: there was no observable evolution of heat, and the metal remained coated, even under argon. The use of vinyl chloride was considered impractical because of its high volatility.

In order to keep the reaction time as short as possible, a considerable excess of lithium should be used in the preparation of the lithiocycloalkenes. All chlorocycloalkene can be added in one portion, if the reaction is carried out on a modest scale (0.3–0.5 molar), the reaction can be kept under control by changing the rate of stirring. Würtz coupling to C_{12} or C_{14} hydrocarbons and/or HCl elimination (under the influence of lithiocycloalkene) do not occur.

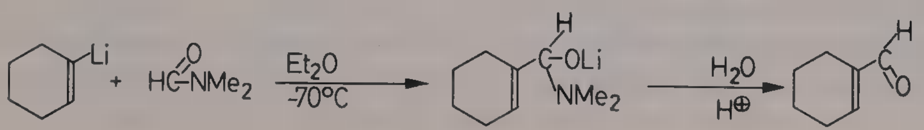
Procedure

A flattened piece of 10 g (1.4 mol) of lithium (ca. 40 cm^2) is cut directly into the flask (pieces of about 2 × 8 mm) containing diethyl ether (350 ml). Subsequently, two Pasteur pipettes are cautiously broken into pieces with a hammer, and introduced into the flask (lengths varying from 0.5 to 1.5 cm). After replacing the air in the flask completely by nitrogen or (preferably) argon, 0.5 mol (58.3 or 65.3 g) of the chlorocycloalkene (see Exp. 20) (Note 1) is added in one portion. The blade of the stirrer is placed at such a level, that during stirring at a moderate rate the pieces of glass and lithium are rotating together in a small circle on the bottom of the flask (care should be taken that no bumping occurs). After 10–15 min a turbidity appears, and the temperature (initially about 20 °C) begins to rise. When it has reached 30 °C (after 30–40 min), the thermometer-outlet combination is replaced with a reflux condenser. Either occasional cooling or insolation of the flask with cotton wool may be necessary to maintain a gentle reflux of the ether under a slow stream of inert gas . After a period varying from 3 to 5 h, refluxing has stopped (Note 2). If attempts to restart the reflux (by varying the rate of stirring and/or by placing the blade of the stirrer at a lower level) are unsuccessful, the flask is placed in a heating bath, and stirring and refluxing are continued for an additional 1.5 h. After cooling the greyish suspension to room temperature, the supernatant solution is transferred into a 1 l flask filled with argon (Note 3). The salt is rinsed three times with small (30 ml) portions of Et_2O and combined with the main solution. The total volume of the solution is brought to 500 ml (for the storage flask see Fig. 2). We presume that the solution can be stored at room temperature. The strength can be determined as described for alkyllithium (compare Refs. [31–34]).

Notes

1. It is essential to use carefully distilled, and dry chlorocycloalkene.
2. The bright color of polished silver disappears when the reaction has stopped.
3. The lithium should be destroyed immediately by adding a mixture (7:3) of ethanol and water.

4.6 Cyclohexenecarboxaldehyde and Cycloheptenecarboxaldehyde



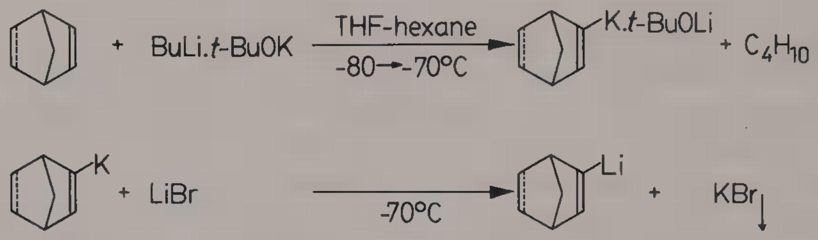
Scale: 0.3 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Procedure

A solution of 0.30 mol of 1-lithiocyclohexene or -cycloheptene in about 200 ml of Et_2O is cooled to -70 °C, and 0.32 mol (23.4 g) of DMF is added over 10 min, while keeping the temperature of the white suspension between -70 and -50 °C. After an additional 15 min (-40 °C) the suspension is poured with manual swirling into a mixture of 70 g of 36 % hydrochloric acid and 300 ml of ice water, contained in a 3 l conical flask. After vigorously shaking for 30 s, the layers are separated (the pH of the aqueous layer should be lower than 5). The aqueous layer is extracted three times with Et_2O and the combined solutions are washed with brine and then dried over $MgSO_4$. After removal of the ether under reduced pressure, the remaining liquid is distilled through a 40 cm Vigreux column to give cyclohexenecarboxaldehyde, b.p. 66 °C/12 mm, n_D^{20} 1.4954, in 78 % yield, and cycloheptenecarboxaldehyde, b.p. 82 °C/12 mm, n_D^{20} 1.4982, in 86 % yield, respectively.

4.7 Metallation of Norbornene and Norbornadiene



Scale: 0.10 molar (in base).

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

Although norbornene and norbornadiene possess bridgehead allylic hydrogen atoms, these are not likely to be abstracted by bases, since this would result in an unacceptably high strain (Bredt's rule). Compared to ethene, the olefinic hydrogen atoms have an increased acidity, and earlier investigations showed that these olefins are metallable. The vinylic protons in the diene are more acidic than those in norbornene [68, 78, 198]. Applying the "conventional" basic systems results in undesired reactions, such as cyclofragmentation [69]. These processes can be suppressed by using the kinetically very active couple BuLi · *t*-BuONa (or K) in THF or a THF-hexane mixture at very low temperatures [77, 236]. The best results were obtained by us when an excess of the olefin was used (compare Ref. [198]) to suppress the competitive metallation of THF. This is not felt as a serious drawback, since the olefins are not very expensive. The potassio derivatives initially formed in the metallation can be directly used for the preparation of a number of derivatives.

For other functionalization reactions, particularly those with enolizable aldehydes and ketones, potassium has to be replaced by lithium, this can be done by addition of a solution of anhydrous lithium bromide in THF [241].

Procedure

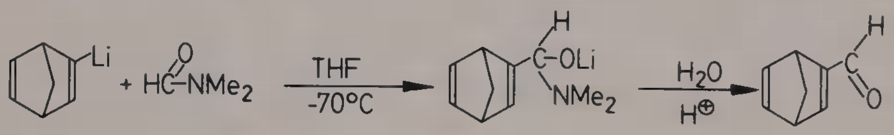
A solution of 0.11 mol (12.3 g) of *t*-BuOK in 60 ml of THF is added to a solution of 0.40 mol (37.6 g) of norbornene or 0.20 mol (18.4 g) of norbornadiene in 50 ml of THF with cooling to below −20 °C. The mixture is cooled to −80 °C and a solution of 0.11 mol (Note 1) of BuLi in 77 ml of hexane is added dropwise over 45 min. During this addition, the temperature is maintained between −75 and −85 °C. A light-brown solution (in the case of the diene a fine suspension in a brown solution) is formed. In the case of norbornadiene the cooling bath is removed after the addition, and the temperature allowed to rise to −40 °C, in the case of norbornene the mixture is stirred for an additional hour at −70 °C before the cooling bath is removed. Derivatization reactions are carried out without delay.

To obtain the lithium reagents, a solution of 11 g (excess, Note 2) of anhydrous lithium bromide in 40 ml of THF is added in 1 min with cooling to about −80 °C. Ten min after this addition further reactions can be carried out with the gelatinous suspension obtained.

Notes

1. The slight excess is used to "neutralize" traces of moisture adhering to the glass and present in the solvents and reagents, and small amounts of *t*-BuOH in the *t*-BuOK.
2. Obtained by heating the commercial anhydrous salt during 30 min at about 150 °C in a vacuum of 10 mmHg or less.

4.8 Norbornadienecarboxaldehyde



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

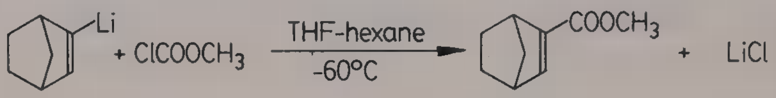
Procedure

The suspension of norbornadienyllithium (see preceding Exp.) is cooled to −70 °C and 0.13 mol (9.5 g) of DMF is added over 10 min, while keeping the temperature below −60 °C. After the addition, the cooling bath is removed and the temperature allowed to rise to −40 °C. The gelatinous white suspension is cautiously poured into a vigorously stirred mixture of 50 g of 36 % hydrochloric acid and 300 ml of ice water in a three-necked round-bottomed flask (3 l) equipped with a mechanical stirrer and with the outer necks open (Note 1). The first flask is rinsed twice with small portions of Et_2O, the rinsings being added to the acid solution. After separation of the layers, the aqueous layer is extracted four times with small portions of Et_2O. The combined organic solutions are washed with water and subsequently dried over $MgSO_4$. The residue, remaining after removal of the solvents in *vacuo*, is distilled through a 30 cm Vigreux column to give the aldehyde, b.p. 70 °C/15 mm, n_D^{23} 1.5162, in 72 % yield.

Notes

1. If the dilute hydrochloric acid is added to the reaction mixture, part of the amine liberated in the hydrolysis may add to the system C=C—C=O. Therefore, efficient stirring during the hydrolysis seems essential.

4.9 Reaction of Norbornenyllithium with Methyl Chloroformate



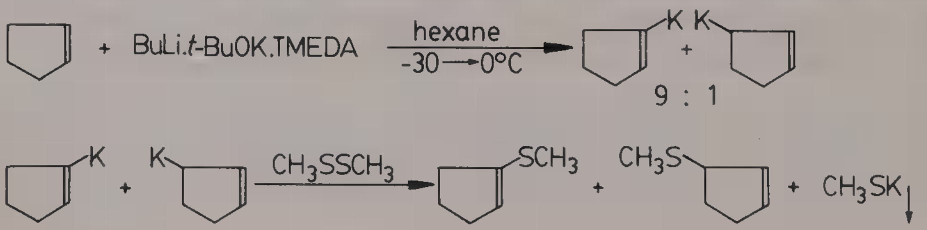
Scale: 0.10 molar (Li-compound).

Apparatus: 2 l three-necked, round-bottomed flask, provided with a thermometer-inlet combination and a mechanical stirrer. The suspension of the lithium compound is poured through the third neck.

Procedure

A mixture of 0.25 mol (large excess) of methyl chloroformate and 70 ml of THF is cooled to −60 °C. A solution of lithionorbornene (see Exp. 7) is added over ca. 10 min, into the vigorously stirred mixture of THF and methyl chloroformate and the remainder of the suspension is rinsed into the reaction flask with small amounts of Et_2O. During the addition the temperature of the reaction mixture is kept between −60 and −40 °C. After an additional 15 min, 300 ml of water is added with vigorous stirring. After separation of the layers, three extractions with ether are carried out. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated in a water aspirator vacuum. Careful distillation of the remaining liquid affords the ester, b.p. 85 °C/15 mm, n_D^{22} 1.4824, in 78 % yield.

4.10 Metallation of Cyclopentene and Subsequent Methylthiolation



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

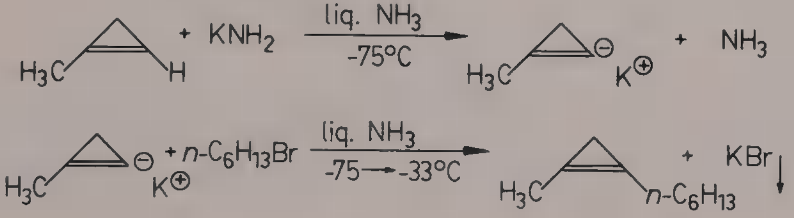
If BuLi · *t*-BuOK and a large excess of cyclopentene are allowed to interact under conditions similar to those used in the case of norbornene (Exp. 7), low to moderate yields of derivatization products are obtained after subsequent reaction with electrophilic reagents. Obviously, cyclopentene is metallated less easily than the strained olefin, and a considerable part of the base is consumed by reaction with THF. If this solvent is omitted, the conversion is very incomplete because of the slight solubility of the base couple in apolar solvents. The system BuLi · *t*-BuOK · TMEDA (equimolar amounts) has a good solubility in alkanes and is stable at temperatures up to about 0 °C [22]; at higher temperatures TMEDA is attacked. The procedure below shows that cyclopentene can be metallated with satisfactory results using this ternary system.

Procedure

A mixture of 0.40 mol (27.2 g) of cyclopentene, 0.11 mol of TMEDA, 40 ml of hexane and 0.11 mol (11.2 g) of powdered *t*-BuOK is cooled to −60 °C and a solution of 0.11 mol of BuLi in 77 ml (see Note 1 of Exp. 7) is added over 2 min, while keeping the temperature below −30 °C. This temperature is maintained for 1.5 h, then the cooling bath is removed, and the temperature is allowed to rise to 0 °C and stirring is continued for an additional hour. The suspension is then cooled to −40 °C and 60 ml of THF is added. Subsequently 0.11 mol (10.3 g) of dimethyl disulfide is added dropwise over 5 min keeping the temperature below 0 °C. After an additional 15 min 50 ml of water is added with vigorous stirring. The aqueous layer is extracted twice with small portions of Et_2O and the combined organic solutions are washed six times with 50 ml portions of water in order to remove the TMEDA and *t*-BuOH. After drying over $MgSO_4$, the greater part of the solvent is removed in a water-pump vacuum (bath temperature not higher than 30 °C) and the remaining liquid carefully distilled through a 40 cm Vigreux column. A 9:1 mixture of the "vinylic" and "allylic" sulfides, distilling at 50 °C/15 mmHg, n_D^{23} 1.5183, is obtained in 78% yield.

Cyclobutene presumably can be metallated under similar conditions (compare Ref. [198]). It is expected that this deprotonation will proceed much faster than that of cylopentene, and thus only a slight excess of cyclobutene needs to be used and the reaction time may be shortened considerably.

4.11 2-Hexyl-1-Methylcyclopropene



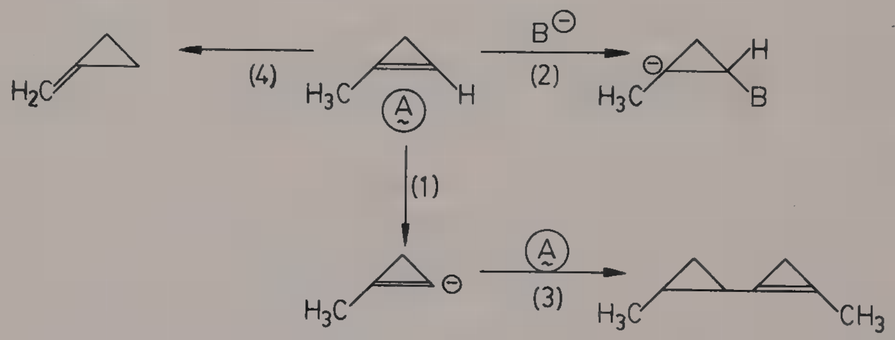
Scale: 0.10 molar (hexyl bromide)

Apparatus: Chap. I, Fig. 1, 1 l.

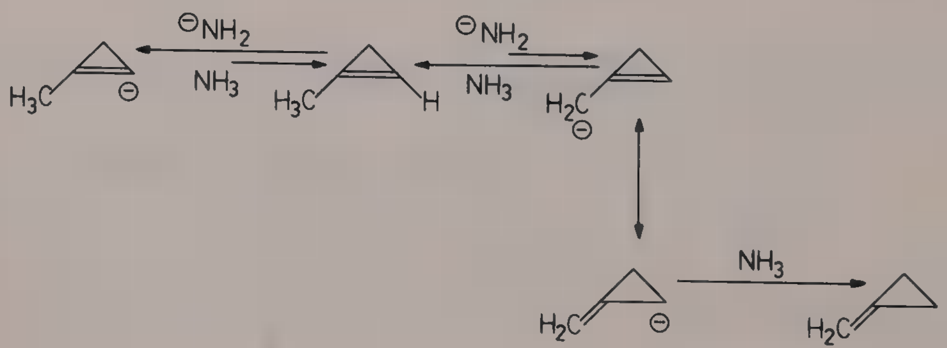
Introduction

The considerable strain in cyclopropenes gives rise to an increased acidity of vinylic hydrogen atoms. The pK values of vinylic hydrogen lie somewhere between those of acetylene and ethene [8]. Cyclopropenes and their alkali metal derivatives resemble to some extent 1-alkynes and alkynylides, respectively. There are however, also differences. The double bond in cyclopropenes is more prone to addition (of the basic reagent) than the triple bond in 1-alkynes. Because of their greater basicity cyclopropenylides are expected to be more reactive towards "electrophiles" than alkynylides. Interaction between 1-methylcyclopropene and a base may give rise to the following conversions:

1. Abstraction of the vinylic proton with formation of a cyclopropenylide.
2. Addition of the base across the double bond.
3. "Anionic" dimerization initiated by addition of a cyclopropenyl anion to the double bond of the free cycloalkene [16].
4. Base-induced isomerization to methylenecyclopropane.



Alkyllithium has been reported to add to cyclopropene [54]. In the presence of alkali amides this hydrocarbon can form oligomers. The chance of these additions, however, will be less great if the double bond bears an alkyl group. The kinetically favoured reaction between 1-methylcyclopropene and potassium amide undoubtedly will be formation of the cyclopropenyl anion. Although the deprotonation equilibrium is expected to be strongly on the side of the anion, (compare Ref. [8]) in the protic solvent ammonia it may easily shift to the other direction to give (*via* the "allylic" anion) methylenecyclopropane:



In order to minimize the chance of this isomerization, the deprotonation is carried out at a low temperature (strongly cooled liquid ammonia). The use of the soluble, and therefore kinetically more active, potassium amide, in combination with a large excess of 1-methylcyclopropene, warrants a sufficiently fast conversion into the cyclopropenyl anion. Ammonia is a particularly suitable solvent for alkylation reactions. As expected from its higher basicity the anion of 1-methylcyclopropene reacts more easily with bromohexane than do acetylides (compare Ref. [6]).

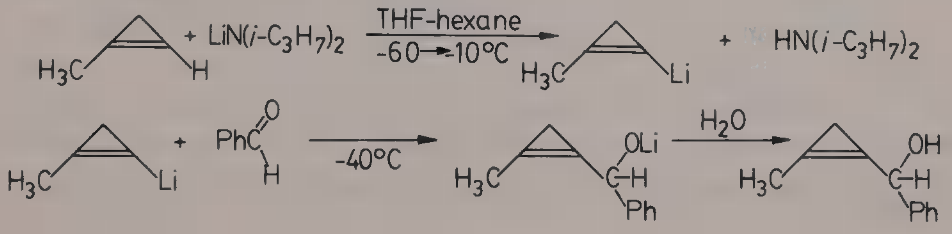
Procedure

A solution of potassium amide in ca. 250 ml of liquid ammonia is made from 5.0 g (0.13 mol) of potassium in a separate flask (see Chap. I, Exp. 8). The solution is filtered through glass wool and transferred into the reaction flask. The solution is cooled to about −75 °C, using a liquid nitrogen bath (solidification of the ammonia, m.p. about −80 °C, should be avoided). During this cooling operation nitrogen is passed through the flask. A mixture of 1-methylcyclopropene and methylenecyclopropane (Exp. 23, composition varying from 2:1 to 10:1) cooled to ca. −80 °C is quickly poured into the flask. The added quantity of this mixture is such that it corresponds to an amount of 0.15 mol or somewhat more. Five min after this addition 0.10 mol of bromohexane is added in one portion and the cooling bath is removed. When after some 20 min, the ammonia has started to boil, b.p. ~ −33 °C, the equipment on the outer necks of the flask is removed and stirring is continued for another half hour. The flask is then placed in a water bath at 35 to 40 °C. When practically all ammonia has evaporated, 50 ml of dichloromethane and 300 ml of water are added successively with vigorous stirring. After the lower layer has been separated (Note 1), the aqueous layer is extracted three times with 30 ml portions of dichloromethane. The combined organic solutions are washed with cold (0 °C) 2N hydrochloric acid in order to remove small amounts of hexylamine. After drying over $MgSO_4$ the solution is concentrated in a water-aspirator vacuum, using a water bath of 35 to 40 °C. Distillation of the remaining liquid through a 30 cm Vigreux column gives 2-hexyl-1-methylcyclopropene, b.p. 52 °C/15 mm, n_D^{19} 1.4376, in 70% yield. The compound appears to be reasonably stable at room temperature.

Notes

1. If more than 100 mg of ferric nitrate is used in the preparation of potassium amide, difficulties may be encountered in the separation of the layers owing to the formation of a gel of ferric hydroxide.

4.12 Lithiation of 1-Methylcyclopropene and Subsequent Reaction with Benzaldehyde



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction (compare also introduction to Exp. 11)
For couplings of metallated cyclopropenes with carbonyl compounds liquid ammonia seems to be generally a less suitable solvent since enolizable carbonyl compounds may easily undergo deprotonation under strongly polar conditions, while aldehydes such as benzaldehyde may react with the solvent. For the lithiation of 1-methylcyclopropene both BuLi · THF and LDA · THF seem suitable systems. We prefer to use, however, the latter base because of its decreased tendency to add across multiple bonds. The thermodynamic basicity of LDA will be sufficient though in the less polar THF the rate of deprotonation might be lower than that with potassium amide in liquid ammonia.

Procedure
A solution of 0.06 mol of LDA in about 50 ml of THF and 50 ml of hexane is prepared as described in Chap. I, Exp. 5. The solution is cooled to −60 °C and a cold (−30 °C) mixture of 20 ml of THF, 1-methylcyclopropene and methylenecyclopropane (corresponding to about 0.1 mol of 1-methylcyclopropene) is added in one portion. The cooling bath is removed and the temperature allowed to rise to −10 °C (Note 1). The solution is then recooled to −70 °C and a mixture of 0.05 mol (5.3 g) of benzaldehyde in 10 ml of THF is added over 5 min. The solution is kept at −50 °C for an additional 15 min, then 100 ml of water is added with vigorous stirring. The organic layer and three ethereal extracts are combined and dried over $MgSO_4$. The solvent is removed by evaporation in a vacuum of 10 mmHg, the last traces in an oil-pump vacuum (1 mmHg or less). During this operation the bath temperature is kept below 40 °C. The resulting liquid is practically colourless (~100 % yield), n_D^{20} 1.542, and was established to be practically pure carbinol.

Notes
1. We have the impression that the deprotonation is slower than that of 1-alkynes under the same conditions.

4.13 1,3-Dimetallation of Vinylacetylene and Subsequent Reaction with two Equivalents of Me_3SiCl and one Equivalent of n-$C_7H_{15}Br$

$$HC{\equiv}C{-}CH{=}CH_2 + 2\,BuLi \cdot t\text{-}BuOK \xrightarrow[-95\ \rightarrow\ -10\ ^\circ C]{THF\text{-}hexane}$$

$$KC{\equiv}C{-}C(K){=}CH_2 + 2\,C_4H_{10} + 2\,t\text{-}BuOLi$$

$$KC{\equiv}C{-}C(K){=}CH_2 + C_7H_{15}Br \xrightarrow[-30\ \rightarrow\ +30\ ^\circ C]{}$$

$$KC\equiv C-C(C_7H_{15})=CH_2 \xrightarrow{H_2O} HC\equiv C-C(C_7H_{15})=CH_2$$

$$KC\equiv C-C(K)=CH_2+2\,Me_3SiCl \xrightarrow[-65\ \rightarrow\ +10\ ^\circ C]{}$$

$$Me_3Si-C\equiv C-C(SiMe_3)=CH_2+2\,KCl$$

Scale: 0.05 molar (vinylacetylene).

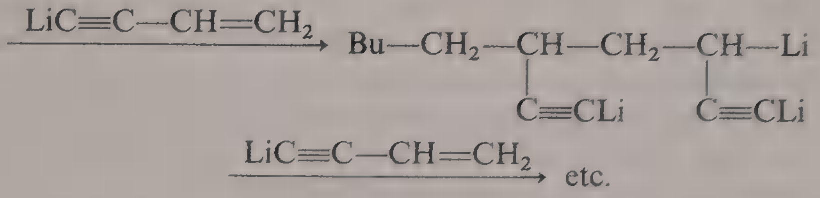
Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

Although the conversions described in this experiment do not have much practical importance, they are interesting for a number of reasons. After abstraction of the acetylenic proton from vinylacetylene there are three possible reactions with the base:
addition across the double bond,
abstraction of the proton in the 3-position or
one of the protons in the 4-position.

Interaction at low temperatures between vinylacetylene and an excess of butyllithium (or BuLi · TMEDA) in Et_2O or THF gives rise to the formation of polymeric material, containing terminal acetylenic functions (identified by IR spectroscopy). This result may be explained by assuming a chain of additions across the double bond in $LiC\equiv C-CH=CH_2$, initiated by addition of butyllithium:

$$LiC\equiv C-CH=CH_2+BuLi \longrightarrow LiC\equiv C-CH(Li)-CH_2Bu$$



$$\xrightarrow{LiC\equiv C-CH=CH_2} Bu-CH_2-\underset{\displaystyle C\equiv CLi}{\underset{|}{CH}}-CH_2-\underset{\displaystyle C\equiv CLi}{\underset{|}{CH}}-Li$$

$$\xrightarrow{LiC\equiv C-CH=CH_2} \text{etc.}$$

Interestingly, the polymerization of ethene takes place at considerably higher temperatures and only under high pressure [2]. The $^{\ominus}C\equiv C$-grouping apparently activates the double bond for addition. Deprotonation of the vinyl group in lithiovinylacetylene can be brought about with the strongly "protophilic" basic system BuLi · *t*-BuOK in THF at very low temperatures. Subsequent reaction with an excess of trimethylchlorosilane gives 1,3-bis(trimethylsilyl)vinylacetylene in 60–70% yields. Conjugative stabilization of $^{\ominus}C\equiv C-\overset{\ominus}{C}=CH_2$ might be invoked to explain the preference for the removal of the proton in the 3-position. When considering the difference in basicity (pK of terminal acetylenes about 25, pK of ethene about 36), one might expect that addition of one equivalent of an electrophilic reagent E to $KC\equiv C-C(K)=CH_2$ would result in regiospecific formation of $HC\equiv C-C(E)=CH_2$. This turns out to be the case with alkylations, reaction with one equivalent of a higher alkyl bromide RBr gives the enynes $HC\equiv C-C(R)=CH_2$ in reasonable yields, the isomeric $RC\equiv C-CH=CH_2$ are apparently not formed. Reaction with dialkyl disulfides or alkyl thiocyanates affords unstable compounds $HC{\equiv}C{-}C(SR){=}CH_2$ regiospecifically. In contrast, silylation with Me_3SiCl is at random and $Me_3SiC{\equiv}C{-}CH{=}CH_2$, $HC{\equiv}C{-}C(SiMe_3){=}CH_2$ are produced in comparable amounts [9].

Procedure

A solution of 0.14 mol of butyllithium in 95 ml of hexane (large excess, Note 1) is cooled to −100 °C (Note 2). A solution of 0.15 mol (16.8 g) of *t*-BuOK in 65 ml of THF is then added over 10 min, while keeping the temperature below −90 °C (Note 3). After this addition the solution is stirred for an additional 10 min at −95 °C. Subsequently a mixture of 0.05 mol (2.6 g) of vinylacetylene (Exp. 22) in 40 ml of THF is added dropwise over 40 min, while keeping the temperature close to −95 °C. The cooling bath is then removed and the temperature allowed to rise to 0 °C (Note 4). At about −15 °C a light-brown suspension appears (Note 5). The mixture is cooled again to −65 °C and 25 g (large excess) of trimethylchlorosilane is added in a few seconds with vigorous stirring. The cooling bath is removed and the temperature allowed to rise to +10 °C whereupon the white suspension is poured into 500 ml of ice water. After vigorous shaking and separation of the layers, three extractions with 40 ml portions of pentane are carried out. The combined organic solutions are washed four times with brine and are subsequently dried over $MgSO_4$. The solvent and volatile products ($Me_3SiOSiMe_3$, *t*-$BuOSiMe_3$) are removed *in vacuo*, keeping the bath temperature between 30 and 35 °C (Note 6). Careful distillation of the remaining, almost colorless liquid, through a 40 cm Vigreux column gives the disilyl derivative, b.p. 65 °C/15 mm, n_D^{20} 1.4525, in 60–68 % yield.

To prepare the alkyl derivative $HC{\equiv}C{-}C(C_7H_{15}){=}CH_2$ the brown suspension is cooled to −30 °C and 0.04 mol of heptyl bromide (Note 7) is added in one portion. The cooling bath is removed and the temperature is allowed to rise to +20 °C and stirring is continued for an additional half hour, then the light-brown suspension is poured into 200 ml of ice water. After vigorous shaking and separation of the layers, three extractions with pentane are carried out. The combined organic solutions are washed with brine and subsequently concentrated in vacuo. Distillation of the remaining liquid through a 20 cm Vigreux column gives the enyne, b.p. 81 °C/15 mm, n_D^{20} 1.4481, in 45–56 % yield. There is a viscous residue of about 4 g.

Notes

1. An excess of base is used to compensate for losses owing to metallation of the THF.
2. Formation of a solid crust on the bottom of the flask should be avoided. Therefore cooling should occur occasionally.
3. At higher temperatures metallation of THF may become a serious side reaction.
4. The potassio derivative of THF, formed with the excess of base, decomposes at temperatures above −40 °C, giving ethene and potassium ethenolate (compare Ref. [24]).
5. The precipitate is probably $H_2C{=}CHOK$.

6. If the solvent is removed too quickly, part of the relatively volatile silylation product may be swept off with the solvent.
7. If an equivalent amount of the bromide is used, the product may be contaminated with bromoheptane, which has a comparable volatility.

4.14 Metallation of Allene with Butyllithium

$$H_2C{=}C{=}CH_2 + BuLi \xrightarrow[-90\ \rightarrow\ -60\ °C]{\text{THF-hexane}} H_2C{=}C{=}CH{-}Li + C_4H_{10}$$

Scale: 0.20 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

Whereas ethene and butyllithium do not react at all in THF in the temperature range of −90 to +30 °C, allene is metallated quantitatively in a few minutes at temperatures around −70 °C. If the reaction with butyllithium is carried out at considerably higher temperatures, isomerization into propynyllithium $CH_3C{\equiv}C{-}Li$ may take place. pK values of allene and its derivatives have not been determined, but the resonance stabilization in the anions is expected to give rise to a pK value which is lower than that of ethene. Qualitative comparison of the rates of alkylation with alkyl bromides of metallated allenes and sp^2-metallated alkenes gives the impression that the allenic intermediates react faster in spite of their (presumed) lower basicity. The yield-reducing dehydrohalogenation of the alkyl halides occurs to a lesser extent with metallated allenes [9].

Procedure

THF (120 ml) is added to a solution of 0.20 mol of butyllithium in 140 ml of hexane with cooling below 0 °C. The mixture is cooled to −90 °C (occasional cooling in a bath of liquid nitrogen) and a cold (−50 °C) solution of 0.25 mol (10.0 g) of allene (prepared as described in Organic Synthesis *42*, 12) in 30 ml of THF (obtained by introducing gaseous allene into strongly cooled THF) is added over 10 min. During this addition the temperature is kept between −80 and −60 °C. Stirring at −60 °C is continued for an additional 15 min. The solution is then ready for derivatization reactions (Exps. 15 and 16).

4.15 1,2-Decadiene from Allenyllithium

$$H_2C{=}C{=}CHLi + n\text{-}C_7H_{15}Br \xrightarrow[-60\ °C]{\text{THF-hexane, HMPT}} H_2C{=}C{=}CH{-}C_7H_{15} + LiBr$$

Scale: 0.2 molar.

Apparatus: see Exp. 14.

Procedure
HMPT (15 ml; dried as described in Chap. I-2) is added over 1 min to a solution of 0.20 mol of allenyllithium, while keeping the temperature around −90 °C. Heptyl bromide (0.18 mol, 32.2 g) is then added over 15 min, while keeping the temperature between −60 and −70 °C. After stirring for an additional 45 min at −60 °C, 200 ml of water is added with vigorous stirring. After separation of the layers, two extractions of the aqueous phase with Et_2O or pentane are carried out. The combined organic solutions are washed four times with water and are subsequently dried over $MgSO_4$. The liquid remaining after removal of the solvent in vacuo, is distilled through a 40 cm Vigreux column to give the allene (b.p. 62 °C/15 mm, n_D^{20} 1.4432) in 90 % yield.

4.16 2,3-Butadienoic Acid from Allenyllithium

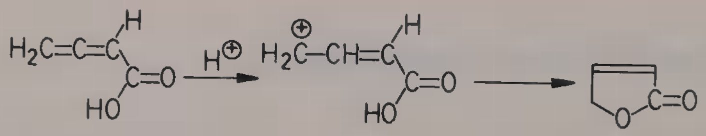
$$H_2C{=}C{=}CH{-}Li + CO_2 \xrightarrow[-70\ °C]{\text{THF-hexane}} H_2C{=}C{=}CHCOOLi$$

$$\xrightarrow[H_2O]{H^+} H_2C{=}C{=}CHCOOH$$

Scale: 0.20 molar.

Apparatus: 2 l round-bottomed, three-necked flask, provided with an inlet tube (for CO_2), a mechanical stirrer and a combination of thermometer and gas outlet.

Introduction
The experimental conditions for the carboxylation of allenyllithium are governed by the consideration that introduction of the COOLi group renders the allenic protons more acidic (resonance stabilization). If the normal order addition is used (introduction of CO_2 into the solution of allenyllithium), the allenic carboxylate primarily formed may easily be deprotonated by the strongly basic allenyllithium. The new species (either $LiCH{=}C{=}CHCOOLi$ or $H_2C{=}C{=}C(Li)COOLi$) may react also with CO_2. To avoid this situation the solution of allenyllithium is gradually added to a strongly cooled solution of carbon dioxide in THF. As usual, liberation of the acid occurs by adding mineral acid. In view of the possibility of an acid-catalyzed cyclization to a lactone too strongly acidic conditions should be avoided:



Procedure
THF (200 ml) is cooled to −90 °C (occasional cooling with liquid nitrogen, care being taken that no solid is formed on the bottom of the flask, Note 1). A vigorous stream of carbon dioxide (about 1 l/min) is introduced for 5 min with efficient stirring, while keeping the temperature between −80 and −95 °C. The thermometer-outlet combination is then removed and a solution of 0.20 mol of

allenyllithium (Exp. 14), cooled at −60 °C, is poured through the open neck (Note 2), while continuing the introduction of CO_2 and occasional cooling with liquid nitrogen (Note 1). After this addition, which is carried out over 3 min, the cooling bath is removed and the introduction of CO_2 is stopped. The thermometer is placed again in the flask and the temperature of the white suspension is allowed to rise to −20 °C. The suspension is then cautiously poured, with manual swirling, into a mixture of 22 g of 36 % hydrochloric acid and 150 ml of water, which is contained in a 3 l wide-necked conical flask. After separation of the layers the aqueous layer is saturated with ammonium chloride and subsequently extracted 5 times with small portions of THF. The unwashed organic solutions dried over 100 g of $MgSO_4$ (shaking or stirring for 15 min). After filtration through sintered glass and rinsing the desiccant with Et_2O, the solvent is removed in a water-aspirator vacuum. The last traces of volatile components are removed by warming the residue during 30 min at 40 °C in a vacuum of 0.5 to 1 mmHg. The remaining liquid solidifies upon cooling to room temperature and consists of practically pure 2,3-butadienoic acid in at least 80 % yield. The m.p. after recrystallization from a 1:5 mixture of dichloromethane and pentane is 62 °C.

Notes

1. In that case the rate of stirring should be reduced until the solid has disappeared.
2. The solution may also be transferred using a syringe.

4.17 Allenylmagnesium Bromide

$$HC{\equiv}C{-}CH_2Br + Mg \xrightarrow[0-5\,^\circ C]{Et_2O} H_2C{=}C{=}CH{-}MgBr$$

Scale: 0.6 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Procedure

Magnesium turnings (24 g, 1 mol) are covered with 100 ml of Et_2O. Mercury(II)chloride (1.5 g) is added, and the mixture is stirred for 30 min at room temperature. The flask is then placed in a bath with crushed ice and ice water. When the temperature of the ether has reached 0 °C, 5 ml of freshly distilled propargyl bromide are added. As a rule the reaction starts within 15 min, as is shown by a gradual rise in temperature, if the reaction has not started after 30 min, a second portion of 5 ml of the bromide is added. If after the start of the reaction the temperature threatens to rise above 10 °C, the flask is temporarily cooled in a bath with dry ice and acetone. After the exothermic reaction has subsided the remainder of 0.65 mol (77.4 g) of propargyl bromide is added dropwise over a period of 1 h, keeping the temperature of the mixture between 0 and +5 °C. The mixture is stirred for an additional 1 h at this temperature, after which the grey solution is carefully decanted from the excess of metal. The magnesium is rinsed two times with small portions of Et_2O and the rinsings combined with the main solution. The reagent may be stored in a refrigerator at −20 to −30 °C.

The solution contains about 0.5 mol of allenylmagnesium bromide. This estimation is based upon the results of several derivatization reactions carried out in the laboratory (compare also Refs 6 and 7). Reaction at room temperature with Me_3SiCl (0.5 mol, 54.3 g), followed by aqueous hydrolysis, gives a mixture of $Me_3SiCH_2C{\equiv}CH$ and $Me_3SiCH{=}C{=}CH_2$ (ratio 92:8), b.p. 92 °C/760 mm, in an excellent yield.

4.18 Lithiation of 1,1-Dimethylallene

$$(CH_3)_2C{=}C{=}CH_2 + BuLi \xrightarrow[-60\ \rightarrow\ -30\ ^\circ C]{\text{THF-hexane}}$$

$$(CH_3)_2C{=}C{=}CH{-}Li + C_4H_{10}$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction (see also introduction of Exp. 14)
The reaction conditions for the metallation of propadiene show that this compound is readily metallated. Introduction of alkyl substituents causes a marked decrease of the kinetic acidity of the allenic protons. This is reflected in the higher temperature in the lithiation of 1,1-dimethylallene.

Procedure
THF (80 ml) is added to a solution of 0.10 mol of butyllithium in 70 ml of hexane, cooled at about −20 °C. The mixture is cooled to −60 °C and 0.12 mol (8.2 g) of 1,1-dimethylallene (see Ref. [7] for the preparation) is added over a few min. The cooling bath is removed and the temperature allowed to rise to −30 °C. After stirring for an additional period of 30 min the solution is ready for further conversions.

4.19 Metallation of 2-Alkynes with Butyllithium

$$CH_3C{\equiv}C{-}R + BuLi \xrightarrow[0\ \rightarrow\ 25\ ^\circ C]{\text{THF-hexane}}$$

$$H_2C{=}C{=}C(Li)R + C_4H_{10}\ (R{=}\text{alkyl})$$

$$\xrightarrow{(CH_3)_3SiCl} R{-}C{\equiv}C{-}CH_2{-}Si(CH_3)_3$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

2-Alkynes $CH_3C{\equiv}C{-}R$ with $R{=}CH_3$ or an higher alkyl group are metallated under relatively mild conditions by butyllithium [71]. The deprotonation is regiospecific, affording species which could be considered as 3-metallated 1,2-dienes. Reactions with electrophilic reagents, e.g. alkyl halides and dialkyl disulfides, in general give both the acetylenic and the allenic derivative [9], so that the synthetic utility is limited. Reactions with Me_3SiCl, however, afford the acetylenic derivative regiospecifically [9]. Exchange of lithium for another counter ion (K, Mg, Zn, Cu) in some derivatizations could lead to a synthetically useful regioselectivity.

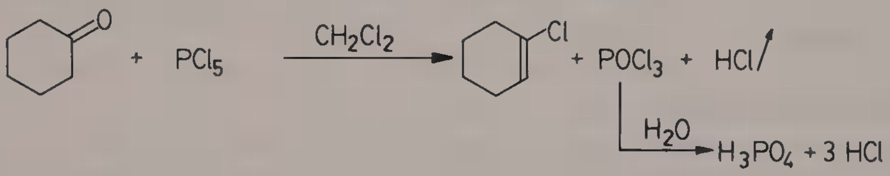
Procedure

THF (80 ml) is added to a solution of 0.10 mol of butyllithium in 70 ml of hexane, cooled below −10 °C. The 2-alkyne (0.11 mol) is added over 5 min, while keeping the temperature between 0 and 10 °C. After stirring for 5 min at 10 °C the solution is warmed to 25 °C and held at that temperature for 30 min. Addition of 0.12 mol (13.0 g) of trimethylchlorosilane (at −60 °C) to the resulting solution, followed by aqueous work-up, gives $C_6H_{13}C{\equiv}C{-}CH_2SiMe_3$ ($R{=}C_6H_{13}$), b.p. 95 °C/15 mm, n_D^{20} 1.4467, in 96 % yield.

Notes

1. The preparation of $CH_3C{\equiv}C{-}R$, $R{=}CH_3$, is described in Ref. [6], p. 146. $CH_3C{\equiv}C{-}C_6H_{13}$ is prepared by adding $HC{\equiv}C{-}CH_2{-}C_6H_{13}$ [6] (0.10 mol, 12.2 g) to a solution of 2 g of *t*-BuOK in 50 ml of DMSO. The mixture is kept between 25 and 35 °C. After 15 min water (300 ml) is added, after which the isomerization product is isolated in the usual way.

4.20 1-Chlorocyclohexene and 1-Chlorocycloheptene

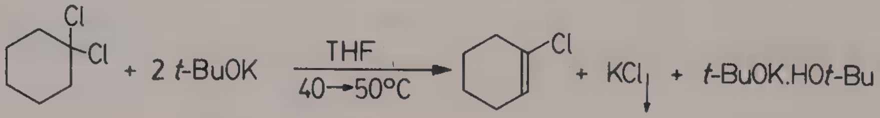


Scale: 1.0 molar.

Apparatus: 2 l three-necked flask, fitted with a dropping funnel, a mechanical stirrer and a combination of thermometer and outlet.

Procedure (compare Ref. [76])

A mixture of 1.1 mol (227 g) of Phosphorus pentachloride and 150 ml of dichloromethane is cooled to +5 °C, and 1.0 mol (98 and 112 g) of the cycloalkanone is added over a period of 30 min. There is no strong heating effect (escaping of HCl from the solution!), and occasional cooling is sufficient to keep the temperature of the mixture between 5 and 10 °C. When the ketone has been added, practically all PCl_5 has dissolved. The cooling bath is removed and the light-brown solution is stirred for an additional 2.5 h at 25 °C. Ice water (500 ml) is then added, and the mixture is vigorously stirred. Its temperature is kept below 35 °C by occasional cooling. When no more heat is evolved and the temperature of the mixture has dropped (without external cooling) by 3 °C, the organic layer is separated off. The aqueous layer is extracted twice with small portions of dichloromethane and the combined organic solutions are washed twice with a dilute aqueous solution of potassium hydroxide and subsequently dried over $MgSO_4$. The greater part of the solvent is then distilled off at normal pressure through a short column and the remaining liquid carefully distilled through a 40 cm Widmer column. 1-Chlorocyclohexene, b.p. 36 °C/12 mmHg, n_D^{20} 1.4812, and 1-chlorocycloheptene, b.p. 50 °C/12 mmHg, n_D^{20} 1.4862, are obtained in yields up to ~80 %. The residues of the distillations consist mainly of the geminal dichlorocycloalkanes. If desired, these compounds can be converted into the 1-chlorocycloalkenes by reaction with a solution of *t*-BuOK in THF:



4.21 1-Bromo-2-Methylpropene

$$(CH_3)_2C{=}CH_2 + Br_2 \xrightarrow[\text{low temperature}]{Et_2O} (CH_3)_2C(Br){-}CH_2Br$$

$$(CH_3)_2C(Br){-}CH_2Br + NaOC_2H_5 \xrightarrow[30\ \to\ 80\ °C]{C_2H_5OH}$$

$$(CH_3)_2C{=}CHBr + NaBr\downarrow + HOC_2H_5$$

Scale: 1.0 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Procedure

Isobutene (1.2 mol, 67.2 g) is condensed in a cold trap, and the liquid is mixed with 350 ml of dry Et_2O cooled to −30 °C. The mixture is cooled to −80 °C and dry bromine (1.0 mol, 160 g), obtained by shaking technical bromine with concentrated sulfuric acid and subsequently distilling the lower layer) is added dropwise at a rate such that the temperature can be easily kept below −40 °C (cooling in a bath of liquid nitrogen permits a rapid addition). The resulting, almost colourless solution is concentrated in a water-aspirator vacuum. The remaining liquid is added over a few min to a solution of 1.3 mol of sodium ethoxide in 350 ml of 96 % ethanol (prepared by dissolving sodium in ethanol). The temperature of the mixture rises gradually and salt separates from the solution. When the exothermic reaction has subsided, a reflux condenser is placed on the flask, and the mixture is heated for 30 min under reflux. After cooling to room temperature the suspension is poured into 2 l of ice water. After separation of the layers, the aqueous layer is extracted three times with 30 ml portions of dichloromethane. The combined extracts are washed with small portions of water and subsequently dried over $MgSO_4$. The undiluted product is also washed with water and dried over a small amount of $MgSO_4$. After the greater part of the dichloromethane has been distilled off through a long (40 to 60 cm) Widmer column, and the temperature in the head of the column begins to rise rapidly, the distillation is interrupted, and the other part of the product is poured into the distillation flask. Distillation gives the bromoalkene, b.p. 92 °C/760 mm, n_D^{20} 1.4538, in 76 % yield.

4.22 Vinylacetylene

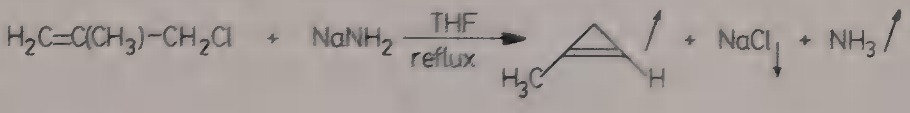
$$ClCH_2CH{=}CHCH_2Cl \xrightarrow[\text{xylene} + \text{DMSO, } 120\ ^\circ\text{C}]{\text{KOH} + \text{CaO}} HC{\equiv}C{-}CH{=}CH_2$$

Scale: 1.0 molar.

Apparatus: 2 l three-necked, round-bottomed flask, fitted with a combination of a dropping funnel and a gas inlet, a gas-tight mechanical stirrer and a combination of a thermometer (this should dip into the liquid) and a very efficient reflux condenser. The top of the condenser is connected with a cold trap (−80 °C) via plastic tubes and a tube filled with anhydrous calcium chloride. A slow stream of nitrogen is passed through the apparatus.

Procedure
The flask is charged with 350 ml of xylene, 140 ml of DMSO, 200 g of freshly, machine-powdered KOH and 120 g of powdered calcium oxide. The mixture is heated to 110 °C, and 1.0 mol (125 g) of *trans*-1,4-dichloro-2-butene (if the commercially available 1:1-mixture of 1,4-dichlorobutene and 1,2-dichloro-3-butene is used, yields are 20–30 % lower) is added dropwise with vigorous stirring. During this addition, which is carried out over 30 min, the temperature of the mixture is kept between 110 and 120 °C (occasional cooling). The conversion is terminated by heating the mixture under gentle reflux for an additional 30 min. The cold trap is placed in a water bath (the temperature of the bath being gradually raised from 15 to 30 °C) and the gas is condensed in another trap, cooled at −80 °C. Pure vinylacetylene is obtained in ca. 85 % yield, b.p. at normal pressure ca. +5 °C.

4.23 1-Methylcyclopropene

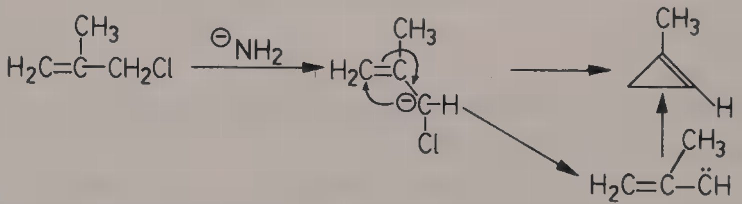


Scale: 0.5 molar.

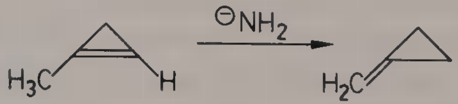
Apparatus: 500 ml three-necked, round-bottomed flask, fitted with a dropping funnel, a gas inlet (placed on the middle neck and reaching 1 cm above the level of the liquid in the flask), and a reflux condenser. The reaction mixture is stirred magnetically, using a stirring bar not longer than 2 cm. The gasses are led through two washing bottles filled with 4N sulfuric acid, and through two drying tubes filled with lumps of anhydrous calcium chloride, and are condensed in two traps cooled at −80 °C. All connections are made gas-tight. The end of the inlet tube in the washing bottles should not dip more than 3 cm into the acid solution. A slow stream of nitrogen (150–200 ml/min) is passed through the apparatus during the preparation.

Introduction

In spite of the relatively low yields, reaction of an allylic chloride with an alkali amide in an organic solvent is the most simple way to prepare cyclopropene and some methyl derivatives. The transient carbenoid, generated by abstraction of an allylic proton, rearranges to the cyclopropene, either via a cycloelimination of chloride or via a free carbene:



The modest yields may be ascribed to a number of side reactions. Allylic halides are very prone to nucleophilic attack, which in this case will give rise to the formation of an allylic amine. One could also imagine a nucleophilic attack of the intermediary carbenoid on the allylic halide, or metallation of the cyclopropene by alkali amide and subsequent coupling of the cyclopropenylide with the allylic halide. The relatively high temperatures in the preparations of the cyclopropenes will certainly favour oligomerization, which may be a merely thermal one or an ionic process (similar to that observed by Dutch investigators [16] in the case of the parent hydrocarbon). Such reactions afford products which are considerably less volatile than the cyclopropenes and therefore will remain in the reaction mixture. One obvious subsequent reaction is the irreversible base-induced isomerization to methylenecyclopropane, which cannot be separated from the desired product [79]:



We have carried out the procedure for 1-methylcyclopropene several times with freshly prepared sodamide (see Chap. I, Exp. 7). In most cases the ratio of 1-methylcyclopropene to methylenecyclopropane was greater than 3, in one experiment even 10. The original paper reports the formation of almost pure 1-methylcyclopropene. The authors used commercial sodamide, which might be less reactive than the freshly prepared base, and therefore unable to cause isomerization. Since the protons in methylenecyclopropane are less acidic than the "vinylic" proton in 1-methylcyclopropene, the exocyclic isomer is not likely to interfere in metallation reactions with alkali amides in liquid ammonia or with LDA in THF.

Procedure
The flask is charged with sodamide, prepared from 16 g (0.7 mol) of sodium (see Chap. I, Exp. 7), and 60 ml of THF. It is then placed in the oil of the heating bath, care being taken that the levels of the oil and the THF are equal. Magnetic stirring is carried out at a rate such that the sodamide is completely suspended and the liquid rotates in a continuous vortex which does not reach the bottom of the flask (splashing should be avoided). The bath temperature is adjusted to 95 °C, which is sufficient to cause a gentle reflux of the THF. Methallyl chloride (0.5 mol, 45.3 g) is added dropwise and after about 15 min liquid begins to condense in the first trap. The addition of the allylic halide is carried out over 45 min and after an additional 1.5 h the evolution of gas (observable by temporarily stopping the flow of nitrogen) has become negligible. The traps are connected to a third one cooled to −80 °C, after which they are placed in a bath at 15 °C. Toward the end of this "distillation" the bath temperature is raised to 25 °C. NMR spectroscopy (CCl_4 as solvent) shows the ratio of 1-methylcyclopropene and methylenecyclopropane. The yield of the mixture varies from 35 to 50%, the ratio of the isomers from 3:1 to 10:1. We have some impression that higher bath temperatures, in combination with too small amounts of THF give rise to less favourable ratios.

4.24 Metallation of Ethene [21]

$$H_2C{=}CH_2 + BuLi \cdot t\text{-}BuOK \xrightarrow[-25\ °C]{\text{TMEDA, hexane}}$$

$$H_2C{=}CH{-}K \cdot t\text{-}BuOLi(TMEDA)\downarrow + C_4H_{10}$$

$$H_2C{=}CH{-}K + LiBr \xrightarrow[0\ °C]{\text{THF-hexane}} H_2C{=}CH{-}Li + KBr\downarrow$$

Scale: 0.10 molar.

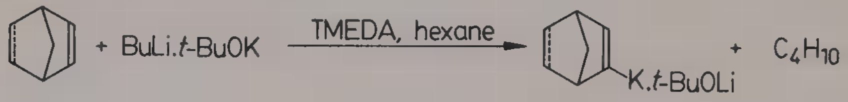
Apparatus: 1 l three-necked, round-bottomed flask, fitted with a gas inlet tube, a mechanical stirrer and a combination of a gas outlet and a thermometer.

Procedure
TMEDA (0.10 mol, 11.6 g) is added to a suspension of 0.10 mol (11.2 g) of *t*-BuOK in 40 ml of hexane. Subsequently a solution of 0.10 mol of BuLi is introduced, using a syringe, while keeping the temperature of the mixture below −40 °C. Most of the suspended material dissolves. The mixture is cooled to −70 °C, and a vigorous stream of dry ethene is passed through the solution for 2 min. The cooling bath is then removed and the temperature allowed to rise to −25 °C using a bath thermostated at −25 °C. Ethene is bubbled through the solution (150–200 ml/min), which is stirred at a moderate rate. After about 1 h a fine suspension appears. Stirring is continued for an additional hour at −25 °C, then 70 ml of THF is added, whereupon most of the suspended material dissolves. The lithium compound is

prepared by adding (at ~0 °C) a solution of 0.12 mol of anhydrous LiBr in 40 ml of THF to the vigorously stirred mixture giving rise to a white gelatinous suspension.

For derivatization reactions (showing the high efficiency of the metallation) see Ref. [21].

4.25 Metallation of Norbornene and Norbornadiene with BuLi · *t*-BuOK · TMEDA



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

Exp. 7 describes the metallation of the olefins with a 1:1 complex of BuLi and *t*-BuOK (prepared in situ) in a THF-hexane mixture. The deprotonations proceed with high efficiency, provided that a large excess of the olefins are used to suppress the competitive attack of THF by the strongly basic reagent. The system BuLi · *t*-BuOK · TMEDA is soluble in hexane and has a reasonable stability below −20 °C. The metallations can be carried out with excellent results in a relatively short time (up to 2 h), using a moderate excess of the olefins.

Procedure

To the 1:1:1 mixture of Buli, *t*-BuOK and TMEDA (see Chap. I, Exp. 4) in about 80 ml of hexane is added the olefin (0.15 mol, 14.1 g of norbornene or 0.12 mol, 11.0 g of the diene) with cooling to below −40 °C. The solution is kept for 2.5 h at −25 °C (for norbornene) or 1 h at −35 °C (norbornadiene). The efficiencies of the metallations can be checked by successive addition at −30 °C of THF (70 ml) and CH_3SSCH_3 (0.12 mol) and subsequently allowing the temperature to rise to 0 °C. The expected sulfides are obtained in yields of at least 90%. For other functionalizations see Exps. 7, 8 and 9.

4.26. (*Z*)-2-Lithio-1-Ethoxyethene

$$(Z)\text{-BrCH=CH—OEt} + \text{EtLi} \xrightarrow[-45\ ^\circ\text{C}]{\text{LiBr, Et}_2\text{O}} (Z)\text{-LiCH=CH—OEt} + \text{EtBr}$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

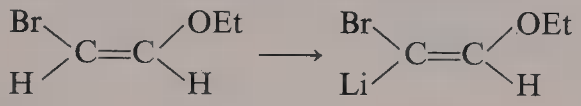
Introduction

(*Z*)-2-lithio-1-ethoxyethene, a synthetic equivalent of the anion of acetaldehyde $^{\ominus}CH_2CH{=}O$, has been generated from (*Z*)-$Bu_3SnCH{=}CHOC_2H_5$ and butyllithium [206, 207]. A disadvantage of this method is the presence of tetrabutyltin, which may give rise to difficulties during the work-up of less volatile products. Schlosser et al. [202] generated the lithiovinylether by reacting the easily obtainable (Z)-$BrCH{=}CHOC_2H_5$ with BuLi in an Et_2O-hexane mixture at a low temperature. The stability of the intermediate, compared to the very short life time of (E)-$LiCH{=}CHOC_2H_5$, even at low temperatures (*trans*-elimination of $LiOC_2H_5$ with formation of acetylene, compare Ref. [211]) may be explained on the basis of a stabilising interaction between Li and —OEt being on the same side of the double bond. Coordinative and (or) inductive action of the ether group might be responsible for the easy Br-Li exchange, compared to the sluggish reaction of compounds such as $(CH_3)_2CH{=}CHBr$ and 2-bromo-1-cyclooctene [9].

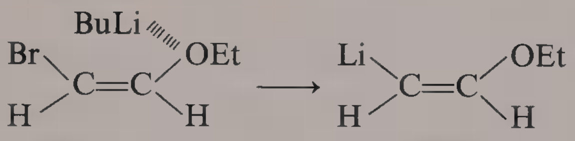
There are two reactions which in principle can compete with the Br-Li exchange:

a) *trans*-elimination of HBr with formation of ethoxyethene

b) Formation of a carbenoid by abstraction of the 2-proton



Formation of ethoxyethyne (a) takes place if (Z)-$BrCH{=}CHOC_2H_5$ is treated with powdered KOH [203]; addition of the (Z)- (and also (E)-)bromovinyl ether with alkali amide in liquid ammonia [6, 203] also results in the formation of the ethynyl ether. It is not known whether a direct *trans*-elimination (a) is involved or an initial deprotonation in the 2-position, followed by a Fritsch-Wiechell-Buttenberg migration of the $—OC_2H_5$ group in $BrCH{=}CHOC_2H_5$ with simultaneous loss of alkali bromide [204]. Ficini et al. [205] succeeded in generating the lithiocarbenoid (Reaction b) by treating the (Z)-bromoether with BuLi-THF at −100 °C. Both the undesired formation of the carbenoid and the halogen-metal exchange are expected to proceed more slowly in the less polar diethyl ether. However, the rate of the Br-Li exchange will be reduced to a lesser extent by this change of solvent, because this reaction can take more profit from "complexation" between $—OC_2H_5$ and BuLi than in THF.



In our opinion $EtLi \cdot LiBr$ in Et_2O is an even more suitable system for the exchange than BuLi in Et_2O-hexane since complexation with lithium halide reduces the kinetic basicity.

Procedure

A solution of 0.11 mol of ethyllithium in 110 ml of Et_2O (see Chap. I, Exp. 1) is cooled to −55 °C. (Z)-2-bromovinyl ethyl ether (0.10 mol, 15.1 g, Note 1) is added in one portion, after which the mixture is stirred for 1 h at −45 °C. The salt suspension disappears within 15 min. Derivatization reactions with aldehydes, ketones and a number of other reactive "electrophiles" can be carried out in the usual way (see Chaps. II and V). In reactions with normal alkyl halides the bromoethane present in the solution can seriously compete.

Reaction of the obtained solution of $LiCH{=}CHOC_2H_5$ with dimethyl disulfide (addition of 0.12 mol, 11.3 g at $-50\,°C$) gives $CH_3SCH{=}CHOC_2H_5$, b.p. 70 °C/15 mm, n_D^{20} 1.4951, in yields between 80 and 85%.

Notes

1. Prepared by addition below $-50\,°C$ of Br_2 to a solution of vinyl ethyl ether in dichloromethane, followed by evaporation of the solvent and treatment of the undistilled dibromoether with a 100% excess of N,N-diethylaniline or tributylamine at temperatures between 80 and 100 °C (compare Refs. [6, 202, 203]). The *E*/*Z*-mixture is distilled through a very efficient column, affording a large higher-boiling fraction (b.p. 36–38 °C/12 mm), consisting of almost pure (*Z*)-$BrCH{=}CHOC_2H_5$.

4.27 1-Lithio-1-Phenylethene

$$PhC(Br){=}CH_2 + EtLi \xrightarrow[-45\,°C]{LiBr,\ Et_2O} PhC(Li){=}CH_2 + EtBr$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 11.

Introduction

A generally applied method for the generation of aryllithium or hetero-aryllithium compounds consists of converting the corresponding bromo compounds with butyllithium in THF or Et_2O (see Chaps. V and VI). The exchange reactions in most cases proceed cleanly. For the preparation of vinyllithium intermediates this exchange reaction is less useful since it is often accompanied by processes induced by deprotonation. $(CH_3)_2C{=}CHBr$, for example, was found to undergo predominant 1,1-dehydrohalogenation and (presumably) subsequent Fritsch-Wiechell-Buttenberg rearrangement in the intermediate carbenoid under the influence of BuLi in THF at $-20\,°C$ or $EtLi \cdot LiBr$ in Et_2O at about 10 °C [9]. 2-Bromo-1-cyclooctene underwent both HBr elimination to cyclooctyne (and subsequent addition of EtLi) and bromine-lithium exchange upon reaction with $EtLi \cdot LiBr$ in Et_2O at 20 °C.

Bromine-lithium exchange in $PhC(Br){=}CH_2$ proceeds under conditions which are similar to those in the preceding experiment and gives an excellent result. The great facility of this exchange reaction may be explained by assuming some stabilizing influence of the phenyl group (inductive?).

Procedure

A solution of 0.11 mol of EtLi · LiBr in 90 ml of Et_2O (Chap. I, Exp. 1) is diluted with 70 ml of Et_2O. The solution is cooled to −65 °C and 0.10 mol (18.3 g) of $PhC(Br){=}CH_2$ (Note 1) is added in one portion. The salt gradually disappears. The solution is stirred for an additional 30 min at −45 °C, then it is cooled to −60 °C and 0.13 mol (12.2 g) of dimethyl disulfide is added in one portion with vigorous stirring. After 10 min 100 ml of water is added and the clear aqueous layer is discarded. The etheral solution is dried over $MgSO_4$ and subsequently concentrated in vacuo. Distillation of the remaining oil through a short Vigreux column affords $PhC(SCH_3){=}CH_2$, b.p. 100 °C/15 mm, n_D^{20} 1.592, in 82% yield.

Notes

1. Preparation of $PhC(Br){=}CH_2$: To a solution of 0.5 mol (52 g) of styrene in 400 ml of Et_2O is added a slight molar excess of bromine with cooling to below −20 °C. The reaction mixture is allowed to warm up to 20 °C after which a solution of 0.6 mol of sodium methoxide in about 200 ml of methanol is added in five equal portions keeping the temperature between 35 and 40 °C. After an additional 15 min 1 l of water is added to the salt suspension. The bromo compound (b.p. 80 °C/15 mm, n_D^{20} 1.589) is obtained in yields of at least 85% after the usual work-up.

Chapter IV
Metallation of Hetero-Substituted Unsaturated Systems

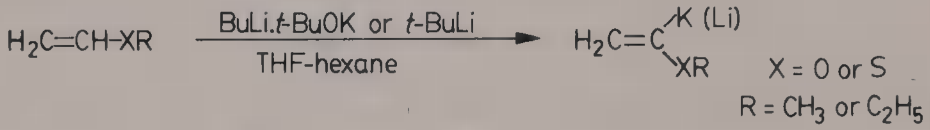
1. Introduction

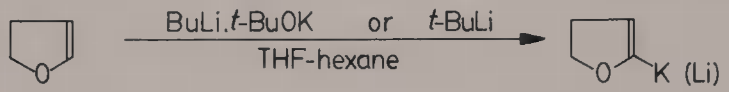
This chapter deals with the generation of polar organometallic intermediates of the type $>C{=}C(M)X$, $>C{=}C{=}C(M)X$ and $>C{=}C{=}C{=}C(M)X$ in which X represents a group containing a heteroatom directly linked to the double-bond system. Practically all these polar metal derivatives are generated by direct metallation of the corresponding unsaturated systems $>C{=}C(H)X$, $>C{=}C{=}C(H)X$ and $>C{=}C{=}C{=}C(H)X$, or the isomeric systems $H{-}C{-}C{\equiv}C{-}X$ and $>C{=}C(H){-}C{\equiv}C{-}X$. The intermediates in which X is halogen (mostly chlorine) are stable only at very low temperatures [80].

Particularly α-metallated olefinic and allenic ethers have found useful applications in organic synthesis [1, 81, 114]. The anions $>C{=}\overset{\ominus}{C}{-}OR$ and $>C{=}C{=}\overset{\ominus}{C}{-}OR$ have been recognized as synthetic equivalents of the inaccessible acyl anions $>C{-}\overset{\ominus}{C}{=}O$ and $>C{=}\underset{|}{C}{-}\overset{\ominus}{C}{=}O$, respectively. The considerable synthetic importance of the α-metallated vinylic and allenic ethers lies in the fact that functionalization with a wide variety of reagents proceeds with excellent yields, and in the case of metallated allenic ethers with perfect α-regiospecificity. Acid hydrolysis of the derivatives $>C{=}C(E){-}OR$ and $>C{=}C{=}C(E)OR$ gives in most cases the systems $>C{-}C({=}O){-}E$ and $>C{=}\underset{|}{C}{-}C({=}O){-}E$, which are not accessible *via* direct metallation of the aldehydes $>\underset{|}{C}{-}CH{=}O$ and $>C{=}\underset{|}{C}{-}CH{=}O$. In principle, analogous transformations are possible with the corresponding sulfur compounds. The thiol liberated in the last step may, however, give rise to problems, because it can react with the carbonyl compounds. In spite of the availability of a number of "remedies", such as mercury salts [82] to remove the thiol, the oxygen-ethers seem more attractive starting material for syntheses on a larger scale.

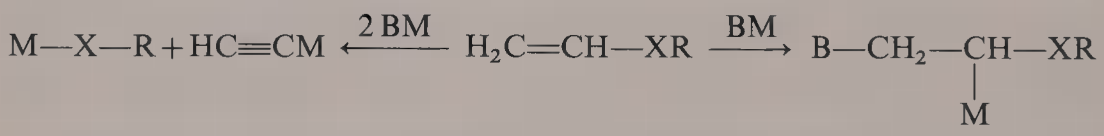
2. α-Metallation of 1-Alkenyl Ethers, -Thioethers and Related Systems

Metallation of the most simple vinyl ether $H_2C{=}CHOCH_3$ in the α-position has been carried out with *t*-butyllithium in THF at low temperatures [81]. Ethene is deprotonated not at all by *t*-BuLi or other strongly basic systems under the same conditions. *Sec*-butyllithium has been used to metallate alkyl vinyl sulfides $H_2C{=}CH{-}SR$ [82]. We found that both vinyl ethers and vinyl thioethers can be metallated with excellent results using the cheaper combination of *n*-BuLi and *t*-BuOK [9]. The cyclic vinyl ethers 2,3-dihydrofuran and 2,3-dihydropyran can be successfully metallated under the same conditions:



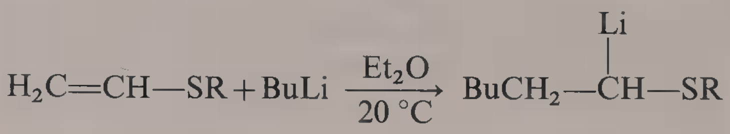


The potassio intermediates give excellent results in a number of derivatizations. For other functionalizations, particularly those with carbonyl compounds, potassium has to be replaced by lithium, this can be done most simply by addition of an equivalent amount of anhydrous lithium bromide, dissolved in THF. Although both vinyl ethers and the corresponding sulfides can be metallated in a short time, it is quite clear from the preparative experiments that the sulfides react faster [9]. A similar difference between oxygen and sulfur compounds has been observed in metallations of other types of substrates. Some authors have invoked d-orbital effects to explain the easier metallations of sulfur compounds [83], but an explanation on the basis of polarizability seems more satisfactory [84]. Using the kinetically very active bases mentioned, clean α-metallations of simple vinylic ethers and -thioethers can be realized at low temperatures. Under modified conditions two other processes have been observed [9, 85]:



$$\mathrm{M{-}X{-}R + HC{\equiv}CM} \xleftarrow{2\,\mathrm{BM}} \mathrm{H_2C{=}CH{-}XR} \xrightarrow{\mathrm{BM}} \mathrm{B{-}CH_2{-}\underset{\displaystyle M}{\underset{|}{C}}H{-}XR}$$

At room temperature butyllithium adds across the double bond of vinyl alkyl sulfides:



$$\mathrm{H_2C{=}CH{-}SR + BuLi} \xrightarrow[20\,^\circ\mathrm{C}]{\mathrm{Et_2O}} \mathrm{BuCH_2{-}\overset{\displaystyle Li}{\overset{|}{C}}H{-}SR}$$

1,2-Elimination of thiol occurred if ethyl vinyl sulfide was allowed to interact with potassium amide in liquid ammonia [9]. The same reaction may be expected with

LDA in THF at somewhat elevated temperatures:

$$H_2C{=}CH{-}SC_2H_5 + 2\,KNH_2 \xrightarrow[-33\,°C]{liq.\ NH_3} KSC_2H_5 + HC{\equiv}C{-}K$$

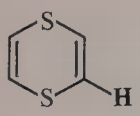
Methoxybutenyne undergoes a similar elimination with BuLi in THF [115]:

$$HC{\equiv}C{-}CH{=}CH{-}OCH_3 + 3\,BuLi \xrightarrow{THF} Li{-}C{\equiv}C{-}C{\equiv}C{-}Li + LiOCH_3 + 3\,C_4H_{10}$$

Phenyl vinyl selenide has been shown to react in three different ways using different base-solvent systems [86]:

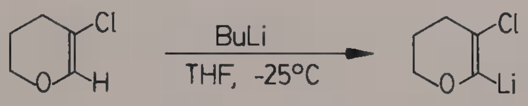
$$\begin{tikzcd}
BuCH_2CH(Li)SePh & H_2C{=}CH{-}SePh \arrow[l, "BuLi"', "Et_2O"] \arrow[r, "LDA,\ THF"] \arrow[d, "BuLi,\ THF"] & H_2C{=}C(Li)SePh \\
 & H_2C{=}CH{-}SeBu + PhLi &
\end{tikzcd}$$

Changes in the nature of the substituents on the double bond and on the hetero atom have a noticeable influence upon the ease of the metallation. Propenyl ethers $CH_3CH{=}CH{-}OR$ [87] and alkenyl sulfides, e.g. $C_4H_9CH{=}CH{-}SCH_3$ [9] are deprotonable in the α-position with BuLi · *t*-BuOK in THF, but the reactions proceed less easily than those with the *vinyl* ethers and corresponding sulfides and our results were less satisfactory [9]. Comparative metallation experiments with different types of unsaturated sulfides suggest their ranking in the following order according to decreasing kinetic acidity of the α-protons [9]:



$\approx H_2C{=}CH\mathbf{S}Ph > Z{-}CH_3S{-}CH{=}C\mathbf{H}{-}SCH_3 > H_2C{=}C\mathbf{H}{-}SCH_3 > E{-}C_4H_9CH{=}C\mathbf{H}{-}SCH_3$

The lithio derivatives of 1,4-dithiin [88] and *Z*-bis(methylthio)ethene [89] are stable only at very low temperatures: fragmentation and elimination of thiol occur if the temperature of the solutions is allowed to rise above −90 °C. The electron-withdrawing action of chlorine in 5-chloro-2,3-dihydropyran permits a fast and quantitative lithiation with BuLi [89, 90]:



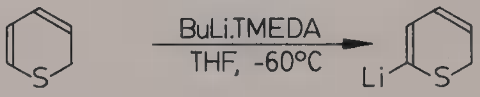
Our attempts to metallate the enamine $CH_3CH{=}CH{-}NMe_2$ with the strongly basic reagent BuLi · *t*-BuOK in THF were unsuccessful [9].

3. Metallation of 1,3-Dienyl Ethers and -Thioethers

Addition of BuLi to a mixture of a 1,3-dienyl ether or -thioether (*E*- or *Z*-) and *t*-BuOK in THF at 50 °C results in an instantaneous, and essentially quantitative α-metallation. In the absence of *t*-BuOK butyllithium adds to the sulfides in a conjugate fashion [91]. α-Metallation of the *oxygen*-ethers also has been carried out with *t*-BuLi in THF [81]:

$$H_2C{=}CH{-}CH{=}CH{-}XR \xrightarrow[\text{THF-hexane, } -50\,^\circ\text{C}]{\text{BuLi}\cdot t\text{-BuOK}} H_2C{=}CH{-}CH{=}C(K)XR$$

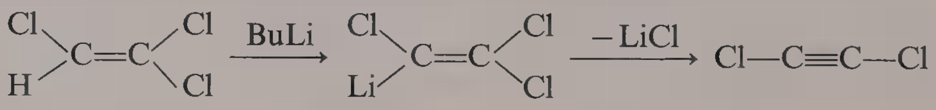
The cyclic dienyl sulfide 2H-thiopyran is metallated in the 6-position by BuLi · TMEDA in THF [93]:

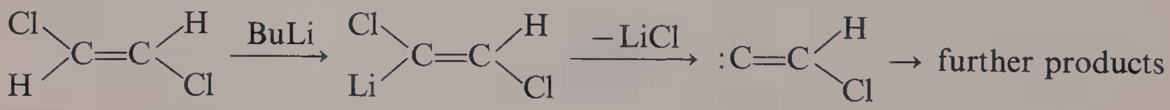


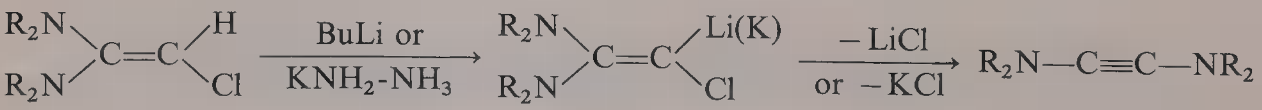
Interaction between 2H-thiopyran and LDA in THF initially gives comparable amounts of the 6-lithio- and 2-lithio derivatives. After about 2 hour at −60 °C only the 2-lithio intermediate is present in the solution. The same end result is obtained if diisopropylamine is added to a solution of the 6-lithio derivative.

4. α-Metallated Haloalkenes

The strong electron-withdrawing properties of chlorine permit a smooth α-metallation of alkenes with the system $>C{=}CHCl$ at very low temperatures. Depending upon the nature of the substituents the α-lithiochloroalkenes can decompose in three ways, as is shown in the following examples [80]:







The species having the metal and the vicinal halogen atom in the *trans*-position have the lowest stability because of the possibility of *trans*-elimination of lithium chloride. In other cases a carbene is formed by 1,1-elimination of lithium chloride. The carbene may give rise to a number of subsequent products. 1,1-Elimination of LiCl with simultaneous migration of a vicinal substituent (Fritsch-Wiechell-Buttenberg rearrangement) results in the formation of acetylenic derivatives. The rearrangement in the transient metallated chloroketeneaminal is synthetically interesting, since it affords the reactive ynediamines [94, 95]. Because of the low thermostability of 1-metallated chloroalkenes, derivatization reactions in general are only successful with reactive electrophiles such as carbon dioxide, aldehydes and ketones. A few 1-lithiobromoalkenes have been prepared by halogen-metal exchange, e.g. [96]:

$$\mathrm{Ph_2C{=}CBr_2 + BuLi \longrightarrow Ph_2C{=}C(Li)Br + BuBr}$$

5. α-Metallated Allenic Ethers, -Thioethers and -Amines

Alkoxypropadienes are easily obtainable by isomerization of propargyl ethers using *t*-BuOK [6, 7]:

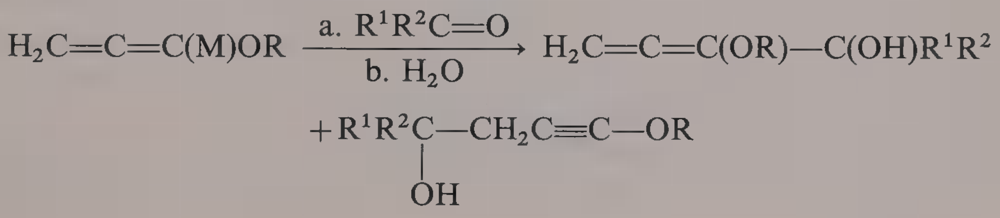
$$\mathrm{HC{\equiv}C{-}CH_2{-}OR \xrightarrow{\textit{t}\text{-BuOK}} H_2C{=}C{=}CH{-}OR}$$

Metallation of methoxyallene with butyllithium in Et_2O or THF is complete in a few minutes at temperatures in the region of −25 °C, and gives exclusively the α-metallated intermediate. It is obvious that alkoxyallenes are deprotonated more easily than propadiene [97] and vinyl ethers $H_2C{=}CH{-}OR$ [9]. All types of electrophiles react with perfect regiospecificity at the α-carbon atom (compare the reactions with metallated allenic hydro*carbons* discussed in Chap. III)

$$\mathrm{H_2C{=}C{=}CHOCH_3 \xrightarrow[\text{THF or Et}_2\text{O}]{\text{BuLi}} H_2C{=}C{=}C(Li)OCH_3}$$

$$\mathrm{\xrightarrow{E} H_2C{=}C{=}C(E)OCH_3}$$

However, the reaction with carbonyl compounds of the α-Grignard or α-zinc halide derivatives (prepared by exchange) affords mixtures of the allenic and acetylenic derivatives [9]:



$$\mathrm{H_2C{=}C{=}C(M)OR \xrightarrow[\text{b. }H_2O]{\text{a. }R^1R^2C{=}O} H_2C{=}C{=}C(OR){-}C(OH)R^1R^2}$$

$$\mathrm{+\,R^1R^2\underset{\displaystyle OH}{\underset{|}{C}}{-}CH_2C{\equiv}C{-}OR}$$

The predominant γ-metallation of *t*-butoxyallene with lithium dicyclohexylamide (LCHA) must be the consequence of a steric repulsion between the two bulky groups: with *n*-butyllithium α-deprotonation is the only reaction, while *methoxy*allene is lithiated also at the α-carbon atom by LCHA [98]:

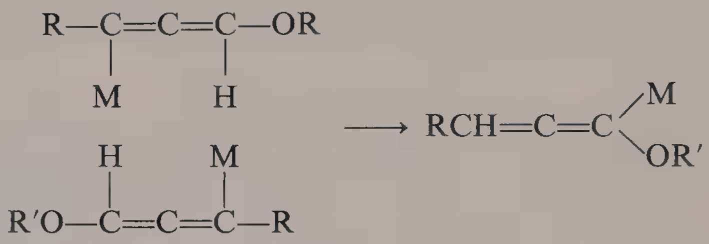
$$H_2C{=}C{=}C(Li)O\textit{t}\text{-}Bu \xleftarrow[\text{THF}]{\text{BuLi}} H_2C{=}C{=}CH{-}O\textit{t}\text{-}Bu \xrightarrow[\text{THF}]{\text{LCHA}}$$

$$LiCH{=}C{=}CH{-}O\textit{t}\text{-}Bu \quad (10\,\%\ \alpha\text{-lithiation})$$

γ-Lithiated allenic ethers are obtained by reacting 2-alkenyl ethers with BuLi in THF:

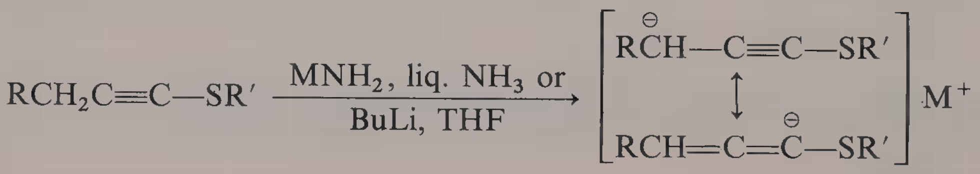
$$R{-}C{\equiv}C{-}CH_2{-}OR' \xrightarrow[\text{THF}]{\text{BuLi}} \left[\underset{\ominus}{RC}{=}C{=}CH{-}OR' \leftrightarrow R{-}C{\equiv}C{-}\underset{\ominus}{CH}{-}OR'\right] Li^+$$

Subsequent interaction with electrophilic reagents in general yields a mixture of the allenic and the acetylenic derivative: trimethylsilylation and alkylation, however, seem to afford the γ-functionalized allenic ether [99]. Under strongly polar conditions, i.e. if lithium is replaced by potassium (by addition of *t*-BuOK) and HMPT is added as co-solvent, the γ-metallated allenic ethers rearrange into the α-metallic derivatives [100]. This remarkable isomerization may take place *via* a head-to-tail arrangement of two metallated molecules:



$$\begin{array}{c} R{-}\underset{M}{\underset{|}{C}}{=}C{=}\underset{H}{\underset{|}{C}}{-}OR \\[4pt] R'O{-}\overset{H}{\overset{|}{C}}{=}C{=}\overset{M}{\overset{|}{C}}{-}R \end{array} \longrightarrow RCH{=}C{=}C\begin{matrix} \diagup M \\ \diagdown OR' \end{matrix}$$

Although α-metallated allenic thioethers are readily formed from the corresponding thioethers and strong bases, it is in general more practical to generate these intermediates from the isomeric acetylenic sulfides. This can be done either with butyllithium (or BuLi · TMEDA) [9] in THF or with alkali amides in liquid ammonia [44]:



$$RCH_2C{\equiv}C{-}SR' \xrightarrow[\text{BuLi, THF}]{\text{MNH}_2\text{, liq. NH}_3\text{ or}} \left[\begin{array}{c} R\overset{\ominus}{C}H{-}C{\equiv}C{-}SR' \\ \updownarrow \\ RCH{=}C{=}\overset{\ominus}{C}{-}SR' \end{array}\right] M^+$$

It is interesting to note in this connection that α-metallated *oxygen*-analogues (with M = Li, Na or K) undergo protolysis or (if R = H) are converted into metallated propargylic ethers in liquid ammonia [101]. As in many other anionic species, sulfur stabilizes a negative charge better than oxygen.

Functionalization of metallated allenic sulfides has only been investigated with alkyl halides [44], epoxyethane [7] and a few carbonyl compounds [48, 102]. Liquid ammonia is a suitable solvent for the alkylation and reaction with epoxides [7, 9]. The allenic sulfide anions behave as very reactive nucleophiles. Coupling of lithiated allenic sulfides with aldehydes and ketones in Et_2O affords mixtures of the acetylenic and allenic carbinols [49, 102].

Metallated allenic tertiary amines have been obtained in three ways. In a few cases, direct metallation with BuLi in THF at about -30 °C is the most attractive way: dimethylaminoallene and morpholinoallene can be obtained with a purity of about 95% by base-catalyzed isomerization of the easily accessible propargylic amines [7, 103]:

$$H{-}C{\equiv}C{-}CH_2{-}NR_2 \xrightarrow[\text{THF—HMPT}]{t\text{-BuOK}} H_2C{=}C{=}CH{-}NR_2 \xrightarrow[\text{THF}]{\text{BuLi}}$$

$$H_2C{=}C{=}C(Li){-}NR_2$$

If carefully conducted, the t-BuOK-catalyzed isomerization of $HC{\equiv}CCH_2NEt_2$ yields a 80:20 mixture of $H_2C{=}C{=}CHNEt_2$ and $CH_3C{\equiv}CNEt_2$, if the isomerization is allowed to go to completion, the product contains ca. 80% of the ynamine and 20% of the allenic isomer [6, 7]. If α-metallated dimethylaminoallene is to be prepared, it therefore seems more practical to treat the last-mentioned mixture with BuLi · t-BuOK [9]. Potassium can be replaced by lithium by adding a solution of anhydrous lithium bromide in THF:

$$\begin{array}{c} CH_3C{\equiv}C{-}NEt_2 \\ + \\ H_2C{=}C{=}CHNEt_2 \end{array} \xrightarrow[\text{THF, low temp.}]{\text{BuLi}\cdot t\text{-BuOK}} H_2C{=}C{=}C(K)NEt_2 \xrightarrow[\text{THF}]{\text{LiBr}}$$

$$H_2C{=}C{=}C(Li)NEt_2$$

Up to now only the reaction of lithiated diethylaminoallene with trimethylchlorosilane, resulting in (exclusively) $Me_3SiCH_2C{\equiv}C{-}NEt_2$, has been reported [104]. The metallation of the easily accessible 2-alkynylamines [6] can be brought about with BuLi · t-BuOK in THF. Under suitable conditions free allenic amines can be obtained in a reasonable state of purity; if the protonation is carried out with the *lithium* compounds (obtained from 2-alkynylamines and BuLi in THF, see Ref. [219]), the ratio of allenic and acetylenic amine is less favourable [9].

$$RC{\equiv}CH \xrightarrow[\text{Cu(OAc)}_2]{(CH_2O)_n + Me_2NH} RC{\equiv}C{-}CH_2NMe_2 \xrightarrow[\text{THF, }-20\,^\circ\text{C}]{\text{BuLi}\cdot t\text{-BuOK}}$$

$$\begin{array}{c} R\overset{\ominus}{C}{=}C{=}CHNMe_2 \\ \updownarrow \\ RC{\equiv}C{-}\overset{\ominus}{C}HNMe_2 \end{array} K^{\oplus} \xrightarrow{t\text{-BuOH}}$$

$$\underset{\sim 90\%\ \text{(rel.)}}{RCH{=}C{=}CHNMe_2} + \underset{\text{minor}}{RC{\equiv}C{-}CH_2NMe_2}$$

In the case of $\mathrm{R{=}CH_3}$, however, butyllithium abstracts a proton from the methyl group, and after aqueous work up the allenic amines $\mathrm{H_2C{=}C{=}CH{-}CH_2NR'_2}$ are obtained along with some of the acetylenic amines $\mathrm{CH_3C{\equiv}C{-}CH_2NR'_2}$ [9].

Lithiated propynyltrimethylsilane has been used as a substitute for the anion $\mathrm{HC{\equiv}CCH_2^{\ominus}}$: as a highly nucleophilic species (strongly basic and polarizable) it reacts smoothly with alkyl- and allyl halides to give predominantly acetylenic products [105]:

$$\mathrm{CH_3C{\equiv}CH \xrightarrow[Me_3SiCl]{BuLi} CH_3C{\equiv}C{-}SiMe_3 \xrightarrow[THF]{BuLi}}$$

$$\mathrm{[H_2C{=}C{=}\overset{\ominus}{C}{-}SiMe_3 \leftrightarrow {}^{\ominus}CH_2C{\equiv}C{-}SiMe_3]\,Li^{\oplus} \longrightarrow}$$

$$\mathrm{\xrightarrow{RX} RCH_2C{\equiv}C{-}SiMe_3\ (+H_2C{=}C{=}C(R)SiMe_3)}$$

6. Metallated 1,2,3-Butatrienyl Ethers, -Sulfides and -Amines

α-Metallated hetero-substituted cumulenes have been obtained *via* 1,4-elimination processes and by metallation of hetero-substituted enynes with strongly basic reagents as is illustrated by the following schemes [7, 106]:

$$\mathrm{ROCH_2C{\equiv}CCH_2OR \xrightarrow[Et_2O\ or\ THF]{BuLi} [ROCH{=}C{=}C{=}CH_2] \xrightarrow{BuLi}}$$
$$\mathrm{ROC(Li){=}C{=}C{=}CH_2}$$

$$\mathrm{ROCH_2C{\equiv}CCH(OR)_2 \xrightarrow[Et_2O\ or\ THF]{BuLi} [ROCH{=}C{=}C{=}CHOR] \xrightarrow{BuLi}}$$
$$\mathrm{ROC(Li){=}C{=}C{=}CHOR}$$

$$\mathrm{CH_3O{-}C(CH_3)_2C{\equiv}CCH_2NR_2 \xrightarrow[THF]{BuLi} [(CH_3)_2C{=}C{=}C{=}CHNR_2] \xrightarrow{BuLi}}$$
$$\mathrm{(CH_3)_2C{=}C{=}C{=}C(Li)NR_2}$$

$$\mathrm{RSC{\equiv}C{-}CH{=}CH_2 \xrightarrow[THF]{LDA} RS{-}C(Li){=}C{=}C{=}CH_2}$$

$$\mathrm{R_2NC{\equiv}C{-}CH{=}CH_2 \xrightarrow[THF]{BuLi\cdot \mathit{t}\text{-}BuOK} R_2N{-}C(K){=}C{=}C{=}CH_2}$$

Protonation of the intermediates under carefully controlled conditions proceeds regiospecifically, giving hetero-substituted cumulenes in good yields [106]. Functionalization reactions have been carried out only with the oxygen compounds [107]. In these cases, too, the reactions are completely regiospecific.

7. Addendum: Metallation of *N*,*N*-Dialkylformamides and -Thioamides

Successful (sp^2)metallation of *N*,*N*-disubstituted formamides and -thioamides with LDA was reported some ten years ago [108–111]:

$$\mathrm{HC({=}X)NR_2} \xrightarrow[\mathrm{THF},\ -100\ ^\circ\mathrm{C}]{\mathrm{LDA}} \mathrm{Li{-}C({=}X)NR_2} \qquad (\mathrm{X{=}O\ or\ S})$$

The deprotonations proceed with extreme ease, even at temperatures in the region of −100 °C. Most of the reactions reported are couplings with carbonyl compounds. The species have a low thermostability, and one may wonder whether their basicity (and polarizability) is sufficiently high to warrant good yields with electrophiles that are considerably less reactive than carbonyl compounds, e.g. alkyl halides.

8. Experimental Procedures

All temperatures are internal, unless indicated otherwise.

8.1 Metallation of Ethyl Vinyl Ether

$$\mathrm{H_2C{=}CH{-}OEt + BuLi \cdot \mathit{t}\text{-}BuOK} \xrightarrow[-80\ ^\circ\mathrm{C}]{\text{THF-hexane}} \mathrm{H_2C{=}C(K)OEt}$$

$$+\, \mathit{t}\text{-}\mathrm{BuOLi} + \mathrm{C_4H_{10}}$$

$$\mathrm{H_2C{=}C(K)OEt + LiBr} \longrightarrow \mathrm{H_2C{=}C(Li)OEt + KBr}\downarrow$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction
Although *t*-butyllithium has been successfully applied to metallate methyl vinyl ether, one might prefer to use the cheaper and less dangerous combination of *n*-BuLi and *t*-BuOK for the metallation of simple vinyl ethers. If an excess of ethyl vinyl ether is used, quantitative metallation can be obtained. Some derivatization reactions give much better results with the *lithium* compounds. The requisite transformation into the lithiovinyl ethers can be carried out by addition of a solution of anhydrous lithium bromide in THF.

Procedure

Ethyl vinyl ether (21 g, 0.3 mol, large excess) is added to a solution of 0.11 mol (12.3 g) of *t*-BuOK in 90 ml of THF cooled to below 0 °C. The mixture is cooled to −90 °C and a solution of 0.11 mol (Note 1) of butyllithium in 70 ml of hexane is added dropwise over 20 min. During this addition the temperature is kept between −70 and −80 °C by occasional cooling in a liquid nitrogen bath. After the addition, stirring at −70 °C is continued for an additional 15 min, then the temperature is allowed to rise to −50 °C (Note 2). The lithium compound is prepared by adding (at −30 to −50 °C) a solution of 0.12 mol (10.5 g) of anhydrous lithium bromide (Note 3) in 40 ml of THF. Five min after this addition derivatization reactions can be carried out. The solutions of the potassium and lithium compound are assumed to contain about 0.10 mol.

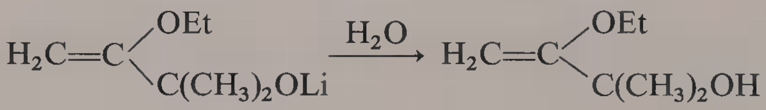
Notes

1. An excess of 0.01 mol is used to compensate for losses caused by small amounts of oxygen and moisture present in the solvents and the apparatus and by *t*-BuOH in the *t*-BuOK.
2. An alternative, efficient way to prepare potassiated ethyl vinyl ether consists in treating the vinyl ether with BuLi · *t*-BuOK · TMEDA in hexane at −20 °C.
3. The commercially available anhydrous salt (0.13 mol, 11.3 g) is heated during 30 min in a 250-ml round-bottom at 150 °C in a vacuum of 10 to 20 mmHg.

8.2 Coupling of Metallated Ethyl Vinyl Ether with Nonyl Bromide and Acetone

$$H_2C{=}C(K)OEt + C_9H_{19}Br \xrightarrow[-50\ \rightarrow\ +20\ ^\circ C]{\text{THF-hexane}} H_2C{=}C(C_9H_{19})OEt + KBr$$

$$H_2C{=}C(Li)OEt + (CH_3)_2C{=}O \xrightarrow[-70\ ^\circ C]{\text{THF-hexane}}$$



$$H_2C{=}C\begin{cases}OEt\\ C(CH_3)_2OLi\end{cases} \xrightarrow{H_2O} H_2C{=}C\begin{cases}OEt\\ C(CH_3)_2OH\end{cases}$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 11.

Introduction

This procedure gives typical reaction conditions for the alkylation and hydroxyalkylation of alkyl vinyl ethers *via* the 1-potassio- and 1-lithio derivatives, respectively. The alkylation of the potassium compounds with alkyl bromides proceeds smoothly at temperatures in the region of −40 °C. Alkylation is often accompanied by dehydrohalogenation. In the experiment described below the ratio alkylation : dehydrohalogenation is high. Under similar conditions vinylpotassium $H_2C{=}CH{-}K$ gave a much lower yield of the alkylation product (1-decene) in its reaction with bromooctane, and an appreciable amount of the dehydrobromination product 1-octene was isolated [21]. Dehydrohalogenation is in general less serious in reactions with *lithium* compounds. They react less smoothly however, and reaction temperatures of the alkylations are at least 30 °C higher.

Couplings of potassium compounds with enolizable carbonyl compounds give often low yields owing to formation of enolates. With lithium and Grignard compounds the results are mostly satisfactory.

Procedure

Alkylation with nonyl bromide.

A solution of 0.10 mol of potassiated ethyl vinyl ether (see Exp. 1) is cooled to −50 °C, after which 0.08 mol, 16.6 g (Note 1) of nonyl bromide is added in one portion. The cooling bath is removed and the temperature rises to 0 °C or higher in 10 min. When the exothermic reaction has subsided, 15 ml of HMPT (Note 2) is added and stirring is continued for 30 min at 20 °C. Water (200 ml) is added to the white suspension. After separation of the layers the aqueous phase is extracted three times with Et_2O. The combined organic solutions are washed with brine (four times) and subsequently dried over $MgSO_4$. After removal of the solvents *in vacuo* the remaining liquid is carefully distilled through a 30-cm Vigreux column, affording after a forerun of 1.5 g of 1-nonene, b.p. 40–50 °C/15 mm, the desired alkylation product, b.p. 107 °C/15 mm, n_D^{18} 1.4364, in 86% yield.

Reaction with acetone.

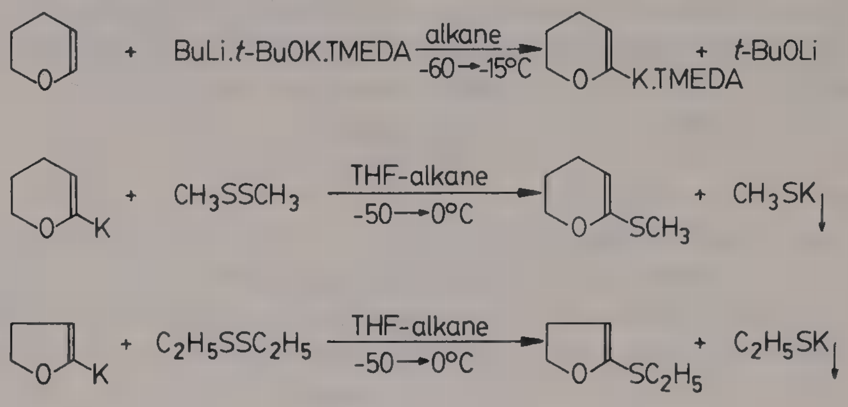
Acetone (0.12 mol, 7.0 g) is added to a solution of 0.10 mol of $H_2C{=}C(Li)OC_2H_5$ (Exp. 1) with cooling at about −70 °C. Five min after this addition the clear solution is treated with 200 ml of an aqueous solution of 20 g of ammonium chloride. The organic layer and three ethereal extracts are dried (washing is not carried out) over potassium carbonate and subsequently concentrated in a water-pump vacuum. The remaining liquid is distilled through a 30-cm Vigreux column to give the carbinol, b.p. 45 °C/12 mm, n_D^{20} 1.4306, in 82% yield.

The reaction with cyclopentanone is carried out in a similar way and affords the corresponding carbinol as a solid in ~80% yield (Note 3).

Notes

1. Since nonyl bromide and the product cannot be separated by distillation, a short measure of the alkyl halide is added.
2. The addition of HMPT helps to ensure the completion of the reaction.
3. Enolizable carbonyl compounds can undergo aldol condensation at temperatures in the region of 0 °C under the influence of *t*-BuOLi present in the reaction mixture. For this reason no large excess of the carbonyl compound should be added, while the temperature should be kept below −40 °C during the addition. The couplings are generally very fast, so that the aqueous work-up can be carried out soon after addition of the carbonyl compound.

8.3 Metallation of 2,3-Dihydrofuran and 2,3-Dihydropyran and Subsequent Alkylthiolation



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 11.

Introduction

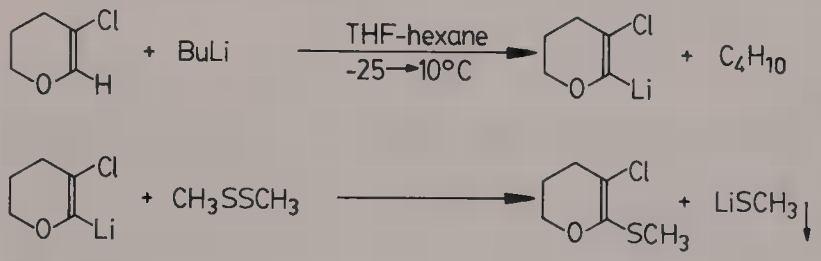
In the preceding chapter we have seen that cyclohexene is deprotonated in the allylic position, whereas smaller rings are preferentially deprotonated at the double bond. Under similar experimental conditions the cyclic vinyl ethers 2,3-dihydrofuran and 2,3-dihydropyran are metallated exclusively in the α-position. Furthermore, the metallations of the heterocycles are more facile than those of the analogous cycloalkenes. Undoubtedly the activation by oxygen (inductive and/or coordinative) is responsible for the perfect regiospecificity and relative facility of the metallation. The greater rigidity of the cyclic vinyl ethers may explain why their metallation proceeds more easily than that of non-cyclic systems such as $H_2C{=}CHOC_2H_5$ and $CH_3CH{=}CHOC_2H_5$ [9]. The experimental procedures given below are examples of the use of the ternary system BuLi · *t*-BuOK · TMEDA which has a reasonable solubility in alkanes. The great advantage over the system BuLi · *t*-BuOK · THF is that no large excess of the vinyl ether needs to be used, since there is no solvent that can compete with the substrate (TMEDA is not attacked below −10 °C). Of course the ternary system can also be used for the metallation of non-cyclic vinyl ethers. The potassium compounds formed in this metallation can be transformed into the lithium compounds by adding a solution of anhydrous lithium bromide in THF. The potassiations with the ternary system proceed with high efficiency as appears from the excellent yields of the sulfides formed upon addition of dialkyl disulfides.

Procedure

50 ml of pentane or hexane, 0.11 mol of powdered *t*-BuOK, and 0.11 mol of TMEDA are placed in the flask and, mixture is cooled to −70 °C. A solution of 0.11 mol of butyllithium (see Note 1 of Exp. 1) in 77 ml of hexane is added over 30 s, while keeping the temperature of the mixture below −30 °C. After stirring for 10 min at −50 to −60 °C, 0.13 mol (9.1 or 10.9 g) of freshly distilled 2,3-di-

hydrofuran or 2,3-dihydropyran is added in a few seconds. The cooling bath is removed and the temperature is allowed to rise to −20 °C. This temperature is maintained for 15 min, then stirring is continued for 15 min at −15 °C during which time a fine suspension in a light-brown solution is formed. Diethyl ether (100 ml) is added at −20 °C, after which the mixture is cooled to −50 °C. The dialkyl disulfide (0.12 mol, 11.3 or 14.6 g) is then added in one portion with vigorous stirring and without external cooling. After 10 min 100 ml of water is added to the white suspension. The organic layer is washed five times with 30 ml portions of water. The original aqueous layer and the washings are combined and subsequently extracted once with 50 ml of pentane. After drying the organic solutions over $MgSO_4$ the solvents are removed *in vacuo*. Careful distillation gives the expected sulfides in yields of at least 90%: 2,3-dihydrofuranyl ethyl sulfide, b.p. 65 °C/12 mm, n_D^{20} 1.5071; 2,3-dihydropyranyl methyl sulfide, b.p. 70 °C/12 mm, n_D^{20} 1.5179. The sulfides must be stored under nitrogen, because they undergo auto-oxidation upon exposure to air.

8.4 Metallation of 5-Chloro-2,3-Dihydropyran and Subsequent Methylthiolation



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

Experiment 3 describes the α-metallation of 2,3-dihydropyran with the strongly basic system BuLi · *t*-BuOK · TMEDA. If in the *β*-position an electron-withdrawing substituent is present, the metallation becomes more facile. Thus, 5-chloro-2,3-dihydropyran can be metallated in a short time by the much less basic butyllithium in THF. The high thermostability of the lithio derivative resembles that of 2-lithio-3-halofurans and analogous thiopene derivatives (see Chap. V), but stands in sharp contrast with the trancient existence of species without an oxygen or sulfur atom, e.g. 1-halo-2-lithiocycloalkanes [208] and with the instability of "arynoids" [221].

Procedure

THF (40 ml) is added to a solution of 0.055 mol of butyllithium in 38 ml of hexane, cooled below 0 °C. 5-Chloro-2,3-dihydropyran (0.05 mol, 5.9 g, see Exp. 32) is added in one portion at −25 °C, after which the temperature is allowed to rise to

+10 °C (occasional cooling may be necessary). The clear solution obtained is cooled to −50 °C and 0.07 mol (6.6 g) of dimethyl disulfide is added in one portion with vigorous stirring. After 5 min 100 ml of water is added to the white suspension, the layers are separated, and two extractions with Et_2O are carried out. The organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Distillation of the remaining liquid through a short Vigreux column gives the expected sulfide, b.p. 80 °C/1 mm, n_D^{21} 1.5408, in 97% yield.

8.5 α-Metallation of Methyl Vinyl Sulfide

$$H_2C{=}CH{-}SCH_3 + BuLi \cdot t\text{-}BuOK \xrightarrow[-90\ \to\ -60\ ^\circ C]{\text{THF-hexane}} H_2C{=}C(K)SCH_3\downarrow$$

$$+\, t\text{-}BuOLi + C_4H_{10}$$

$$H_2C{=}C(K)SCH_3 + LiBr \longrightarrow H_2C{=}C(Li)SCH_3 + KBr\downarrow$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 11.

Introduction

It appears from several reactions that sulfur stabilizes a negative charge better than does oxagen. In general "anions" derived from sulfur compounds are also formed more easily than the oxygen analogues. Thus, if methyl vinyl sulfide is added at −80 °C to a solution of $BuLi \cdot t\text{-}BuOK$ in THF, a precipitate of the potassium compound is formed immediately: the reaction conditions applied in the metallation of ethyl vinyl ether show that this metallation proceeds less easily (see Exp. 1). An other consequence of the better stabilization of a negative charge by sulfur is that vinylic sulfides are more prone to *addition* of the basic reagent. At room temperature butyllithium gives an adduct $BuCH_2CH(Li)SR$ with vinyl sulfide [85]. With the strongly "protophilic" reagent $BuLi \cdot t\text{-}BuOK$, however, α-deprotonation of methyl vinyl sulfides is favoured and derivatization reactions show that this metallation proceeds with a high efficiency. Transformation of the potassium compound into lithiovinyl methyl sulfide can be effected quantitatively by adding a solution of LiBr in THF.

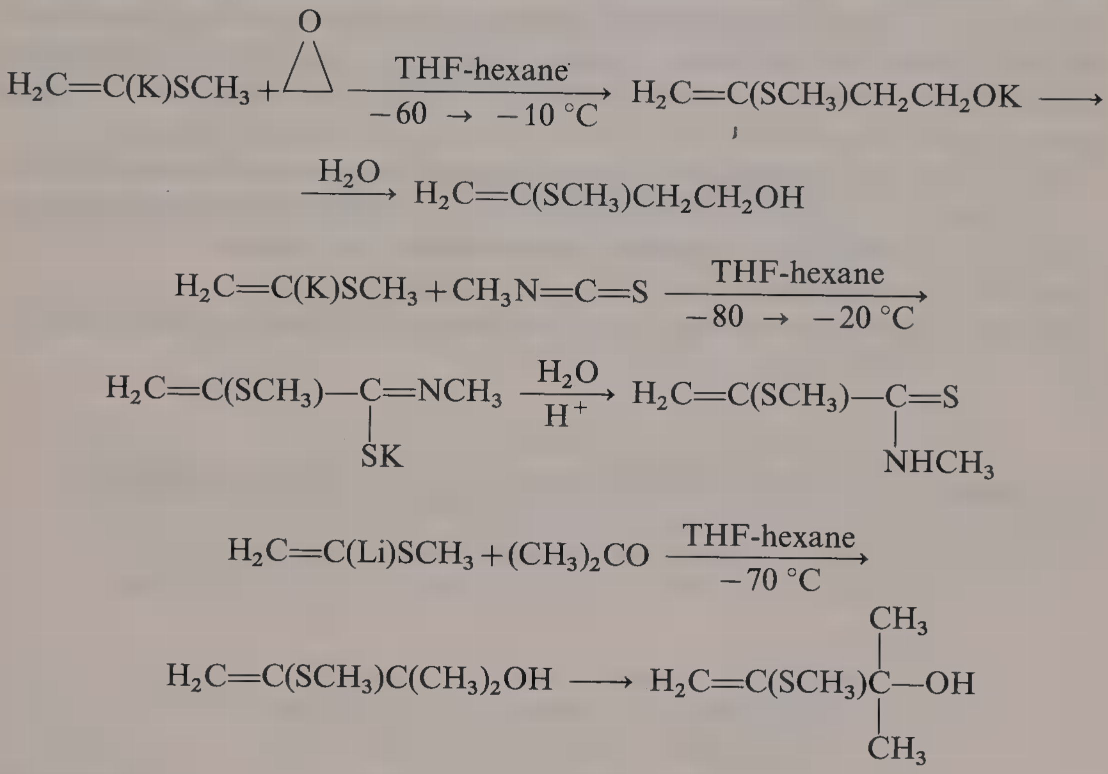
Procedure

A solution of 0.11 mol (12.3 g) of *t*-BuOK in 70 ml of THF is cooled to −100 °C and 0.11 mol of butyllithium in 77 ml of hexane is added over 5 min with efficient stirring and cooling between −90 and −100 °C (Note 1). Subsequently 0.13 mol (9.6 g) of freshly distilled methyl vinyl sulfide (Exp. 23) is added over 2 min. A suspension is formed almost immediately. The temperature is allowed to rise to −60 °C. The lithium compound is obtained by adding (at −60 °C) a solution of 0.12 mol (10.4 g) of anhydrous lithium bromide (obtained as described in Exp. 1, Note 3) in 40 ml of THF and stirring for an additional 5 min at −50 °C. The solution is assumed to contain about 0.10 mol of metallated vinyl sulfide; the excess of 0.01 mol of base serves to compensate for losses due to the presence of small traces of oxygen and moisture, and of *t*-BuOH in the *t*-BuOK.

Notes

1. The flask is occasionally cooled in a bath of liquid nitrogen, care being taken that no solid THF is formed.

8.6 Reaction of Metallated Methyl Vinyl Sulfide with Oxirane, Acetone and Methyl Isothiocyanate



$$H_2C{=}C(K)SCH_3 + \overset{O}{\triangle} \xrightarrow[-60\ \rightarrow\ -10\ ^\circ C]{\text{THF-hexane}} H_2C{=}C(SCH_3)CH_2CH_2OK \longrightarrow$$

$$\xrightarrow{H_2O} H_2C{=}C(SCH_3)CH_2CH_2OH$$

$$H_2C{=}C(K)SCH_3 + CH_3N{=}C{=}S \xrightarrow[-80\ \rightarrow\ -20\ ^\circ C]{\text{THF-hexane}}$$

$$H_2C{=}C(SCH_3){-}\underset{SK}{\underset{|}{C}}{=}NCH_3 \xrightarrow[H^+]{H_2O} H_2C{=}C(SCH_3){-}\underset{NHCH_3}{\underset{|}{C}}{=}S$$

$$H_2C{=}C(Li)SCH_3 + (CH_3)_2CO \xrightarrow[-70\ ^\circ C]{\text{THF-hexane}}$$

$$H_2C{=}C(SCH_3)C(CH_3)_2OH \longrightarrow H_2C{=}C(SCH_3)\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}{-}OH$$

Procedure

Oxirane (0.14 mol, 6.2 g), dissolved in 20 ml of THF, is added to the suspension of 0.10 mol of $H_2C{=}C(K)SCH_3$, cooled at −60 °C. The cooling bath is removed and the temperature allowed to rise to −20 °C keeping the exothermic reaction under control by occasional cooling. After stirring the almost colourless solution for an additional 15 min at −20 °C, 50 ml of water is added with vigorous stirring. After separation of the layers, three extractions with Et_2O are carried out. The unwashed combined organic solutions are dried over magnesium sulfate and subsequently concentrated *in vacuo*. Distillation of the remaining liquid through a 20-cm Vigreux column affords the alcohol, b.p. 87 °C/12 mm, n_D^{19} 1.5137, in 88% yield.

Methyl isothiocyanate (0.10 mol, 7.3 g) is added over 5 min to a suspension of 0.10 mol of $H_2C{=}C(K)SCH_3$ with cooling at −80 °C. The cooling bath is removed and the temperature allowed to rise to −20 °C. A mixture of 100 ml of ice water and

22 g of fuming (36 %)hydrochloric acid is then added with vigorous stirring to the yellow suspension. After adjusting the pH at 7–8 (addition of KOH or HCl), the layers are separated. The aqueous layer is extracted three times with Et_2O and the combined organic solutions are dried over $MgSO_4$ and subsequently concentrated in a water-pump vacuum. The last traces of volatile components are removed by warming at 40 °C for 20 min in a vacuum of 0.5 mmHg or less. The viscous residue (corresponding to a yield of ca. 95 %) is reasonably pure thioamide according to the NMR spectrum.

Acetone (0.12 mol, 7.0 g) is added to the suspension of lithiated methyl vinyl sulfide, cooled at −70 °C to −90 °C. Five min after this addition the reaction mixture (solution) is treated with 200 ml of water. The aqueous layer is extracted three times with Et_2O. The unwashed organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Distillation of the remaining liquid through a 20-cm Vigreux column gives the carbinol, b.p. 70 °C/12 mm, n_D^{20} 1.5012, in 84 % yield.

Reactions of the lithium compound with *carbon dioxide* (introduction of CO_2 at −80 °C) and with *N,N-dimethylcarbamoyl chloride* (addition of a 10 % excess of this compound at −80 °C in one portion gave unsatisfactory results.

Alkylation with *alkyl bromides* can be carried out in a similar way to that in the case of the metallated *oxygen* ethers (see Exp. 2).

8.7 Lithiation of *Z*-bis(Methylthio)Ethene and Subsequent Methylation

$$CH_3S{-}CH{=}CH{-}SCH_3 + BuLi \cdot TMEDA \xrightarrow[-110\ ^\circ C]{\text{THF-hexane}}$$

$$CH_3S{-}C(Li){=}CH{-}SCH_3 + C_4H_{10}$$

$$CH_3SC(Li){=}CH{-}SCH_3 + CH_3I \longrightarrow$$

$$\xrightarrow[-110\ \rightarrow\ -100\ ^\circ C]{} CH_3S{-}C(CH_3){=}CH{-}SCH_3 + LiI$$

Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction
Treatment of *Z*-bis-thioethers RS—CH=CH—SR with alkali amides or organolithium results in a smooth elimination of thiol with formation of metallated ethynyl sulfides M—C≡C—SR [203]. If *Z*-bis(methylthio)ethene and the reactive basic system BuLi · TMEDA in THF are allowed to interact at very low temperatures, no elimination occurs, but a precipitate of the lithio derivative is formed. It has a reasonable stability below −100 °C, thus permitting functionalizations

with reactive electrophilic reagents. The temperature range, available for derivatization reactions, is limited as 1,2-elimination of lithium methanethiolate occurs at temperatures above −90 °C.

Procedure

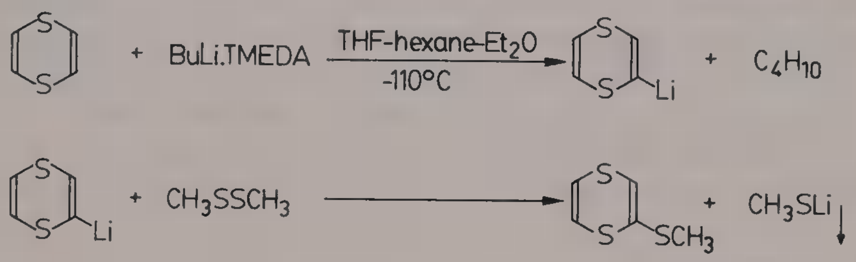
THF (45 ml) and Et_2O (15 ml, Note 1) are added to a solution of 0.055 mol of butyllithium in 38 ml of hexane, cooled below 0 °C. The mixture is cooled to −110 °C (Note 1) and 0.06 mol of TMEDA is added dropwise over 3 min. Subsequently *Z*-bis(methylthio)ethene (0.05 mol, 6.0 g, see Exp. 24) is added over 5 min, while keeping the temperature of the mixture at −110 °C. Stirring at this temperature is continued for an additional period of 1 hour, then methyl iodide (0.15 mol, 21.3 g, large excess) is added dropwise over 10 min, while keeping the temperature between −100 and −110 °C. A rather thick, white suspension is formed. After an additional 15 min the cooling bath is removed and the temperature is allowed to rise to −60 °C. After addition of water (200 ml) 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*. The product is distilled through a 20-cm Vigreux column: b.p. 85 °C/15 mm, n_D^{20} 1.5738, yield 90%.

A similar result can be obtained if the metallation is carried out with a 15% excess of BuLi · *t*-BuOK in THF (60 ml), Et_2O (30 ml) and hexane (42 ml), and methyl iodide is added after 15 min.

Notes

1. Et_2O renders the mixture less viscous at the low temperature.
2. This temperature can be reached by occasionally dipping the flask in liquid nitrogen, and can be maintained by keeping the bottom of the flask just above the level of the nitrogen. Stirring is carried out at a low rate and the upper part of the flask is covered with cotton wool.

8.8 Lithiation of 1,4-Dithiin and Subsequent Functionalization



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

Compared to 1,2-bis(methylthio)ethene, the structural and electronic conditions for metallation of 1,4-dithiin are even more favourable. The additional double bond is likely to exert an electron-withdrawing influence, while the greater rigidity of 1,4-dithiin is an additional favourable factor. Furthermore, 1,4-dithiin possesses twice as many vinylic protons as bis(methylthio)ethene. Indeed, 1,4-dithiin is completely mono-metallated in 10 to 15 min, whereas 1 h is needed for the metallation of bis(methylthio)ethene under the same conditions (compare Exp. 7). Lithiodithiin undergoes ring opening at temperatures above −90 °C with formation of $LiC{\equiv}C{-}S{-}CH{=}CH{-}SLi$ [88], so that the possibilities for successful functionalizations are confined to reactions with very reactive electrophiles, such as disulfides, trimethylchlorosilane.

Procedure

A solution of 0.055 mol of butyllithium in 40 ml of hexane is added to a mixture of 50 ml of THF, 20 ml of Et_2O (compare Exp. 7, Note 1) and 0.06 mol of TMEDA with cooling to below −30 °C. The mixture is cooled to −110 °C (see Exp 7) and 0.05 mol (5.8 g) of 1,4-dithiin (for syntheses of this compound see Refs. [190–191]) is added dropwise over 5 min. After an additional 15 min (at −110 °C) 0.07 mol (6.6 g) of dimethyl disulfide is added over 3 min, while keeping the temperature of the light-yellow suspension between −110 and −105 °C. After an additional 10 min the temperature is allowed to rise to −60 °C, and 100 ml of water is added with vigorous stirring. After separation of the layers, extraction with Et_2O and drying of the extracts over $MgSO_4$, the solvent is removed in a water-pump vacuum. Distillation of the remaining oil through a short column gives methylthio-1,4-dithiin, b.p. 90 °C/0.7 mm, n_D^{20} 1.6727, in 90% yield.

Trimethylsilylation (addition of 0.07 mol, 7.6 g of Me_3SiCl) and methylation (addition of 0.15 mol of CH_3I) are carried out in a similar way (compare also Exp. 7), and afford (trimethylsilyl)1,4-dithiin, b.p. 102 °C/12 mm, n_D^{20} 1.5561, in 88% yield, and methyl-1,4-dithiin, b.p. 50 °C/0.5 mm, n_D^{20} 1.6010, in 86% yield.

8.9 Metallation of *E*- and *Z*-1-Methoxy-1,3-Butadiene and 1-Methylthio-1,3-Butadiene

$$H_2C{=}CH{-}CH{=}CH{-}XCH_3 + BuLi \cdot t\text{-}BuOK \xrightarrow[-70\ ^\circ C]{\text{THF-hexane}}$$

$$H_2C{=}CH{-}CH{=}C(K){-}XCH_3 \qquad (X{=}O \text{ or } S)$$

Scale: 0.10 molar.

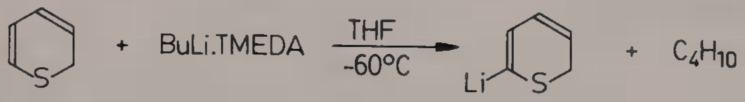
Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

The 1-proton in 1,3-dienyl ethers and -thioethers is expected to be more acidic than that in vinyl ethers and vinyl sulfides, because the outer double bond is likely to exert some electron-withdrawing influence. However, addition of the base (in a conjugate fashion) will also be more facile than with the simple vinyl ethers and -thioethers. Reaction of 1-methylthio-1,3-butadiene with butyllithium or butyllithium. TMEDA in THF has been shown to result in conjugate addition [91]. The chance of this reaction is less great, when using the combination of BuLi and *t*-BuOK, because this system has pronounced deprotonating abilities. In the procedure below this base couple is formed *in situ*.

Procedure
The dienyl ether or -thioether (0.10 mol, 8.4 and 10.0 g see Refs. [112] and [113]) is added to a cold (−50 °C) solution of 0.11 mol of *t*-BuOK in 100 ml of THF. The mixture is cooled to −70 °C and a solution of 0.11 mol of butyllithium in 77 ml of THF is added dropwise over 15 min, while keeping the temperature of the mixture between −65 and −75 °C. After an additional 15 min derivatization reactions can be carried out with the suspensions. For couplings with enolizable carbonyl compounds it is advisable to first exchange potassium for lithium. This can be done by adding (at about −60 °C) a solution of 0.12 mol (10.5 g) of anhydrous lithium bromide in 40 ml of THF to the suspension of the potassium compound. The required anhydrous LiBr is prepared by heating 0.13 mol of the commercial anhydrous salt for 30 min at 150 °C in a vacuum of 10 mmHg or less. If the temperature of the suspensions of the potassium compounds is allowed to rise to −20 °C (or higher) partial isomerization into the other (*Z* or *E*) isomer occurs.

8.10 Metallation of 2H-Thiopyran



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 11.

Introduction
The most obvious reactions between 2H-thiopyran and a base are deprotonation of carbon atom 6 or 2 and conjugate addition. Whereas BuLi gives a 1,4-adduct with the open-chain system $CH_3SCH{=}CH{-}CH{=}CH_2$ in THF, the only reaction with 2H-thiopyran under the same conditions is deprotonation of carbon atom 6. This difference in behaviour may be explained by assuming that the 6-proton in the more rigid cyclic system is more acidic than the 1-proton in $CH_3SCH{=}CH{-}CH{=}CH_2$. Furthermore, conjugate addition of the base to the heterocycle (attachment of Bu on C-atom 3) will be less easy, because C-atom 3 is linked to C-atom 2. Under aprotic conditions abstraction of the 6-proton is the kinetically favoured process. Removal of a 2-proton gives a species in which the negative charge is delocalized. This reaction is observed under more polar conditions, e.g. with potassium amide in liquid ammonia. Interaction between 2H-thiopyran and LDA in THF primarily gives comparable amounts of the 6-lithio- and 2-lithio derivatives, but after a few hours only the 2-lithio derivative is present in the solution. The conversion of the 6-lithio- into the 2-lithio derivative proceeds *via* proton donation (by diisopropylamine) and abstraction.

Procedure
A solution of 0.11 mol of butyllithium in 77 ml of hexane is added over 15 min to a mixture of 0.10 mol (11.6 g) of TMEDA, 100 ml of THF and 0.10 mol (9.8 g) of 2H-thiopyran (Exp. 25) with cooling to between −60 and −70 °C. After the addition the temperature is allowed to rise to −40 °C. The light-brown solution is then ready for derivatization reactions. Addition (over 1 min at −50 °C) of 0.15 mol (23.4 g) of ethyl iodide, followed by raising the temperature to +10 °C, gives 6-ethyl-2H-thiopyran, b.p. 56 °C/14 mm, n_D^{20} 1.5397, in ca. 75% yield.

8.11 Metallation of *E*-Dichloroethene and Subsequent Alkylation with Bromohexane [9]

$$E\text{—ClCH=CHCl} + \text{BuLi}\cdot t\text{-BuOK} \xrightarrow[-110\ ^\circ\text{C}]{\text{THF-hexane-ether}} \text{ClC(K)=CHCl}$$

$$+\,t\text{-BuOLi} + \text{C}_4\text{H}_{10}$$

$$\text{ClC(K)=CHCl} + \text{C}_6\text{H}_{13}\text{Br} \xrightarrow[-110\ \rightarrow\ -30\ ^\circ\text{C}]{\text{HMPT (co-solvent)}} \text{ClC(C}_6\text{H}_{13}\text{)=CHCl} + \text{KBr}$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction
The procedure described in Exp. 11 is an illustration of a general method for the generation of carbenoids developed by Köbrich et al. [80]. The base-solvent system in the original procedures is BuLi · THF. Metallations of vinyl halides proceed smoothly under these conditions. Carbonoids have a low thermostability, notably those having a vicinal halogen atom in the trans position of the lithium atom. In general, conversions of the lithio carbenoids with very reactive electrophiles, such as carbon dioxide and carbonyl compounds, can be successfully carried out at a very low temperature. Reactions with most alkyl halides, however, are too slow under these conditions. Addition of relatively small amounts of HMPT causes an enormous increase of the rates of alkylation. An additional favourable effect is obtained by replacing lithium by potassium. It is for this reason that the metallation is carried out with BuLi · *t*-BuOK (in fact BuK) instead of with BuLi. The alkylation is not carried out with the (more reactive) iodo compound, because distillative separation of the desired product and traces of unconverted iodohexane is expected to be difficult.

Procedure
The flask is charged with 100 ml of THF, 30 ml of Et_2O, 30 ml of pentane (compare Note 1 of Exp. 7) and 0.13 mol (14.6 g) of *t*-BuOK. The mixture is cooled to −110 °C (compare Note 2 of Exp. 7) and a solution of 0.13 mol of BuLi in 90 ml of hexane is added, while keeping the temperature below −100 °C. Ten min after this addition 0.10 mol (9.7 g) of *E*-dichloroethene is added dropwise over 10 min at ca.

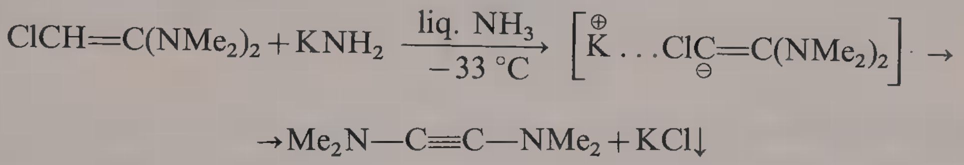
−110 °C. After an additional 5 min, 0.10 mol (16.5 g) of bromohexane is added over 2 min. A mixture of 60 ml of HMPT and 30 ml of THF is then added with vigorous stirring over 5 min. The white suspension is stirred for 45 min at about −105 °C and subsequently for 30 min at −90 °C. The cooling bath is then removed and the temperature allowed to rise to −40 °C (Note 1). Water (250 ml) is added with vigorous stirring and after separation of the layers, the aqueous layer is extracted four times with small portions of pentane. The combined organic solutions are washed five times with brine to remove the HMPT. After drying over $MgSO_4$, the solvent is removed in a water-pump vacuum. Careful distillation of the remaining light-brown liquid through a 40-cm Vigreux column gives 1,2-dichloro-1-octene, b.p. 75 °C/12 mm, n_D^{20} 1.4582, in 72% yield.

Similar experiments with vinyl chloride and trichloroethene did not give the desired alkyl derivatives.

Notes

1. At higher temperatures a small amount of $ClC{\equiv}C{-}K$, resulting from HCl elimination from the carbenoid, may react with bromohexane.

8.12 Conversion of 2-Chloro-1,1-bis(Dimethylamino)Ethene into bis(Dimethylamino)Ethyne



$$\mathrm{ClCH{=}C(NMe_2)_2 + KNH_2 \xrightarrow[-33\,^\circ C]{liq.\ NH_3} \left[\overset{\oplus}{K}\ldots Cl\underset{\ominus}{C}{=}C(NMe_2)_2\right] \rightarrow}$$

$$\rightarrow \mathrm{Me_2N{-}C{\equiv}C{-}NMe_2 + KCl}\downarrow$$

Scale: 0.20 molar.

Apparatus: 1-l one-necked flask, provided with a vent (stopper, perforated by a glass tube with ca. 7 mm internal diameter.

Introduction

This procedure gives a synthetically useful example of the Fritsch-Wiechell-Buttenberg rearrangement [95, 204]. The intermediate anionic species cannot be intercepted, because it immediately loses potassium chloride with simultaneous migration of a dimethylamino group. Other ynediamines can be prepared in a similar way. The ynediamine is extremely water-sensitive, so that a “dry” work-up is required.

Procedure

A solution of 0.25 mol of potassium amide in 175 ml of liquid ammonia is prepared in the reaction flask (Exp. 8 of Chap. I; the filtration operation need not to be carried out). The vent is temporarily removed and 0.20 mol (29.7 g) of the chloroketene aminal (Exp. 26) is added over 15 min using a Pasteur pipette. During this addition the reaction mixture is occasionally swirled by hand. The reaction is almost instantaneous and potassium chloride precipitates. After the addition, most of the ammonia is removed by placing the flask in a water bath at 30–35 °C. When the volume has decreased to about 50 ml, 100 ml of a 1:1 mixture of Et_2O and pentane is added. The vent is replaced on the flask and warming at 35° is continued until the stream of escaping ammonia has become very faint. After cooling to 20 °C, the light-brown solution is carefully decanted from the salt and the salt rinsed four times with small portions of the solvent. The combined solutions (total volume not more than 250 ml) are concentrated in a water-pump vacuum, using a bath temperature not exceeding 25 °C. The remaining liquid is distilled through a 40-cm Vigreux column. The distillate is collected in a *single* receiver cooled at 0 °C. Bis(dimethylamino)acetylene, b.p. ca. 40 °C/20 mm, n_D^{20} 1.4610, is obtained in 90% yield.

General note: The entry of moisture during the oprations must be scrupulously avoided and glass ware must be perfectly dry. The salt filtered off may contain small particles of potassium. The safest way to destroy this is to spread the salt on a large surface: as soon as the adhering solvent has evaporated, the salt is collected and thrown in a beaker filled with water.

8.13 Metallation of Methoxyallene (compare Ref. [7])

$$H_2C{=}C{=}CH{-}OCH_3 + BuLi \xrightarrow[-30\ ^\circ C]{\text{THF-hexane}} H_2C{=}C{=}C(Li)OCH_3 + C_4H_{10}$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Procedure
THF (80 ml) is added to a solution of 0.11 mol of butyllithium in 77 ml of hexane, cooled to below −10 °C. The mixture is cooled to −30 °C and 0.12 mol (8.4 g) of methoxyallene [6, 7] is added over 5 min, while keeping the temperature at −30 °C. After an additional 15 min the clear solution can be used for derivatization reactions. The solution is assumed to contain about 0.10 mol of lithiomethoxyallene. The excess of BuLi serves to compensate for losses due to the presence of small traces of oxygen and water in the apparatus and in the reagents and solvents. The solution turns brown upon warming above 0 °C, and above +20 °C decomposition becomes serious.

8.14 Metallation of 1-Alkynyl Sulfides in Organic Solvents [9]

$$CH_3C{\equiv}C{-}SR + BuLi \xrightarrow[-20\ \rightarrow\ 0\ ^\circ C]{\text{THF-hexane}} H_2C{=}C{=}C(Li)SR + C_4H_{10}$$

$$R'CH_2C{\equiv}C{-}SR + BuLi\cdot t\text{-}BuOK \xrightarrow[-80\ \rightarrow\ -60\ ^\circ C]{}$$

$$R'CH{=}C{=}C(K)SR \cdot LiOt\text{-}Bu + C_4H_{10}$$

$$R'CH{=}C{=}C(K)SR + LiBr \longrightarrow R'CH{=}C{=}C(Li)SR + KBr\downarrow$$

R = alkyl or phenyl
R′ = alkyl

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

Solutions of metallated allenic sulfides in liquid ammonia can be prepared from 1-alkynyl sulfides and alkali amides [6, 7]. These solutions are particularly suitable for reactions with alkylating agents. The procedure below describes the generation of metallated allenic sulfides in *THF*. The metallation of 1-*propynyl* sulfides can be conveniently carried out with BuLi. The hydrogen atom in the 3-position of the homologues $R'CH_2C{\equiv}C{-}SR$ are kinetically less acidic and higher temperatures are required for their metallation with BuLi, which involves the risk of side reactions (e.g. attack of BuLi on sulfur with formation of BuSR and $RC{\equiv}CLi$) and decomposition. Clean metallation of $R'CH_2C{\equiv}CSR$ can be achieved by using the highly reactive combination of BuLi and *t*-BuOK. The potassium ion in $R'CH{=}C{=}C(K)SR$ can be replaced by lithium by addition of anhydrous lithium bromide.

Procedure

Propynyl sulfides. A solution of 0.11 mol of butyllithium in 77 ml of hexane is added over 15 min to a mixture of 0.10 mol of the propynyl sulfide [6] and 80 ml of THF, while keeping the temperature at ~ −20 °C. After the addition the temperature is allowed to rise to 0 °C. A light-brown solution is formed which is assumed to contain about 0.10 mol of the lithiated allenyl sulfide.

Homologues. The 1-alkynyl sulfide (0.10 mol, Ref. [6]) is added at −70 °C to a solution of 0.11 mol (12.3 g) of *t*-BuOK in 80 ml of THF. A solution of 0.11 mol of butyllithium in 77 ml of hexane is then added dropwise over 10 min, while keeping the temperature of the suspension between −65 and −75 °C. After an additional 10 min the mixture is ready for further conversions. The lithio derivative can be obtained by adding a solution of 12 g (0.14 mol) of anhydrous lithium bromide in 45 ml of THF (in order to remove traces of water, the commercial anhydrous salt is first heated for 30 min at 150 °C in a vacuum) at about −60 °C.

8.15 Metallation of Allenic Amines and Acetylenic Amines

$$H_2C{=}C{=}CH{-}NMe_2 + BuLi \xrightarrow[-30\,^{\circ}C]{\text{THF-hexane}} H_2C{=}C{=}C(Li)NMe_2 + C_4H_{10}$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction
N,*N*-Dimethylaminopropadiene is the most easily obtainable allenic amine. Its metallation can be carried out in the same way as for allenic *ethers*. Most of the tertiary propadienylamines cannot be obtained in a pure state, but the desired 1-metallated allenic amines can also be obtained by treatment of 1-propynylamines $CH_3C{\equiv}CNR_2$ with strongly basic reagents. Metallation of the homologues $R'CH_2C{\equiv}CNR_2$ gives $R'CH{=}C{=}C(M)NR_2$ (compare the metallation of $R'CH_2C{\equiv}CSR$ to $R'CH{=}C{=}C(M)SR$, Exp. 14).

Procedure
A 95:5 mixture of $H_2C{=}C{=}CHNMe_2$ and $CH_3C{\equiv}CNMe_2$ [7] (0.12 mol, 10.0 g) is added to a solution of 0.11 mol of butyllithium in 77 ml of hexane and 80 ml of THF at −30 to −40 °C over 10 min. After an additional 30 min (at −30 °C) further reactions can be carried out with the solution which is assumed to contain about 0.10 mol of lithiated dimethylaminopropadiene.

A solution of 0.11 mol (12.3 g) of *t*-BuOK in 80 ml of THF is cooled to below 0 °C. The yneamine $R'CH_2C{\equiv}CNR_2$ (0.11 mol, Ref. [6]) or a 80:20 mixture of $CH_3C{\equiv}CNEt_2$ and $H_2C{=}C{=}CHNEt_2$ (0.11 mol, 12.2 g, Ref. [6, 7]) is added and the solution is cooled to −85 °C (occasional cooling in a bath with liquid nitrogen, care being taken that the solvent does not solidify at the bottom of the flask). A solution of 0.11 mol of butyllithium in 77 ml of hexane is added dropwise over 5 min with cooling between −65 and −80 °C. After an additional 5 min, the temperature is allowed to rise to −60 °C over 15 min. The solution is then ready for further reactions. The *lithiated* intermediates can be obtained by adding (at about −50°) a solution of 12 g (0.14 mol) of anhydrous lithium bromide (obtained by heating the commercial anhydrous salt for 30 min at 150 °C in a vacuum) in 40 ml of THF.

8.16 Trimethylsilylation of Metallated Diethylaminoallene

$$H_2C{=}C{=}C(Li)NEt_2 + Me_3SiCl \xrightarrow[-60\ \rightarrow\ -10\ ^\circ C]{\text{THF-hexane}}$$

$$Me_3SiCH_2C{\equiv}CNEt_2 + LiCl$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

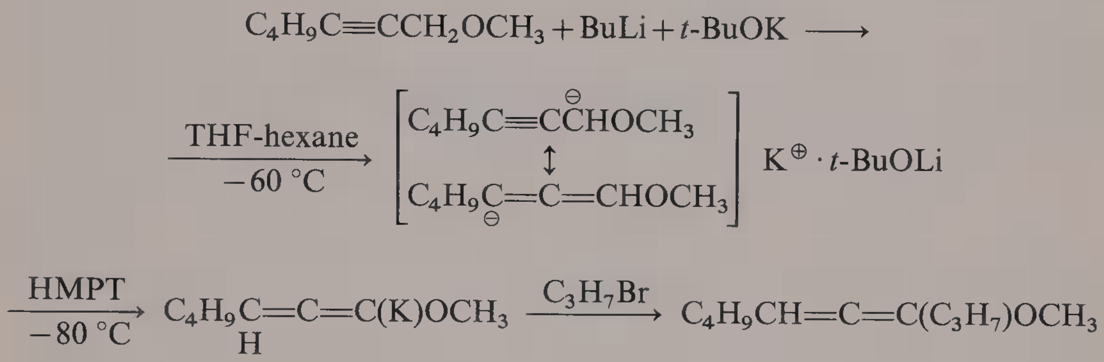
Introduction
Derivatization of 1-lithiated and 1-potassiated allenyl *ethers* results in the exclusive formation of allenic compounds [7]. The results with the *nitrogen* analogues [9, 104] show that steric effects and the nature of the metal ion may both influence the ratio of the isomeric functionalization products. Whereas $H_2C{=}C{=}C(Li)NEt_2$ and

Me_2SiCl give exclusively $Me_3SiCH_2C{\equiv}C{-}NEt_2$, a 2:1 mixture of the latter compound and $H_2C{=}C{=}C(SiMe_3)NEt_2$ is produced in the silylation of the *potassium* compound. In the case of the lithiated *dimethyl*aminoallene equal amounts of the silylated allene and acetylene are obtained [9].

Procedure

Trimethylchlorosilane (0.12 mol, 13.0 g) is added to a suspension of $H_2C{=}C{=}C(Li)NEt_2$ (Exp. 15) in THF and hexane maintained between −50 and −60 °C. After the addition, which takes 10 min, the temperature is allowed to rise to +10 °C. The mixture is then poured into 150 ml of an aqueous solution of 5 g of potassium carbonate. After vigorous shaking, the layers are separated and the aqueous layer is extracted three times with Et_2O. The combined organic solutions are dried over potassium carbonate and subsequently concentrated under reduced pressure. Distillation of the remaining liquid through a 30-cm Vigreux column gives $Me_3SiCH_2C{\equiv}C{-}NEt_2$, b.p. 75 °C/15 mm, n_D^{20} 1.4538, in 84% yield.

8.17 Conversion of a 2-Alkynyl Ether into a 1-Alkylated Allenyl Ether



$$C_4H_9C{\equiv}CCH_2OCH_3 + BuLi + t\text{-}BuOK \longrightarrow$$

$$\xrightarrow[-60\,^\circ C]{\text{THF-hexane}} \left[\begin{array}{c} C_4H_9C{\equiv}C\overset{\ominus}{C}HOCH_3 \\ \updownarrow \\ C_4H_9\underset{\ominus}{C}{=}C{=}CHOCH_3 \end{array}\right] K^{\oplus}\cdot t\text{-}BuOLi$$

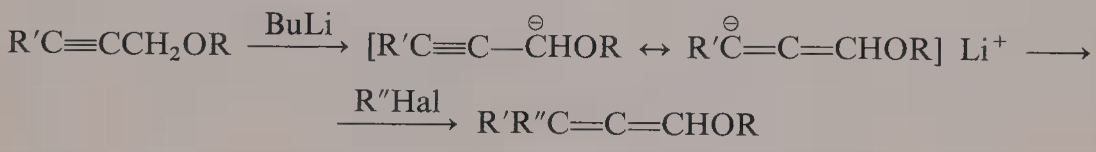
$$\xrightarrow[-80\,^\circ C]{\text{HMPT}} C_4H_9\underset{H}{C}{=}C{=}C(K)OCH_3 \xrightarrow{C_3H_7Br} C_4H_9CH{=}C{=}C(C_3H_7)OCH_3$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 11.

Introduction

Metallation of 2-alkynyl ethers $R'C{\equiv}CCH_2OR$ with BuLi in THF, followed by quenching with water, affords comparable amounts of starting material and the isomer $R'CH{=}C{=}CHOR$ [99, 223]. Alkylation, however, proceeds regiospecifically, giving a 3-substituted allenic ether [99]:



$$R'C{\equiv}CCH_2OR \xrightarrow{BuLi} [R'C{\equiv}C{-}\overset{\ominus}{C}HOR \leftrightarrow R'\overset{\ominus}{C}{=}C{=}CHOR]\ Li^+ \longrightarrow$$

$$\xrightarrow{R''Hal} R'R''C{=}C{=}CHOR$$

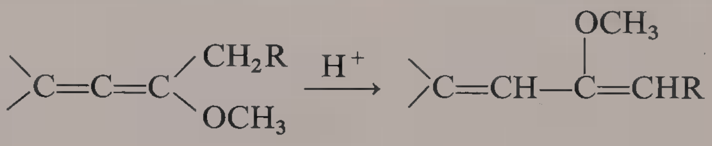
Under more polar conditions, i.e. HMPT as a co-solvent and replacement of Li^+ by K^+ (addition of *t*-BuOK), a 1-metallated allenyl ether is formed, and subsequent addition of an alkyl halide results in a *1*-alkylated allenyl ether [100].

Procedure

A solution of 0.12 mol of butyllithium in 84 ml of hexane is added over 5 min to a mixture of 0.10 mol (12.6 g) of 1-methoxy-2-heptyne [6] and 70 ml of THF, maintained at about −60 °C. After an additional 15 min the solution is cooled to −80 °C (occasional cooling in a bath with liquid nitrogen, care being taken that the solvent does not solidify at the bottom of the flask) and a solution of 0.12 mol (13.4 g) of *t*-BuOK in 40 ml of THF is added over 5 min, while keeping the reaction mixture between −70 and −80 °C. After an additional 10 min 50 ml of purified HMPT (Chap. I-2) is added dropwise over 10 min, keeping a temperature of ca. −80 °C. After an additional 20 min 0.16 mol (19.7 g) of propyl bromide is added over 10 min. Stirring at −70° is continued for 30 min, then the temperature is allowed to rise to −20 °C. Water (200 ml) is added with vigorous stirring and, after separation of the layers, five extractions with pentane are carried out. The combined organic solutions are washed six times with brine, containing a small amount of ammonia (Note 1). After drying over potassium carbonate, the solvent is removed under reduced pressure and the remaining liquid distilled through a 40-cm Vigreux column. Prior to the distillation the glass ware is flushed with gaseous ammonia or a dilute ethereal solution of triethylamine (Note 1). The product, b.p. 75 °C/15 mm, n_D^{20} 1.4535, is obtained in 72% yield.

Notes

Allenic ethers having an alkyl substituent in the 1-position isomerize readily to conjugated dienes under the influence of acids [9, 92]:



8.18 Conversion of a Tertiary Acetylenic Amine into the Allenic Isomer *via* Metallic Intermediates

$$C_4H_9C{\equiv}CCH_2NMe_2 + BuLi \xrightarrow[-40\ \rightarrow\ -20\ ^\circ C]{\text{THF-hexane}}$$

$$C_4H_9C{\equiv}CCH(Li)NMe_2 + C_4H_{10}$$

$$C_4H_9C{\equiv}CCH(Li)NMe_2 + t\text{-}BuOK \xrightarrow[-30\ \rightarrow\ -15\ ^\circ C]{}$$

$$C_4H_9C{\equiv}C{-}CH(K)NMe_2 + t\text{-}BuOLi$$

$$C_4H_9C{\equiv}C{-}CH(K)NMe_2 + t\text{-}BuOH \longrightarrow \underset{(90\ \text{rel. }\%)}{C_4H_9CH{=}C{=}CHNMe_2}$$

$$+ C_4H_9C{\equiv}CCH_2NMe_2$$

Introduction

In some cases, *t*-BuOK-catalyzed isomerization of propargyl amines affords reasonably pure allenic derivatives $H_2C{=}C{=}CHNR_2$ [9, 103]. The homologues $R'CH{=}C{=}CHNR_2$ cannot be obtained from $R'C{\equiv}CCH_2NR_2$ or $R'CH_2C{\equiv}CNR_2$ in a similar way, since no satisfactory accumulation can be effected [9]. At elevated temperatures 1,3-dienyl amines $C{=}C{-}C{=}C{-}NR_2$ are formed. A more promising approach involves metallation of 2-alkynyl amines $R'C{\equiv}CCH_2NR_2$ with BuLi followed by protolysis ([219], compare [223]). Thus, treatment of $C_4H_9C{\equiv}CCH_2NMe_2$ with BuLi in a THF-hexane mixture, followed by addition of one equivalent of *t*-butylalcohol, afforded the desired homologue $C_4H_9CH{=}C{=}CHNMe_2$, but the protonation is not regiospecific, some 20% of the acetylenic amine being present as a contaminant. A better regioselectivity can be attained, if, prior to the protolysis, an equivalent amount of *t*-BuOK is added. In view of the water-sensitivity of allenic amines, protonation is carried out with the less acidic *t*-butylalcohol, while the isolation of the product from the reaction mixture occurs by a "dry" work-up (i.e. distillation from the reaction mixture). The regioselectivity of the metallation of $R'C{\equiv}CCH_2NR''_2$ seems to be strongly dependent on the groups R′ and R″: if $R'{=}CH_3$, only $LiCH_2C{\equiv}CCH_2NR''_2$ is formed, and subsequent protonation affords an isomeric allenyl amine $H_2C{=}C{=}CHCH_2NR''_2$ together with an appreciable amount of the acetylenic amine [9]. There are indications that *diethyl*aminoalkynes, $RCH_2C{\equiv}CCH_2NEt_2$, undergo also partial deprotonation at the carbon atom remote from nitrogen [9]. Since NR_2 groups have only weak electron-withdrawing properties, the relative importance of *steric* effects may be considerable.

Procedure

The acetylenic amine (0.10 mol (13.9 g), for the preparation see Ref. [6]) is added over 10 min to a mixture of THF (60 ml) and butyllithium (0.12 mol in 84 ml of hexane) at −40 °C. The temperature is then allowed to rise to −20 °C and is kept at this level for 20 min. Then the mixture is cooled again to −40 °C and a solution of 0.12 mol (13.4 g) of *t*-BuOK in 30 ml of THF is added, while allowing the temperature to rise to −20 °C. After an additional 10 min (at −20°) the solution is cooled to −40 °C and 0.12 mol (8.9 g) of *t*-butylalcohol is added in one portion with vigorous stirring. After addition of 70 ml of paraffin oil (Note 1), the solvent is removed on a rotary evaporator. The flask is then equipped for a vacuum distillation, using a 10–20-cm Vigreux column, a condenser and a *single* receiver and connected to the oil pump. The receiver is cooled at −78 °C and the system evacuated. After the last traces of solvent have condensed in the receiver, the pressure should drop below 0.5 mmHg. The temperature of the heating bath is gradually raised to 80 °C. Redistillation of the contents of the receiver through a 30-cm Vigreux column gives reasonably pure (ca. 92% by NMR) allenic amine, b.p. 55 °C/12 mm, n_D^{20} 1.4615, in 75% yield. The contaminants are $C_4H_9C{\equiv}CCH_2NMe_2$ and possibly $C_3H_7CH{=}C{=}CHCH_2NMe_2$.

Notes

1. If no paraffin oil is added, the transfer of heat from the bath is unsatisfactory due to the presence of much solid material.

8.19 Preparation of Dimethylaminobutatriene *via* the Metallic Intermediate

$$\mathrm{H_2C{=}CH{-}C{\equiv}C{-}NMe_2 + BuLi\cdot \mathit{t}\text{-}BuOK} \xrightarrow[-90\,°\mathrm{C}]{\text{THF-hexane}}$$

$$\mathrm{H_2C{=}C{=}C{=}C(K)NMe_2\cdot \mathit{t}\text{-}BuOLi + C_4H_{10}}$$

$$\mathrm{H_2C{=}C{=}C{=}C(K)NMe_2 + 2\,\mathit{t}\text{-}BuOH} \longrightarrow$$

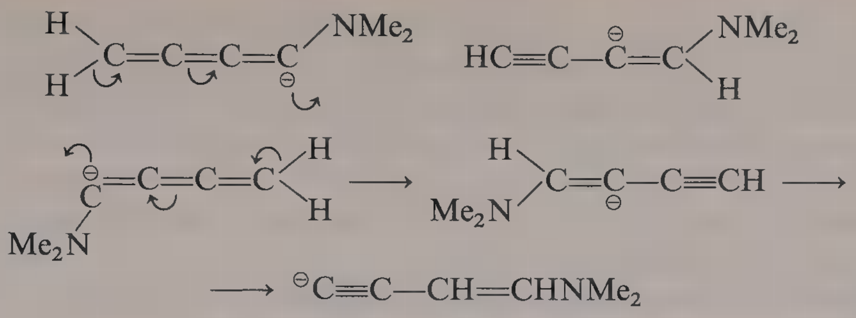
$$\longrightarrow \mathrm{H_2C{=}C{=}C{=}CHNMe_2 + \mathit{t}\text{-}BuOK\cdot HO\text{-}\mathit{t}\text{-}Bu}$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

Treatment of the enyne amine $H_2C{=}CH{-}C{\equiv}CNMe_2$ with a catalytic amount of t-BuOK in DMSO or HMPT results in the formation of $HC{\equiv}C{-}CH{=}CHNMe_2$ [116]. The first steps in this isomerization are the vinylic deprotonation at C-3 and subsequent protonation of the trancient anion to give the cumulenic amine $H_2C{=}C{=}C{=}CHNMe_2$. It is, however, impossible to achieve any accumulation of this amine, since it is thermodynamically less stable than the ynene amine $HC{\equiv}CCH{=}CHNMe_2$, and the rate of its conversion into the ynene amine is higher than the rate of its formation from the starting compound. If this is treated at −90° with the strongly basic BuLi · t-BuOK in THF, the intermediate $[H_2C{=}\overset{\ominus}{C}{-}C{\equiv}CNMe_2 \leftrightarrow H_2C{=}C{=}C{=}\overset{\ominus}{C}{-}NMe_2]K^{\oplus}$ is formed immediately. Since water and primary alcohols cause a rapid proton-catalyzed isomerization of the butatriene amine into $HC{\equiv}CCH{=}CHNMe_2$ [117], the protonation of the potassium compound is carried out with the less acidic t-BuOH, affording the cumulenic amine regiospecifically. Its isolation has to be carried out by a distillative procedure, and under the conditions of the distillation the t-BuOK formed in the protonation may cause isomerization of the cumulenic amine to $HC{\equiv}CCH{=}CHNMe_2$. This reaction can be suppressed by using a 100% excess of t-BuOH for the quenching reaction. The excess forms the 1:1 complex with t-BuOK which is a considerably less active isomerization catalyst. Isomerization can even occur in the absence of proton donors. If the temperature of the mixture containing the metallated cumulenic amine is allowed to rise above −70 °C, appreciable amounts of $HC{\equiv}CCH{=}CHNMe_2$ are formed in the quenching reaction with t-butylalcohol. We assume that the metallic derivative of this amine is formed by a charge shift, which may take place *via* two successive dimeric head-to-tail arrangements of metallated intermediates:



Procedure

A solution of 0.14 mol of butyllithium in 98 ml of hexane is added to a strongly cooled (below −70°) mixture of 0.10 mol (9.5 g) of dimethylaminobutenyne [7] and 60 ml of THF. Subsequently a solution of 0.14 mol (15.7 g) of *t*-BuOK in 50 ml of THF is added over 5 min, while maintaining the temperature betwen −90 and −100 °C (occasional cooling in a bath with liquid nitrogen, care being taken that the solvent does not solidify at the bottom of the reaction flask). A yellow suspension soon appears. The temperature is allowed to rise to −80 °C over 5 min, then the mixture is cooled again to −90° and a mixture of 0.30 mol (22.2 g) of *t*-butylalcohol (water-free!) and 20 ml of Et_2O is added over ca. 2 min with vigorous stirring. During this protonation operation the temperature should be kept below −60°. After having allowed the temperature to rise to −20°, 100 ml of paraffin oil (Note 1) and anti-bumping granules are added. The thermometer-outlet combination and the dropping funnel-inlet combination are replaced by stoppers and a 20-cm Vigreux column is placed on the middle neck. The column is connected to a condenser and a *single* receiver. A 20 cm long tube filled with KOH pellets is placed between the receiver and the water pump. The receiver (500-ml flask) is cooled at −78 °C and the system is evacuated. To avoid foaming, the flask with the solution of the metallated cumulenic amine is first placed in a bath with ice water. The temperature of the bath is gradually raised to 30° as the amount of solvent in the reaction flask decreases. Evacuation is continued until the evaporation of the solvents has stopped (the depression in the centre of the surface of the liquid in the receiver has disappeared). Nitrogen is then admitted and the receiver is replaced by a smaller one (100-ml), which is cooled in a bath at −50 °C. The system is evacuated with the mercury diffusion pump ($p < 0.1$ mm). Warming of the flask is not started until the pressure has dropped below 0.1 mm. The bath temperature is gradually raised from 25 to 70 °C as more of the yellow amine is collected in the receiver. When no longer yellow condensate is visible in the receiver, nitrogen is admitted and the contents of the receiver warmed to 35 °C. After adding anti bumping granules, the receiver is evacuated at 15 mm for about 0.5 h (bath temperature ca. 35°). Traces of *t*-butylalcohol and THF are removed during this operation. After admitting nitrogen, the refractive index n_D is determined and a NMR spectrum is recorded (Note 2). The yield of the cumulenic amine with n_D^{20} 1.639 (Note 3) is at least 70% and the purity 90 to 95% (5–10% $HC{\equiv}CCH{=}CHNMe_2$).

Notes

1. The paraffin oil serves as a heat conductor during the removal of the solvents and the subsequent distillation of the product.

2. No solvent is used: traces of water and acid in CCl_4 cause isomerization to $HC{\equiv}CCH{=}CHNMe_2$. The NMR tube must be perfectly dry.
3. The yellow colour of the cumulenic amine does not permit an accurate determination of the n_D.

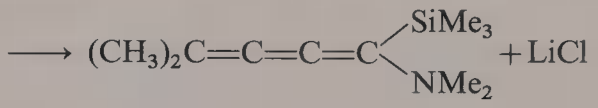
General note: The cumulenic amine is extremely sensitive towards oxygen. Traces of oxygen cause a rapid increase of the viscosity and a darkening of the colour. If treated carefully, the compound remains unchanged during storage at −20 °C for a limited period.

8.20 Preparation of a Metallated Cumulenic Amine *via* 1,4-Elimination, and Subsequent Reaction with Trimethylchlorosilane [118]

$$CH_3O{-}C(CH_3)_2C{\equiv}CCH_2NMe_2 + 2\,BuLi \xrightarrow[-30\,°C]{\text{THF-hexane}}$$

$$(CH_3)_2C{=}C{=}C{=}C(Li)NMe_2 + LiOCH_3$$

$$(CH_3)_2C{=}C{=}C{=}C(Li)NMe_2 + Me_3SiCl \longrightarrow$$



$$\longrightarrow (CH_3)_2C{=}C{=}C{=}C\begin{smallmatrix}\diagup SiMe_3\\ \diagdown NMe_2\end{smallmatrix} + LiCl$$

Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

The best way to prepare cumulenic *ethers* $R^1R^2C{=}C{=}C{=}CHOR$ consists in treatment of 1,4-bis(alkoxy)-2-alkynes, $R^1R^2C(OR){-}C{\equiv}C{-}CH_2OR$ with two equivalents of butyllithium in Et_2O or THF [7]. The intermediate cumulenic ether is immediately metallated in the 1-position by the second equivalent of base and the lithiated ether can be protonated to give the free cumulenic ether or functionalized with electrophilic reagents to afford derivatives. The analogous *amines* can be obtained by a similar procedure, but the scope is limited. If in the starting compounds $R^1R^2C(OR){-}C{\equiv}C{-}CH_2NR_2$ either one, or both groups R^1 and R^2 are hydrogen, 1,4-elimination does not occur, but metallated *allenic* ethers $ROC(Li){=}C{=}CH{-}CH_2NR_2$ or metallated *allenic* amines $R^1CH(OR){-}C(Li){=}C{=}CH{-}NR_2$ are formed. The procedure below describes the generation of a lithiated cumulenic amine and its regiospecific reaction with trimethylchlorosilane.

Procedure

A solution of 0.11 mol of butyllithium in 77 ml of hexane is added over 10 min to a mixture of 0.05 mol (7.8 g) of the amino ether (Exp. 27) and 80 ml of THF with cooling to ca. −30 °C. After stirring for an additional 90 min, the solution is cooled to −80° and 0.07 mol (7.6 g) of Me_3SiCl is added in one portion. The cooling bath is removed and the temperature allowed to rise to −30 °C. Water (100 ml) is then added with vigorous stirring, while keeping the temperature below 5°. The organic layer and two ethereal extracts are dried over potassium carbonate and subsequently concentrated *in vacuo*. Distillation through a 20-cm Vigreux column gives the silylated cumulenic amine, b.p. 52 °C/0.2 mm, n_D^{20} 1.5564, in 68 % yield.

General note: The product is extremely oxygen-sensitive. Entry of carbon dioxide must also be avoided.

8.21 Lithiation of 1-Ethylthio-3-Buten-Yne and Subsequent Hydrolysis to Ethylthiobutatriene

$$H_2C{=}CH{-}C{\equiv}C{-}SEt + LDA \xrightarrow[-40\,^\circ C]{\text{THF-hexane}} H_2C{=}C{=}C{=}C(Li)SEt + HDA$$

$$H_2C{=}C{=}C{=}C(Li)SEt + H_2O \longrightarrow H_2C{=}C{=}C{=}CH{-}SEt + LiOH$$

Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

Alkali amides in liquid ammonia are sufficiently strong bases to convert acetylenic sulfides $R'CH_2C{\equiv}CSR$ into anionic species, $R'CH{=}C{=}\overset{\ominus}{C}{-}SR$ [6, 7]. It may therefore be expected that lithium diisopropylamide (more strongly basic than alkali amides) in THF is a suitable system for the metallation of enyne sulfides, $H_2C{=}CH{-}C{\equiv}C{-}SR$ (BuLi cannot be used, because it adds to the unsaturated system affording metallated allenic sulfides $BuCH_2CH{=}C{=}C(Li)SR$ [224]). Addition of water to the solution of the metallated enyne sulfide results in a regiospecific formation of the cumulenic sulfide. This can be isolated in a reasonable yield, provided that the necessary precautions are taken to avoid polymerization or auto-oxidation of these extremely unstable compounds.

Procedure [9]

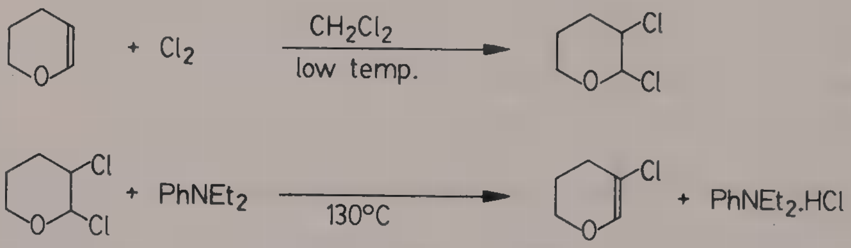
A solution of 0.06 mol of LDA in 40 ml of THF and 42 ml of hexane is prepared as described in Chap. I, Exp. 5. Ethylthiobutenyne (0.05 mol (5.6 g) for the preparation see Ref. [119]) is added over 5 min, while keeping the temperature between −40 and −45 °C. After an additional period of 10 min a mixture of 100 ml of water and 11 g of 36 % hydrochloric acid is added with vigorous stirring and cooling below 0°. The layers are separated as soon as possible and the aqueous layer is extracted twice with pentane. The organic solution is dried over $MgSO_4$ and subsequently poured in a 500-ml round-bottom. After addition of 50 ml of paraffin oil (Note 1) and anti bumping granules the solvent is removed in a water-pump vacuum. During this operation the bath temperature is gradually raised to 35 °C. The evacuation is interrupted (and nitrogen admitted) when the manometer indicates a constant low pressure. After adding new anti bumping granules the flask is equipped with a 20-cm Vigreux column, which is connected to a condenser and a *single* receiver, cooled at −60 °C. The apparatus is evacuated (mercury diffusion pump). Heating is started as soon as the pressure has dropped below 0.1 mmHg. The temperature of the heating bath is gradually raised to 50°. The cumulenic sulfide is obtained as a pale-yellow liquid in about 65 % yield. The n_D may be as high as ca. 1.60, but is strongly influenced by the presence of impurities with a lower n_D.

Notes

1. Explosive decomposition may occur in the final stage of distillations of cumulenic sulfides. Dilution with paraffin oil reduces the chance of an explosion to a minimum.

General note: In view of the thermolability, and sensitivity towards oxygen, extremely careful working is required.

8.22 5-Chloro-2,3-Dihydropyran [90b]



Scale: 0.5 molar.

Apparatus: 1-l three-necked, round-bottomed flask, equipped with a vent, a mechanical stirrer and a thermometer.

Procedure

A mixture of 0.6 mol (50.4 g) of 2,3-dihydropyran and 150 ml of dichloromethane is cooled below −70 °C. A solution of 0.5 mol (35.5 g) of chlorine in the same solvent is cautiously poured into the vigorously stirred solution of dihydropyran. Occasional cooling in a bath with liquid nitrogen allows this addition to be carried out within 10 min. After addition of 5 ml of *N,N*-diethylaniline to the resulting solution, the solvent is distilled off on the rotary evaporator. Diethylaniline (150 ml) is added to the remaining liquid and the mixture is heated at 130 °C with gentle stirring (Note 1). The weakly exothermic reaction can be easily kept under control by varying the rate of stirring (occasional cooling for a few seconds with water may be sufficient). The mixture is heated for 30 min at 135–140 °C, then the temperature is allowed to drop. The HCl salt of diethylaniline crystallizes below 100°. Ice water (250 ml) is then added to the light-brown mass. After addition of 50 ml of dichloromethane and vigorous shaking, the layers are separated. The upper, aqueous layer is extracted twice with small portions of dichloromethane. After drying the organic solution over potassium carbonate, the solvent is removed under reduced pressure. Careful distillation of the remaining liquid through a 40-cm Vigreux column gives 5-chloro-2,3-dihydropyran, b.p. 45 °C/12 mm, n_D^{20} 1.4750, in 64% yield.

Notes
A vigorous reaction (decomposition) may occur if the temperature rises above 150°. For this reason we advise against using an oil bath (with an electric heating system). This does not allow a satisfactory control of the temperature. We prefer heating with a free flame in this case (compare Exp. 25).

8.23 Vinyl Alkyl and Vinyl Aryl Sulfides (compare Ref. [120])

$$HC{\equiv}CH + RSH \xrightarrow[t\text{-BuOK}]{\text{DMSO or HMPT}} H_2C{=}CH{-}SR$$

$$(R = CH_3,\ C_2H_5 \text{ or Ph})$$

Scale: 1.0 molar.

Apparatus: For $H_2C{=}CHSCH_3$: 1-l round-bottomed, four-necked flask (vertical necks), equipped with two gas inlet tubes, a gas-tight mechanical stirrer and a thermometer-outlet combination; the outlet is connected to a cold trap. For $H_2C{=}CHSEt$ and $H_2C{=}CHSPh$: Chap. I, Fig. 1, 1 l; the outlet is connected to a cold trap.

The acetylene is freed from acetone by leading the gas through two (if the pressure in the cylinder is less than 3 atm., three or four) cold traps (−78°). The flow of the gasses is adjusted such that nearly all gas is absorbed. Washing bottles filled with paraffin oil are used to make the flows visible.

a) Vinyl methyl sulfide
"Ionol" CP (2 g, trade name of Shell Ltd. for the antioxidant 2,6-di-*t*-butyl-4-methylphenol) is added to a solution of 7.0 g (0.06 mol) of *t*-BuOK in 250 ml of DMSO. Methanethiol (1.0 mol, 48 g) is liquified in a trap cooled at −80 °C. The solution is heated to 55 °C and saturated with acetylene at this temperature (introduction of a fast stream for 1 min). Methanethiol and acetylene are then introduced simultaneously with very vigorous stirring, while keeping the temperature between 60 and 70°. The intensity of the flow of the thiol can be varied by changing the temperature of the water bath in which the trap with the thiol has been placed (b.p. methanethiol 6.2 °C). The reaction is moderately exothermic. When, after about 45 min, all thiol has been introduced, the traps before and behind the flask are interchanged. If the introduction of the gas streams has been carried out properly, the latter trap contains only a few ml of liquid. After all thiol has been introduced, the mixture is heated at 65° for an additional 15 min while continuing the introduction of acetylene. After cooling to room temperature anti bumping granules are added and the flask is equipped for a vacuum distillation using a 30-cm Vigreux column, a condenser and a *single* receiver cooled at −78 °C. The apparatus

is evacuated by means of the water pump and the flask gradually heated until DMSO begins to reflux in the column. The contents of the receiver are shaken with 50 ml of an aqueous solution of 10 g of potassium hydroxide, the organic layer separated and dried over $MgSO_4$. Repeated evaporation in a water-pump vacuum and condensation in a receiver cooled at $-78°$ gives pure methyl vinyl sulfide, n_D^{20} 1.4817, in yields up to 90%.

The compound should be stored at $-20°$ in the presence of a small amount of a radical inhibitor.

b) Vinyl ethyl sulfide

A solution of 5 g (0.04 mol) of *t*-BuOK and 2 g of "ionol" CP in 150 ml of DMSO is heated to 55°, while acetylene is introduced at a moderate rate (ca. 300 ml/min). Freshly distilled ethanethiol (1.0 mol, 62 g) is then added dropwise with vigorous stirring and the temperature maintained at 55 °C (occasional heating or cooling, ensuring the reaction is kept under control). After the addition of the thiol, which is carried out in 45 min, the contents of the cold trap are cautiously (dissolved acetylene escapes!) poured into the flask and introduction of acetylene and heating are continued for an additional 15 min. Ethyl vinyl sulfide (yield ca. 90%, n_D^{18} 1.4758) is obtained as described for vinyl methyl sulfide. The compound should be stored at $-20°$ in the presence of a radical inhibitor.

c) Vinyl phenyl sulfide

A solution of 6 g (0.05 mol) of *t*-BuOK and 2 g of "ionol" CP in 250 ml of HMPT is heated to 145 °C. Freshly distilled thiophenol (1.0 mol, 110 g) is added dropwise over 45 min with vigorous stirring and simultaneous introduction of acetylene (ca. 500 ml/min). Continuous heating is necessary to maintain a temperature of 140–145 °C. After the addition, acetylene is introduced for an additional 30 min (at 140°). The dark solution is then cooled to room temperature and a cold solution of 20 g of potassium hydroxide in 300 ml of water is added with vigorous stirring. The mixture is extracted four times with small portions of Et_2O. The organic solutions are washed four times with water (to remove the HMPT) and are subsequently dried over $MgSO_4$. After removal of the ether under reduced pressure the remaining oil is distilled in the presence of 1 g of "Ionol" CP. Vinyl phenyl sulfide, b.p. 100 °C/12 mm, n_D^{19} 1.5878, is obtained in 88% yield.

General note: The almost colourless solutions turn grey to black as soon as all dissolved thiol has reacted. This colour may be caused by the inhibitor.

8.24 *Z*-bis(Methylthio)Ethene (compare [121])

$$\underset{E+Z}{\mathrm{ClCH{=}CHCl}} + 2\,\mathrm{NaNH_2} \xrightarrow[-33\,°\mathrm{C}]{\text{liq. }\mathrm{NH_3}} \mathrm{Na{-}C{\equiv}C{-}Cl} + \mathrm{NH_3} + \mathrm{NaCl}\downarrow$$

$$\mathrm{CH_3SSCH_3} + 2\,\mathrm{Na} \longrightarrow 2\,\mathrm{NaSCH_3}$$

$$\mathrm{Na{-}C{\equiv}C{-}Cl} + 2\,\mathrm{NaSCH_3} + 2\,\mathrm{C_2H_5OH} \longrightarrow \underset{Z}{\mathrm{CH_3S{-}CH{=}CH{-}SCH_3}}$$

$$+ 2\,\mathrm{C_2H_5ONa}\downarrow + \mathrm{NaCl}\downarrow$$

Scale: 0.5 molar.

Apparatus: 3-l round-bottomed, three-necked flask provided with a dropping funnel, a mechanical stirrer and a vent.

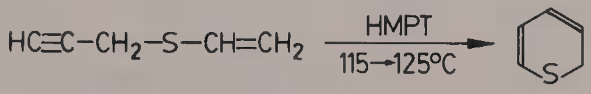
Procedure

A suspension of 1.2 mol of sodamide in 1.5 l of liquid ammonia is prepared as described in Chap. I, Exp. 7. A mixture of *E*- and *Z*-dichloroethene (0.5 mol, 48.5 g) is added dropwise over 30 min to the suspension. During this addition the suspension is stirred at a moderate rate to prevent splashing (Note 1). In a second flask (2 to 3 l) 0.55 mol (51.7 g) of dimethyl disulfide is added dropwise over 20 min to a solution of 1.15 mol (26.5 g) of sodium in 1.2 l of liquid ammonia. The resulting colourless or faintly blue solution is cautiously poured (over 2 min) into the first flask. Absolute ethanol (50 g) is placed into the dropping funnel and is added dropwise over 30 min with stirring at a moderate rate (Note 1). Small amounts of Et_2O are occasionally added to suppress foaming. After the addition, the dropping funnel and mechanical stirrer are removed and the ammonia is allowed to evaporate overnight. Water (500 ml) is added to the dark remaining mass and after dissolution of the salts, the product is extracted with Et_2O. The organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Distillation of the remaining liquid through a 30-cm Vigreux column gives *Z*-bis(methylthio)ethene, b. p. 88 °C/12 mm, n_D^{20} 1.5804, in 84% yield.

Notes

1. If stirring is carried out too vigorously, part of the solution of sodium chloroacetylide may splash into the upper part of the flask or into the necks. If air and moisture enter during the removal of the stirrer, dropping funnel and vent, or in the last stage of work-up water is added, the presence of this unreacted Cl—C≡C—Cl may give rise to an explosion.

8.25 2H-Thiopyran



Scale: 0.30 molar.

Apparatus: Chap. I, Fig. 1, 250 ml.

Procedure

Vinyl propargyl sulfide (0.30 mol (29.4 g), see Ref. [6]) is added dropwise over 20 min to purified HMPT (Chap. I-2, 120 ml) at 115 °C (Note 1). During this addition the solution is stirred at a moderate rate, while the temperature is kept between 115 and 120 °C by occasional cooling or heating. The rearrangement is strongly exothermic and careful control of the temperature is necessary. When the exothermic reaction has subsided after the addition, the temperature is raised to about 125 °C. This temperature is maintained for an additional 10 min, then the light-brown solution is cooled to room temperature and the flask equipped for a vacuum distillation, using a 40-cm Vigreux column, a condenser and a *single* receiver, cooled at 0 °C. The product is distilled off in a water-pump vacuum. The distillation is stopped as soon as HMPT begins to reflux in the column. Redistillation of the contents of the receiver gives 2H-thiopyran, b.p. ca. 40 °C/20 mm, n_D^{20} 1.5708 in yields up to 80%.

Notes

1. Cautious heating with a free flame is preferred to using an oil bath, since it allows a better control of the temperature.

8.26 2-Chloro-1,1-Bis(Dimethylamino)Ethene [9]

$$Cl_2C{=}CHCl + NaNH_2 \xrightarrow[\text{reflux}]{Me_2NH} Cl{-}C{\equiv}C{-}Cl + NaCl\downarrow + NH_3\uparrow$$

$$Cl{-}C{\equiv}C{-}Cl + Me_2NH \longrightarrow ClC(NMe_2){=}CHCl$$

$$ClC(NMe_2){=}CHCl + Me_2NH + NaNH_2 \longrightarrow (Me_2N)_2C{=}CHCl$$
$$+ NaCl\downarrow + NH_3\uparrow$$

Scale: 0.30 molar.

Apparatus: 1-l round-bottomed, three-necked flask, provided with a dropping funnel, a gas-tight mechanical stirrer and a reflux condenser for low-boiling liquids ("cold-finger", filled with solid CO_2 and acetone). The outlet on the top of the condenser is connected *via* a plastic tube with a drying tube filled with KOH pellets. The distance between the drying tube and the condenser is such that no CO_2 can enter.

Introduction

In the published procedure for the ynediamine $Me_2N{-}C{\equiv}C{-}NMe_2$ trichloroethene is added to a suspension of sodamide in dimethylamine [94]. After the dimethylamine has evaporated, the remaining mass is heated *in vacuo*, which results in the isolation of the ynediamine. After several unsuccessful attempts to reproduce these results we came to the conclusion that the amount of ferric nitrate used as a catalyst for the preparation of the sodamide had a considerable influence upon the result. If a relatively large amount of this salt (ca. 800 mg for 1 mol of Na) was used, the literature result could be reproduced in a satisfactory way. Sodamide prepared with a small amount of iron salt (ca. 100 mg for 1 mol of Na) appeared to be much less reactive in the conversion with trichloroethene and impure ynediamine was obtained in low yield. If, however, a small amount of *t*-BuOK was added after the addition of trichloroethene and the reaction mixture was extracted with Et_2O, (instead of heating the dry mass *in vacuo*) the intermediate $ClCH{=}C(NMe_2)_2$ could be isolated in a good yield, along with a small amount of the ynediamine. We assume that the sodamide crystals are smaller (and therefore more active), if a relatively large amount of iron salt is used.

Procedure

Sodamide is prepared from 43 g (1.9 mol) of sodium, using 100 mg of ferric nitrate (compare Chap. I, Exp. 7; with this small amount of catalyst the conversion into sodamide may take at least 1 h). The powder is transferred into the 1-l flask and 250 ml of dimethylamine (cooled at −20 °C) is added. A slow stream of nitrogen (ca. 100 ml/min) is passed through the apparatus. Trichloroethene (0.30 mol, 39.5 g) is added dropwise over 10 min, while stirring at a moderate rate, so that the suspension is not swept along the upper part of the flask. After the addition the dropping funnel is replaced by a combination of a thermometer and a gas inlet. The temperature of the mixture should be 6 to 7 °C just after all trichloroethene has been added. The intensity of the reflux from the cold finger increases gradually, while the temperature of the mixture drops (the ammonia formed in the reaction escapes from the reaction mixture, condenses and returns into the flask with a cooling effect). After 1 to 1.5 h when the temperature has reached a minimum (ca. −10 °C), a solution of 2 g of *t*-BuOK in 5 ml of THF and 5 ml of HMPT is added. Stirring is continued for an additional hour, then the cold finger is removed and 400 ml of a 1:1 mixture of Et_2O and pentane is added. The flask is placed in a water bath at 45 °C. When the volume of the reaction mixture has decreased to about 350 ml, the suspended material is filtered through a sintered-glass funnel (G-2). The solid is rinsed well with the solvent mixture. Paraffin oil (40 ml) is then added to the brown filtrate (volume ca. 500 ml) and most of the solvent is distilled off at normal pressure through a 40-cm Vigreux column: the temperature of the heating bath should not be higher than 60°. The remainder of the solvent is removed by evacuation (water pump). After a first, rough distillation at a pressure of 0.5 mmHg or lower, using a *single* receiver cooled at −70°, careful distillation through a 40-cm Vigreux column is carried out. After a fore run (b.p. 30–55 °C/15 mm, mainly below 45°), consisting of the ynediamine and (sometimes) $Me_2NC(Cl){=}CHCl$, the desired product passes over between 55 and 62 °C/15 mm. Yields are between 60 and 70 %. The compound is very water-sensitive (development of a brown colour).

8.27 3-Methoxy-3-Methyl-1-Butyne and 1-(Dimethylamino)4-Methoxy-4-Methyl-2-Pentyne

$$HC{\equiv}C{-}C(CH_3)_2OH + Me_2SO_4 + KOH \xrightarrow[50\ ^\circ C]{DMSO}$$

$$HC{\equiv}C{-}C(CH_3)_2OCH_3 + K(CH_3)SO_4 + H_2O$$

$$HC{\equiv}C{-}C(CH_3)_2OCH_3 + Me_2NH + (CH_2O)_n \xrightarrow[100\ ^\circ C]{Cu(OAc)_2}$$

$$Me_2NCH_2C{\equiv}C{-}C(CH_3)_2OCH_3 + H_2O$$

Scale: 1.0 molar for the methylation, 0.5 molar for the Mannich reaction.

Apparatus: Chap. I, Fig. 1 for the methylation. For the Mannich reaction: 1-l three-necked, round-bottomed flask, equipped with a dropping funnel, a mechanical stirrer and a reflux condenser.

Procedure

2-Methyl-3-butyn-2-ol (1.0 mol, 84 g) is added to a mixture of 120 g of machine-powdered potassium hydroxide and 250 ml of DMSO (purification of DMSO is not necessary). Dimethyl sulfate (151.2 g, 1.2 mol) is added dropwise with vigorous stirring, while keeping the temperature between 50 and 60 °C. This addition takes 20–30 min, and stirring is then continued for an additional half hour at ca. 55°. The flask is then equipped for distillation, using a 30-cm Vigreux column, a condenser and a *single* receiver cooled at −70 °C. The system is evacuated (water pump) and the heating bath gradually raised to 100 °C. The contents of the receiver are washed three times with brine and subsequently dried over a small amount of $MgSO_4$. The undistilled product, n_D^{20} 1.3997, obtained in 58–70 % yields, is used for the Mannich reaction.

The coupling of $HC{\equiv}CC(CH_3)_2OCH_3$ with Me_2NCH_2OH (prepared from paraformaldehyde and dimethylamine) in the presence of a catalytic amount of copper(II)acetate in 100 ml of dioxane is carried out by heating the mixture for 3 h at 100–110 °C (for experimental details see Ref. [7], p. 132). The compound $CH_3OC(CH_3)_2C{\equiv}CCH_2NMe_2$, b.p. 63 °C/17 mm, n_D^{20} 1.4380, is obtained in 88 % yield.

8.28 Lithiation of *N*,*N*-Dimethylformamide and *N*,*N*-Dimethylthioformamide

$$HC({=}X)NMe_2 + LDA \xrightarrow[-95\,°C]{\text{THF-hexane}} Li{-}C({=}X)NMe_2 + HDA$$

$$(X = O \text{ or } S)$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

Metallated acyl derivatives $(RC{=}X)^-M^+$, in which M represents an alkali metal, R = alkyl or NR'_2 and X = O or S, have been obtained by direct metallation of $RCH{=}O$ [108–111] and by reaction of RM with carbon monoxide at very low temperatures [122, 123, 225, 226]. The lithiations of thioformamides with LDA at ca. −100 °C proceed almost instantaneously, while those of the oxygen analogues are somewhat less fast. Subsequent couplings with carbonyl compounds gave the expected carbinols in good yields, but alkylations appeared to be less successful. The low stability of the lithiated carbamoyl and thiocarbamoyl compounds and their (presumed) moderate basicities are factors implying a limited scope of reactivity towards electrophilic reagents. The acyllithiums RCOLi, in situ generated from alkyllithium and C=O at ca. −110 °C, have been trapped with reactive compounds such as dimethyl disulfide and trimethylchlorosilane.

Procedure

Dimethylformamide (0.10 mol, 7.3 g) or its sulfur analogue (0.10 mol, 8.9 g, see Exp. 29) is added over 3 min to a solution of 0.11 mol of LDA in 80 ml of THF and 77 ml of hexane (see Chap. I, Exp. 5), cooled between −95 and −100 °C. During this addition the flask is occasionally cooled in a bath with liquid nitrogen, care being taken that the solvent does not solidify at the bottom of the flask. In the case of DMF the mixture is stirred for an additional 20 min at −100 °C prior to carry out derivatizations, the solution of the lithiated sulfur analogue can be used almost directly.

The reaction of $LiCONMe_2$ with *t*-BuCH=O and of $LiCSNMe_2$ with PhCH=O, carried out as described in the literature, afforded the coupling products in reasonable yields (the extracts of the reaction with lithiated DMF were not washed with water).

8.29 *N,N*-Dimethylthioformamide

$$HC(=O)NMe_2 + P_2S_5 \xrightarrow{CH_3C\equiv N} HC(=S)NMe_2 + P_2O_5$$

Procedure

Finely powdered phosphorus pentasulfide (0.3 mol, 65 g) is suspended in 500 ml of dry (dried by shaking with 30 g of P_2O_5 and distilling the decanted liquid) acetonitrile. Subsequently 1.5 mol of dry DMF is added and the mixture is stirred for 45 min at 65 °C. The reaction is weakly exothermic. The supernatant liquid is decanted and the solid rinsed four times with small portions of acetonitrile. After addition of 30 g of phosphorus pentasulfide the operations are repeated. The decanted liquid and the rinsings are concentrated under reduced pressure and the remaining liquid distilled to give the thioformamide, b.p. 95 °C/12 mm, n_D^{20} 1.5698, in 80% yield.

Chapter V
Metallated Hetero-Aromatic Compounds

1. Introductions

Thiophenes furans and pyridines are in general the most readily available of the various hetero-aromatic systems and therefore we have carried out a great deal of metallation and derivatization reactions with these compounds. Furan and thiophene are cheap starting compounds and the stability of their easily obtainable 2-lithio derivatives permits reactions with a variety of "electrophilic" reagents. Hetero-aromatics with two or more hetero atoms (e.g. thiazoles, pyrazoles, oxazoles) are less readily available, and some of their metal derivatives have a low thermostability (cyclofragmentations). For these reasons their metallation and functionalization reactions have been studied less extensively [1].

The majority of the metallated hetero-aromatic compounds are obtained by direct metallation [1, 2, 5]. The "hetero-atom effect" (inductive, coordinative and polarizability influence) in most cases directs the metallation to the position α- to the hetero atom and gives rise to an easier deprotonation compared with that of benzene [1]. In some cases, bromine-lithium exchange offers the possibility of introducing the metal in a position that is not accessible by direct deprotonation. In incidental cases, Grignard compounds have been prepared from halogenated hetero aromates and magnesium.

2. Metallated Furans, Pyrroles, Thiophenes, Selenophenes and Tellurophenes

2.1 Direct metallation by strong bases

Furan and thiophene can be metallated quantitatively and quickly with butyllithium in THF or Et_2O at temperatures ranging from −20 to +35 °C [1]. Benzene does not react at all under these conditions. This difference in kinetic acidity parallels the thermodynamic acidities: the determined pK-value of thiophene, 38, is significantly lower than that of benzene, 43 [124]. Furan is slightly less acidic than thiophene (in THF and Et_2O).

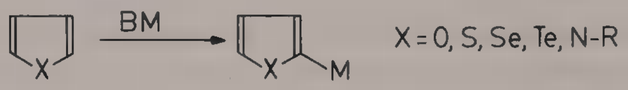
Interaction between thiophene and alkali amides in liquid ammonia gives only small concentrations of the thiophene-"anion" [9]. Complete metallation has been effected with the more strongly basic LDA in THF [125].

Our synthetic experiments suggest that selenophene and tellurophene have kinetic acidities that are comparable to those of thiophene [9].

Thiophene can be di-metallated in the 2- and 5-positions using two equivalents of BuLi · TMEDA in hexane [126]. Similar di-metallations of furan and 1-methylpyrrole have been reported [126], but only that of thiophene seems synthetically attractive.

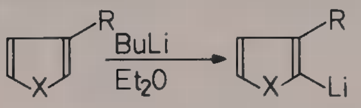
The mono-metallation of 1-methylpyrrole proceeds much less easily than those of furan and thiophene; when it is carried out in THF, a large excess of the pyrrole derivative is necessary to achieve an effective competition with the solvent [9]. More satisfactory procedures involve the use of BuLi · TMEDA in hexane or BuLi · *t*-BuOK in THF-hexane at −80 °C [9].

A common feature of the metallations of the heterocycles mentioned is the preference for the 2-position:



Determination of the relative kinetic acidities of the 2- and 3-protons in thiophene (H/D exchange experiments) shows the 2-proton to be 500 times more acidic than the 3-proton [127]. However, when a sufficient amount of HMPT is added to a solution of 2-lithiothiophene, ring opening to $LiC{\equiv}C{-}CH{=}CH{-}SLi$ occurs, which means that under these conditions exchange between Li and the 3-proton can take place [128]. Selenophene [129] and tellurophene [130] have been lithiated with satisfactory results. We have the impression however, that a more careful control of the reaction conditions is required, and bases with a more moderate reactivity, such as EtLi · LiBr in Et_2O, seem to give better results, especially in the case of tellurophene [9].

The orientation and regioselectivity in metallations of *substituted* furans and thiophenes are determined by the position (2- or 3-) of the substituent and its nature (activating or non-activating) [1]. Thiophens and furans with an activating substituent (inductive or coordinative) in the 3-position have been reported to undergo metallation by BuLi in Et_2O at the vicinal carbon atom 2:



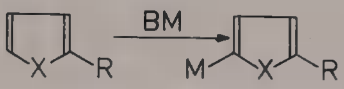
X = O or S; R = R′O, R′S, $R'SO_2$, Cl, Br, F, CH_2OR', $CH_2NR'_2$

Our experimental results confirm the literature reports [131–133]. However, when the reaction of 3-methylthio- or 3-*t*-butoxythiophene with BuLi in THF or Et_2O was carried out at room temperature, introduction of lithium into the 5-position occurred to an appreciable extent [9].

Reaction of 3-bromofuran and 3-bromothiophene with butyllithium does not lead to lithiation in the 2-position, but gives rise to bromine-lithium exchange with formation of 3-lithiofuran and its thiophene analogue [134, 135]. With the weaker bases KNH_2 in liquid ammonia, LDA in THF and PhLi in Et_2O however, complete deprotonation of carbon atom 2 occurs under mild conditions [9, 136–138].

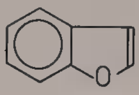
Alkyl- or aryl substituents in the 3-position do not have a directing influence and metallation in the 2- and 5-position occurs with comparable rates [1]. 3-*t*-Butylthiophene however, is metallated exclusively at C-atom 5 [139].

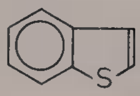
With only a few exceptions, e.g. in the case of the strongly coordinating oxazoline group [140], *2*-substituted thiophenes and furans (and also their Se- and Te-analogues) are metallated in the 5-position [1]:

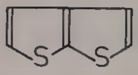


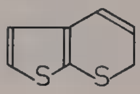
Although one could imagine deprotonation in the methyl group of methylfurans and -thiophenes (as is possible with toluene), this reaction is not likely to afford intermediates with a stability similar to that of the benzyl anion [201].

The structures shown below are examples of condensed furan- and thiophene systems:

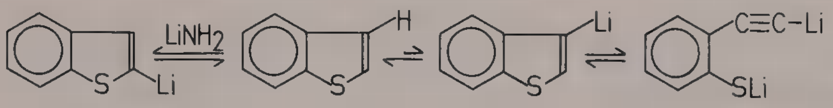




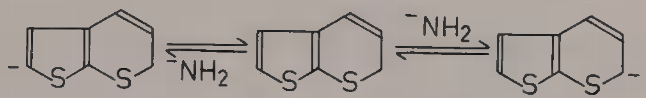




Under conditions of irreversible deprotonation (BuLi in THF or Et_2O), the 2-position of the hetero ring is metallated [1, 2, 9]. The pK values of benzofuran and benzothiophene [124] are slightly lower than those of the non-condensed heterocycles, so that complete metallation in the 2-position presumably can be effected with LDA in THF. However, the difference in acidity between the 2- and 3-protons is probably less than that in furan and thiophene. Ring opening therefore seems relatively easy under suitable basic reaction conditions (compare [141]), e.g.):



In the case of thienothiopyran, metallation in the thiopyran ring is the thermodynamically favoured process:

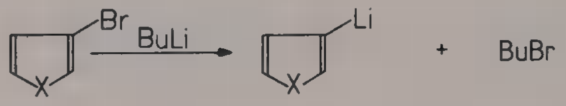


If severely aprotic conditions, i.e. BuLi in THF or Et_2O, are applied, however, the α-proton of the thiophene ring is specifically abstracted. If a not too acidic proton donor, e.g. diisopropylamine, is added, the metallated thiopyran is formed in a process of proton-donation and abstraction [93].

2.2 Halogen-Lithium Exchange

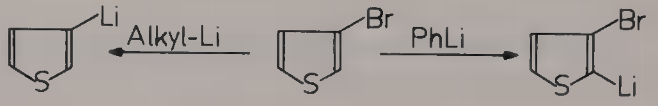
3-Metallated furans and thiophenes are not accessible by direct metallation but can be generated at low temperatures by treating the 3-bromo derivatives with BuLi in

THF or Et_2O [134, 135]:



The readily accessibile 3-bromothiophene (80 % overall yield from thiophene [142]) makes this exchange reaction an attractive route to 3-substituted thiophenes. 3-Bromofuran can be synthesized from furan, but a rather lengthy route must be followed (involving *inter alia* a Diels-Alder reaction with furan and cyclopentadiene [143]).

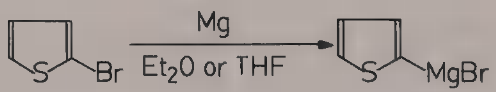
The 3-metallated thiophenes undergo a ring opening to M—C≡C—CH=CH—SM at temperatures above 0 °C [144]. This property, in combination with the presence of butyl bromide in the solutions, may give rise to problems in functionalizations with less reactive electrophiles, such as alkyl halides, epoxides and paraformaldehyde. Butyllithium (or higher-alkyllithiums) is the only suitable reagent for the generation of 3-lithiofurans and 3-lithiothiophenes from the bromo compounds. With phenyllithium (in Et_2O) 3-bromothiophene is metallated in the 2-position [137]:



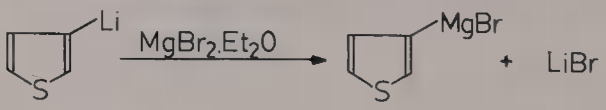
The driving force for the Br/Li exchange is probably much weaker in the case of phenyllithium, because the difference in base strength between PhLi and 3-thienyllithium is not large. On the other hand, the acidity of the 2-proton is sufficient to warrant a fast deprotonation by PhLi.

2.3 Grignard Derivatives

2-Bromothiophene can be readily converted into the Grignard compound under standard conditions:



We could not accomplish this conversion with 3-bromothiophene. However, addition of magnesium bromide etherate to a solution of 3-lithiothiophene gives the 3-bromo-Grignard quantitatively [145]:

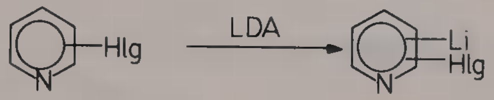


3. Metallated Pyridines

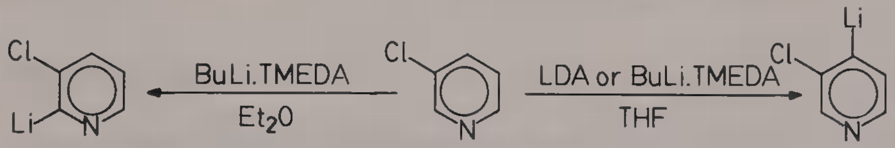
3.1 Direct Metallation

The presence of the nitrogen atom presumably gives rise to an (relatively small) increase of the acidity of the ring protons, compared to benzene. The pK-values of the pyridine protons are not known, but it may be assumed that these are a few units lower than those of benzene (pK 43) but higher than 36, the value of diisopropylamine. Attempts to metallate pyridine did not result in any accumulation of metallated intermediates [146]. The isolation of 2,2′-bipyridyl from this reaction was considered as evidence for the intermediate occurrence of 2-pyridyllithium. Even pyridinecarboxamides Py—C(=O)NR_2 are incompletely metallated by LDA [147].

The extensive investigations on pyridine analogues of benzyne [148] have stimulated recent efforts to generate "pyridynoids" from halogenopyridines and organolithium bases. Chlorine and fluorine strongly activate the vicinal protons for abstraction, and LDA appears to be sufficiently strong to bring about complete lithiation [149]:

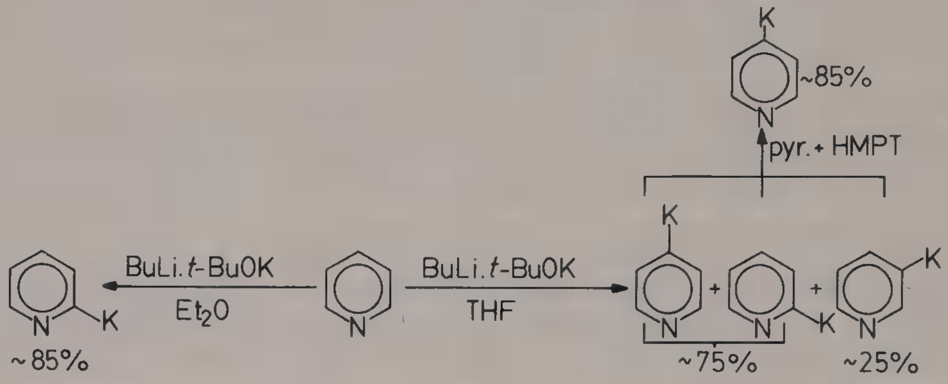


If a halogen is in the 3-position, two lithio derivatives can be formed. It appears to be possible to generate each of the two lithium compounds with high selectivity [150].



Using LDA in THF, lithium is introduced into the 4-position. The same 3-chloro-4-lithiopyridine is formed (in addition to small amounts of 3-chloro-2-lithiopyridine) if BuLi · TMEDA in THF is used [9]. Replacement of THF by Et_2O however, gives rise to predominant formation of the 2-lithio derivative. In Et_2O coordinative interaction between nitrogen in the ring and lithium presumably favours abstraction of the proton at C-atom 2. In THF this coordinative assistance may be smaller, because this solvent competitively complexes with BuLi. Our metallations with butyllithium did not give satisfactory results, probably because of addition of the base to the C=N bond. The metallations have to be carried out at temperatures of −60 °C or lower, in order to prevent elimination of lithium chloride, giving rise to dehydrohetarynes and their subsequent products. The pyridinoids with a fluorine atom are more stable than those with chlorine.

Recently, successful attempts at direct metallation of pyridine have been reported [19]. The problem in addition of the base to the azomethine bond has been solved by using the kinetically very active combination of BuLi and *t*-BuOK in THF and by working at very low temperatures. Under relatively non-polar conditions (Et_2O) the 2-proton is abstracted with a selectivity of at least 85 %. In THF a mixture of comparable amounts of the 2- and 4-potassio derivatives is formed, together with some 3-isomer. Addition of HMPT and a small amount of pyridine (which acts as a proton transfer reagent) to the metallation mixture causes a shift in favour of 4-potassiopyridine (~85 %) [19]. In a number of cases 2- and 4-substituted pyridines can be easily separated by distillation or crystallization, so that reasonably pure derivatives of pyridine can be obtained *via* direct metallation. Attempts to metallate quinoline and isoquinoline have not yet been successful [151].

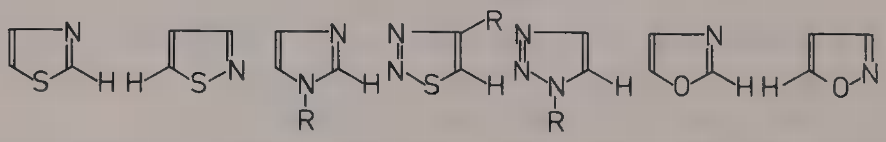


3.2 Halogen-Lithium Exchange

Bromine-lithium exchange in the various isomeric pyridines [152] and quinolines [153] is the method of choice for generating lithiated intermediates free from other isomers. This method is particularly attractive if a bromo compound is easily accessible, e.g. 3-bromoquinoline [156].

4. Metallated Hetero-Aromatics with more than one Hetero Atom

Five-membered aromatic ring compounds with two or more hetero atoms are deprotonated more easily than the one-hetero atom systems [1]. The ease of this proton removal is in part due to inductive electron withdrawal by the additional hetero atom(s), and in some cases coordination of the lithiating reagent by (sp^2) nitrogen may contribute (e.g. in 1,3-thiazole and 1-substituted imidazoles). Some examples of aromatic systems with more hetero atoms are:

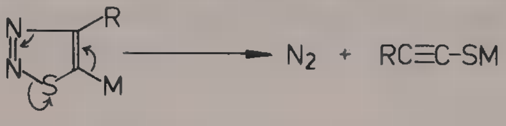


The most easily removable protons are indicated.

1,3-Thiazole and 1-alkylimidazoles are metallated completely within one minute at temperatures in the region of −80 °C, using BuLi in THF [9]. In the case of thiazole which has a pK value of 29 [124] (compare the value of thiophene:

(36 to 38) this facile deprotonation parallels the greater thermodynamic acidity. 1-Methylimidazole, however, does not give a high concentration of the "anion" upon addition to patassium amide in liquid ammonia [9], and therefore it must be considerably less acidic than thiazole. Its easy metallation compared with that of 1-methylpyrrole is probably due to coordinative fixing of BuLi by the sp^2-nitrogen atom.

With the exception of 2-metallated imidazoles, the metal derivatives of the hetero aromates mentioned have a low thermostability. 2-Lithiothiazole, for example, decomposes at temperatures higher than −50 °C. In some cases the metallation can induce a cyclofragmentation, e.g. in the following case [154]:

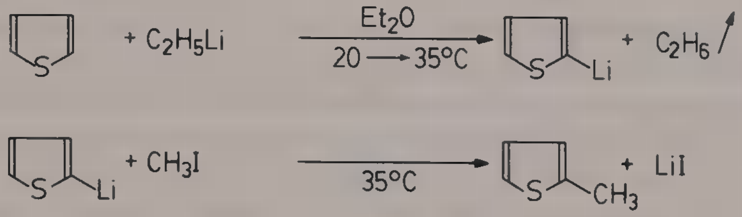


Successful functionalizations therefore can only be carried out with very reactive types of "electrophiles", e.g. carbonyl compounds, trialkylchlorosilane and disulfides.

5. Experimental Procedures

All temperatures are internal, unless indicated otherwise.

5.1 2-Methylthiophene



Scale: 1.0 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

Although the metallation of thiophene with butyllithium in a THF-hexane mixture proceeds much more easily, *ethyl*lithium in Et_2O (prepared from ethyl bromide and lithium) is chosen as the lithiation reagent for the following reasons. 2-Methylthiophene has a boiling point of 112.5 °C, and a distillative separation from the THF and hexane (b.p. between 65 and 70°) would therefore be more difficult and lengthy. Moreover, traces of butanol could be present in the butyllithium solution or could be formed (by oxidation) during transferring the reagent from the stock solution to the reaction flask. Removal of the butanol (b.p. 117.6 °C) which contaminate the methylthiophene would require an additional operation. These difficulties can be avoided by using ethyllithium in Et_2O. For most alkylations Et_2O is less suitable as solvent than THF, but methylation with methyl iodide can be carried out in a relatively short time. Methyl bromide can also be used, but in that case refluxing is not possible, since the volatile compound (b.p. 3.6 °C) would escape from the reaction mixture. Addition of a small amount of HMPT (5–10 vol. %) may render the alkylation with methyl bromide sufficiently fast to be carried out at much lower temperatures (between −10 and 0 °C). The same holds for the ethylation with ethyl bromide. Neither an excess of ethyllithium nor a large excess of thiophene should be used in the preparation of 2-methylthiophene. Reaction of methyl iodide with the excess of EtLi would give *ethyl* iodide by the following exchange reaction:

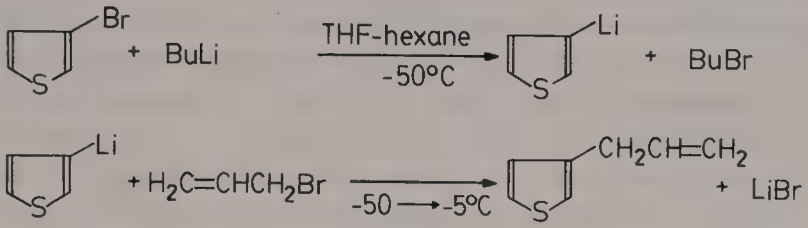
$$CH_3I \quad + \quad EtLi \rightleftharpoons CH_3Li \quad + \quad EtI$$

This equilibrium is probably largely on the right-hand side, because methyllithium is less strongly basic than ethyllithium (compare Ref. [10]). Reaction of 2-lithiothiophene with ethyl iodide would result in 2-ethylthiophene, which cannot be easily separated by distillation from the methyl derivative. On the other hand, the use of a large excess of thiophene should be avoided for similar reasons. In the present procedure a slight excess of thiophene is used, to ensure that all ethyllithium is consumed. It may be noticed that during the metallation of thiophene the temperature rises only slowly, which might give the impression that the reaction does not produce much heat, in spite of the relatively large scale. It should be realized, however, that one mol of ethane is formed, which partly escapes from the reaction mixture at reaction temperatures higher than 20 °C giving rise to an appreciable cooling effect. It is therefore not easy to judge when the lithiation is complete, so the prescribed reaction time may thus be longer than absolutely necessary. 2-Methylselenophene and the tellurium analogue can be prepared by similar procedures, starting from selenophene and tellurophene. The metallation of 2-alkylthiophenes in the 5-position may proceed less easily than that of (unsubstituted) thiophene. Refluxing with EtLi in Et_2O might be necessary to complete the reaction, if, for example, 2-methylthiophene is to be metallated. Therefore BuLi-THF-hexane may be more suitable for the metallation of 2-alkylthiophenes, unless the derivative to be prepared is rather volatile (e.g. 2,5-dimethylthiophene).

Procedure

Thiophene (88.2 g, 1.05 mol) is added over 20 min to a solution of 1.0 mol of ethyllithium in about 700 ml of Et_2O (compare Chap. I, Exp. 1). During, and also for 1 h after this addition the temperature of the mixture is maintained (occassional cooling) between 20 and 25 °C. The thermometer-outlet combination is then replaced by a reflux condenser and the solution is warmed for an additional hour under reflux. Methyl iodide (156.2 g, 1.1 mol) is then added over 20 min, refluxing being continued. After an additional period of 1 h the mixture is cooled to room temperature, after which it is cautiously poured into 500 ml of ice water. After shaking, the upper layer is separated and the aqueous layer is extracted twice with small (50 ml) portions of Et_2O. The combined ethereal solutions are dried over $MgSO_4$. The ether is distilled off as completely as possible through a 40 cm Widmer column. Distillation of the remaining liquid from a 250 ml flask through a 40 cm Vigreux column affords 2-methylthiophene, b.p. 112 °C/760 mm, n_D^{20} 1.5178, in 86 % yield.

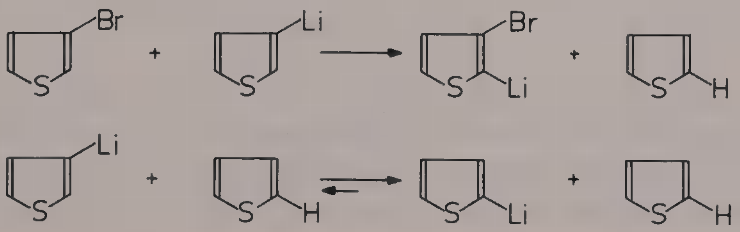
5.2 3-Allylthiophene



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction
The procedure for 3-lithiothiophene is typical for the generation of lithiated heteroaromates by bromine-lithium exchange. 3-Lithiothiophene is not accessible by direct metallation of thiophene, but can be quantitatively generated by reaction of 3-bromothiophene with butyllithium in Et_2O or THF at low temperatures. The exchange proceeds almost instantaneously in both solvents. The order of addition appears to be very essential, particularly when the reaction is carried out in THF. A clean conversion into 3-lithiothiophene can be achieved if the bromo compound is slowly added to a solution of a slight excess of butyllithium. When inversed addition is applied, however, mixtures of 2- and 3-lithiothiophene are formed, the ratio being dependent upon the rate of addition and the nature of the solvent (Et_2O or THF). If the solution of BuLi is slowly added to the THF solution of the bromo compound, appreciable amounts of 2-lithiothiophene are produced. This undesired process may be initiated by lithiation of the bromo compound in the 2-position by 3-lithiothiophene. The thiophene liberated in this reaction may react with 3-lithiothiophene to give the thermodynamically more stable 2-lithiothiophene. Traces of free thiophene (which could also be formed by entrance of moisture!) in principle should be sufficient to catalyze this trans-metallation to 2-lithiothiophene (compare also Refs. [209, 217, 229]):

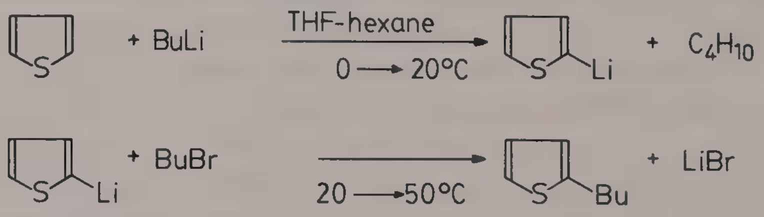


If 3-bromothiophene is added to butyllithium at a sufficiently low rate, no 2-lithiothiophene is formed, because the halogen-lithium exchange is much faster than the vicinal metallation of the bromo compound. Support for the mechanism of trans-metallation was provided by adding an equivalent amount of thiophene to a solution of 3-lithiothiophene in THF, cooled at −30 °C: after 1.5 h only the 2-lithio derivative was present in the solution [9]. In Et_2O this trans-metallation was very slow.

For *alkylations* THF is a better solvent than Et_2O. Since 3-lithiothiophene undergoes ring-opening to $LiC{\equiv}C{-}CH{=}CH{-}SLi$ at temperatures higher than 0 °C, only reactions with very reactive alkyl halides can be successful. Benzyl bromide was found to react very slowly at 0° and benzylthiophene was formed in small amounts only. For the introduction of primary alkyl groups other than butyl the use of alkyl *iodides* could be envisaged, because these are supposed to be able to compete effectively with the butyl bromide present in the solution. The smooth reaction with *allyl* bromide (even at temperatures in the region of −30 °C) might have been caused by catalytic assistance of iron compounds (present in the commercial butyllithium).

Procedure
THF (65 ml) is added to a solution of 0.11 mol of butyllithium in 77 ml of hexane maintained below 0 °C. The mixture is cooled to −60 °C and 0.10 mol (16.4 g) of 3-bromothiophene (Exp. 47) is added dropwise over 15 min, while keeping the temperature of the solution between −50 and −70 °C. After an additional period of 15 min (at −50 °C) allyl bromide (18.2 g, 0.15 mol) is added over 1 min. The cooling bath is removed and the temperature allowed to rise to −5 °C (occasional cooling may be necessary to keep the exothermic reaction under control). Stirring at −5 °C is continued for an additional half hour, then water (200 ml) 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 *in vacuo*, using a water bath at ca. 35 °C. Careful distillation of the remaining liquid through a 40 cm Vigreux column affords 3-allylthiophene, b.p. 50 °C/15 mm, n_D^{18} 1.5253, in 76 % yield.

5.3 2-Butylthiophene



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

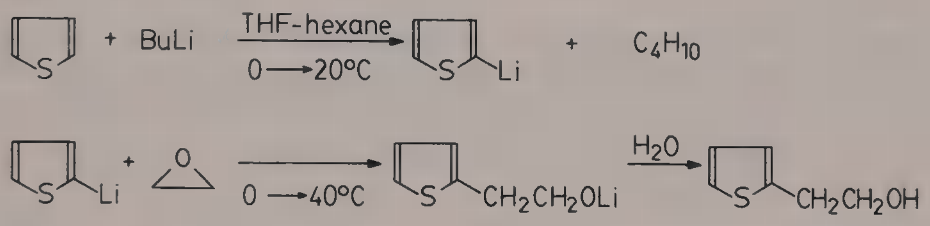
Introduction

In the absence of strongly polar co-solvents 2-lithiothiophene displays moderate reactivity in alkylations and the reactions have to be carried out at elevated temperatures in the region of 50 °C. Careful control of the temperature is therefore not necessary if the reaction is carried out on a modest scale. The reactivity of 2-lithiothiophene in alkylations can be enhanced enormously by addition of a small amount of HMPT (5–10 vol. %): in this case the reaction with butyl bromide proceeds smoothly at 20 °C and is complete within 15 minutes. The organometallic derivative can also be rendered more reactive by adding an equivalent amount of *t*-BuOK dissolved in THF. Subsequent reaction with butyl bromide proceeds smoothly at −10 to 0 °C. The procedure below can also be applied to prepare other non-volatile alkylthiophenes. We expect secondary alkyl halides to react much less easily; dehydrohalogenation may be an important side-reaction, or even the dominant process.

Procedure

THF (70 ml) is added to a solution of 0.10 mol of butyllithium in 70 ml of hexane with cooling to below 0 °C. Thiophene (10.1 g, 0.12 mol) is introduced over 10 min with cooling to between 0 and 10 °C. The cooling bath is then removed and the temperature allowed to rise to 20 °C. Butyl bromide (17.8 g, 0.13 mol) is added in one portion without external cooling. The temperature of the light-brown solution rises to 50 °C or higher (occasional cooling may be necessary). After an additional period of 30 min (at 50°) 200 ml of ice water is added with vigorous stirring. After separation of the layers, two extractions with Et_2O are carried out. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Distillation of the remaining liquid affords 2-butylthiophene, b.p. 68 °C/15 mm, n_D^{23} 1.5007, in 92 % yield.

5.4 2-(2-Thienyl)Ethanol



Scale: 0.10 molar.

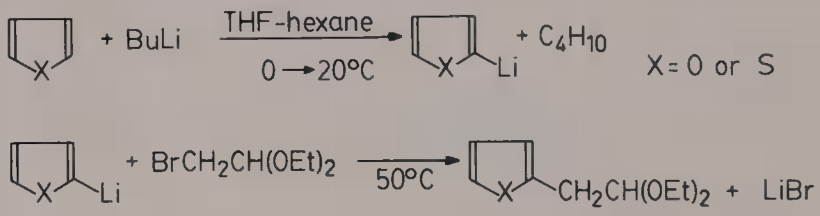
Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

In a mechanistic sense, the hydroxylation of nucleophilic groups with epoxides resembles the alkylation with alkyl halides. In both cases addition of HMPT or DMSO (the latter if the nucleophile is not too strongly basic) causes an acceleration of the reaction. Reactions with epoxides, however, can also take profit from electrophilic assistance. In conversions with organolithium or Grignard reagents coordination between the cation and oxygen can facilitate the attack of the nucleophilic part. In a THF-hexane mixture 2-thienyllithium reacts more smoothly with oxirane than with butyl bromide. In the less polar Et_2O, the coupling with oxirane proceeds with the same ease as in THF, but the reaction with butyl bromide is retarded considerably. If oxirane and butyl bromide are allowed to compete for 2-thienyllithium in a mixture of THF and (a sufficient amount of) HMPT, however, 2-butylthiophene is the only product. The conditions presented here presumably can also be applied for the hydroxyalkylation of 2-furyllithium and other thermostable lithiated hetero-aromatic compounds.

Procedure
A solution of 0.10 mol of 2-thienyllithium in THF and hexane is prepared as described in Exp. 3. The solution is cooled to −5 °C and 6.0 g (0.14 mol, excess) of oxirane is added in one portion. The cooling bath is removed and the temperature allowed to rise to ca. 35 °C (occasional cooling may be necessary). This temperature is reached after about 15 min. The light-brown solution is kept at 30–40 °C for an additional half hour, then 100 ml of water is added with vigorous stirring and cooling in a water bath at 0 °C. After separation of the layers, three extractions with small portions of Et_2O are carried out. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Distillation of the remaining liquid through a short Vigreux column gives the desired alcohol, b.p. 115 °C/15 mm, n_D^{21} 1.5478, in 88 % yield.

5.5 2-Furancarboxaldehyde Diethylacetal and 2-Thiophenecarboxaldehyde Diethylacetal



Scale: 0.10 molar.

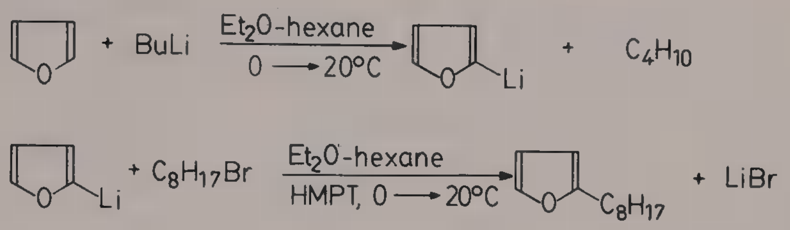
Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction
This procedure describes the coupling of organolithium compounds with bromoacetaldehyde diethylacetal, which is generally poorly reactive (compared with alkyl bromides) in nucleophilic displacements; the low yields in reactions with this bromoacetal are caused by dehydrobromination or elimination of ethanol (depending upon the nature of the nucleophilic reagent). The conversions of 2-thienyllithium and 2-furyllithium with the bromoacetal give reasonable yields of the alkylation products after prolonged heating at 50 °C; if 10 to 20 vol. % of HMPT is

added, the reactions can be carried out at lower temperatures, but yields are lower, probably because the more polar conditions favour elimination reactions. With more strongly basic reagents, e.g. aryllithium, elimination is expected to become more important.

Procedure
Furan (8.8 g, 0.13 mol) or thiophene (0.13 mol) is added to a solution of 0.10 mol of butyllithium in 70 ml of hexane and 70 ml of THF (see preceding experiments). After 20 min (at 20 °C) the solutions are warmed to 40 °C and 0.10 mol (19.7 g) of the bromoacetal is added in one portion. The temperature rises very slowly and the mixtures are kept at 55 °C for 5 h. During this period the color becomes dark-brown. The solutions are then poured into 200 ml of ice water and, after separation of the layers, three extractions with Et_2O are carried out. After drying over $MgSO_4$, the solvent is removed *in vacuo* and the remaining liquid carefully distilled through a 40-cm Vigreux column. The 2-furylacetal, b.p. 87 °C/15 mm, n_D^{20} 1.4512, is obtained in 55 % yield, the 2-thienylacetal, b.p. 110 °C/15 mm, n_D^{20} 1.4946, in 65 % yield.

5.6 2-Octylfuran



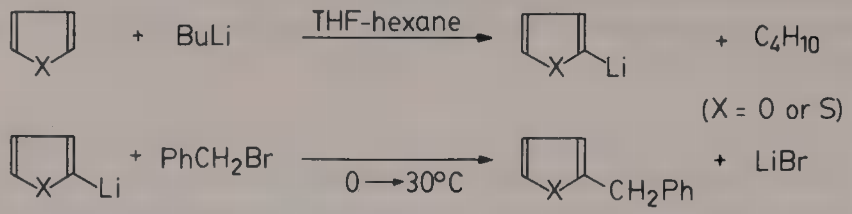
Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction
The procedure for 2-octylfuran illustates how small amounts of HMPT can cause a considerable increase in the rate of alkylation. In view of the decreased stability of 2-lithiofuran in the presence of HMPT, the reaction is carried out at relatively low temperatures. In the absence of HMPT no reaction takes place at 0°.

Procedure
Furan (4.1 g, 0.06 mol) is added to a solution of 0.05 mol of butyllithium in 35 ml of hexane and 35 ml of Et_2O, cooled at 10 °C. The solution is kept for 30 min at 20 °C, then it is cooled to 0 °C and 5 ml of HMPT is added, followed by 8.7 g (0.045 mol) of octyl bromide added over 5 min. The ensuing alkylation is strongly exothermic and occasional cooling is necessary to keep the tmperature below 25 °C. After an additional half hour (at 25 °C) 100 ml of water is added with vigorous stirring. The organic layer and three ethereal extracts are washed five times with water to be sure that the HMPT is removed (comparable volatility!). After drying over $MgSO_4$ and removal of the solvent under reduced pressure, the product is distilled through a 20-cm Vigreux column. 2-Octylfuran, b.p. 100 °C/15 mm, is obtained in 82 % yield.

5.7 2-Benzylfuran and 2-Benzylthiophene



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction
In principle, interaction between nucleophilic species R^-M^+ and benzyl halide may give rise to the following reactions:

$$R'M + PhCH_2X \xrightarrow{\text{nucl. subst.}} R'CH_2Ph + MX$$

$$R'M + PhCH_2X \underset{\text{exchange}}{\overset{\text{Hal/Metal}}{\rightleftharpoons}} R'X + PhCH_2M \xrightarrow[\text{nucl. subst.}]{PhCH_2X} PhCH_2CH_2Ph$$

$$R'M + PhCH_2X \xrightarrow{\text{deprotonation}} R'H + PhCH(M)X \xrightarrow[\text{nucl. subst.}]{PhCH_2X}$$

$$\longrightarrow PhCH(X){-}CH_2Ph \xrightarrow{\text{elim. of HX}} PhCH{=}CHPh$$

The significance of the second and third reaction increases with increasing basicity of the nucleophile. Halogen-metal exchange followed by benzylation of the newly generated metallic intermediate can be a serious side reaction if X = Br or I and the basicities of R′M and $PhCH_2M$ are comparable (or if R′M is a stronger base than $PhCH_2M$). This process is expected to be favoured if M = Li. Formation of stilbene is often observed in conversions of $PhCH_2X$ with strongly basic nucleophiles under strongly polar conditions (e.g. with alkali amides in liquid ammonia). The procedures for 2-benzylfuran and -thiophene are examples of successful benzylations, but they also show that a small change in reaction conditions can result in the formation of side-products, while in the reaction of phenyllithium with benzyl bromide bibenzyl is the main product.

Procedure
Solutions of 0.06 mol of furyl- or thienyllithium in equal amounts of THF and hexane are prepared as described in the preceding experiments. The solutions are cooled to 0 °C and 0.05 mol (8.6 g) of benzyl bromide is added in one portion. After a few minutes the temperature rises to over 20 °C. Occasional cooling (with a dry ice acetone bath) serves to keep the temperature between 20 and 30 °C. Comparison of the reaction of benzyl bromide with furyllithium with that of thienyllithium under similar conditions shows that the latter reacts faster. After keeping the solutions for

an additional half hour between 25 and 30 °C, water (100 ml) is added and two extractions with Et_2O are carried out. The extracts are dried over $MgSO_4$ and concentrated *in vacuo*. The remaining brown liquids are distilled at 1 mm or lower pressure. The distillates are redistilled through a 20-cm Vigreux column to give the pure benzyl derivatives:

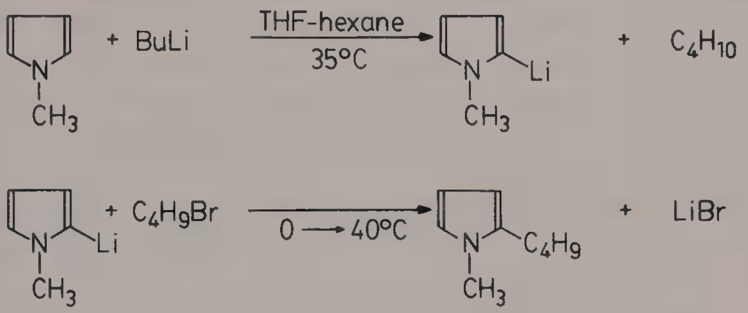
2-furyl—CH_2—C_6H_5, b.p. 95 °C/12 mm, n_D^{19} 1.5462, yield 71 %

2-thienyl—CH_2—C_6H_5, b.p. 125 °C/12 mm, n_D^{19} 1.5917, yield 70 %.

Notes

If an equivalent amount of TMEDA is added to the solution of 2-thienyllithium, benzylation gives the expected product in a yield of only 50 %, a contamination of about 15 % of $PhCH_2CH_2Ph$ being present. If 0.05 mol of *t*-BuOK is added prior to benzylation (which now occurs at temperatures between −40 and 0 °C), the main impurity is probably stilbene. Phenyllithium · TMEDA in THF-hexane reacts with $PhCH_2Br$ even at −40 °C, giving $PhCH_2CH_2Ph$ as the predominant product.

5.8 2-Butyl-1-Methylpyrrole



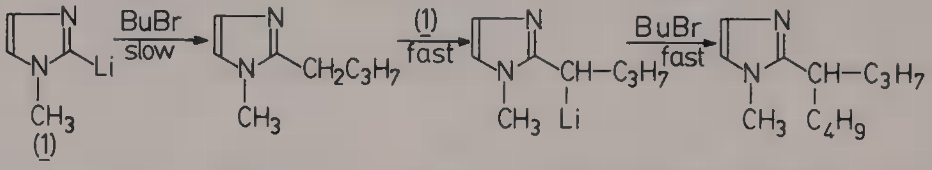
Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

N-alkylpyrroles are metallated much less easily than furan and thiophene. This is reflected in the higher temperature, longer reaction time and excess of the pyrrole derivative necessary to obtain a satisfactory yield in the subsequent alkylation (compare the metallation conditions with those in the preceding experiments). If no excess of *N*-methylpyrrole were used, THF would seriously compete with this substrate for butyllithium in the end stage of the metallation. In other experiments in this chapter (14, 39, 40) *N*-methylpyrrole is metallated under different conditions, which permit a more economic use of this compound.

Comparison of the reaction conditions prescribed for the alkylation of 2-lithio-1-methylpyrrole with those applied in the reaction of 2-lithiothiophene with butyl bromide suggests that the former reacts more smoothly (compare Exp. 3). Since further experimental data is lacking, it cannot be said whether this difference in reactivity must be ascribed to a difference in basicity or to a difference in aggregation state. The reaction of 2-lithio-1-methylimidazole with butyl bromide under similar conditions is markedly slower than that of the lithiated pyrrole. The expected alkylation product was formed in minor amounts together with high-boiling compounds. These might have been produced in the following sequence of conversions:

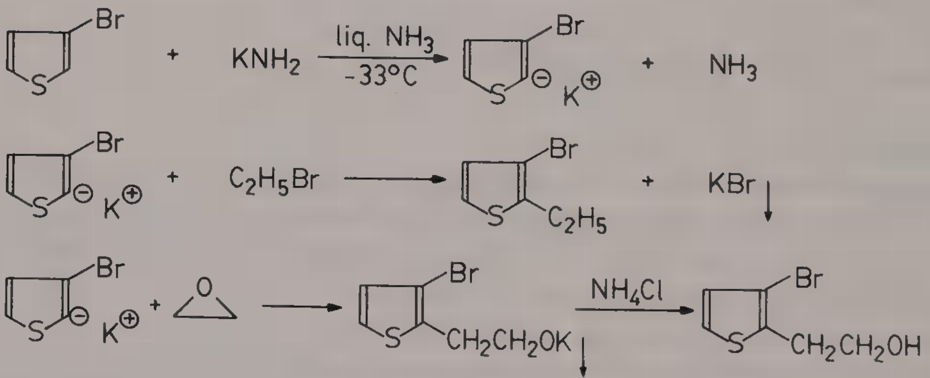


Similar poor results in alkylations may be general with organometallic derivatives having the metal linked to the azomethyne carbon atom.

Procedure

1-Methylpyrrole (16.2 g, 0.20 mol) is added at room temperature to a solution of 0.10 mol of butyllithium in 70 ml of hexane and 70 ml of THF. The temperature of the light-yellow solution rises to ca. 35 °C within a half hour and is kept at the level for an additional period of 90 min. The solution is then cooled to 0 °C and 0.12 mol (16.4 g) of butyl bromide is added in one portion. The temperature rises to about 50 °C within 5 min. Occasional cooling may be necessary. After the temperature has dropped to 40°, 100 ml of water is added and, after separation of the layers, two extractions with Et_2O are carried out. The combined organic solutions are dried over $MgSO_4$, after which the solvent is removed under reduced pressure. Distillation of the remaining liquid through a 30-cm Vigreux column affords 2-butyl-1-methylpyrrole, b.p. 84 °C/12 mm, n_D^{22} 1.4833, in 84 % yield.

5.9 3-Bromo-2-Ethylthiophene and 3-Bromo-2(1-Hydroxyethyl)Thiophene



Apparatus: 1-l three-necked, round-bottomed flask, equipped with a dropping funnel, a mechanical stirrer and a vent (e.g. rubber stopper with a hole of 5–7 mm diameter).

Scale: 0.10 molar.

Introduction

Mixing of equimolar quantities of potassium amide and thiophene in liquid ammonia produces only a small concentration of the thiophene "anion", and subsequent addition of an alkyl halide gives low yields of 2-alkylthiophene. 3-Bromothiophene, however, can be successfully funtionalized with reagents that are stable towards ammonia. The inductive stabilization by bromine and the stabilization by sulfur (polarizability effect rather than d-orbital stabilization) give rise to a regiospecific and (presumably) complete deprotonation in the 2-position. The relative high basicity of the generated "anion" and the strong polarity of the medium are favourable factors for fast alkylations and hydroxyalkylations. We prefer to use *potassium* amide, since in a number of other cases (e.g. diphenylmethane) the deprotonation equilibrium is on the side of the reactants because of the slight solubility of lithium- and sodium amide ([53], see also Ref. [3]). It should be pointed out that the liquid ammonia procedure can be applied only in the case of alkylation and hydroxyalkylation (with epoxides). Alkyl halides with a long chain probably will react slower because of their slight solubility in liquid ammonia. Of course functionalization of 3-bromothiophene can also be realized *via* the 2-lithio compound in THF, generated with LDA (Exp. 29). Addition of a small amount of HMPT might be necessary in the case of the reaction with alkyl bromides. This co-solvent can be omitted in the hydroxyalkylation with oxirane, since coordination between Li^+ and oxygen facilitates the attack of the 3-bromothiophene nucleophile.

Procedure

A solution of 0.13 mol (Note 1) of potassium amide in ca. 200 ml liquid ammonia, prepared as described in Chap. I, Exp. 9, is transferred into the reaction flask. A mixture of 0.10 mol (16.3 g) of 3-bromothiophene (Exp. 47) and 40 ml of Et_2O is added over 10 min. Subsequently a mixture of 0.20 mol (21.8 g) of bromoethane (Note 2) and 30 ml of Et_2O is added over 5 min to the greyish solution. A vigorous reaction ensues and stirring is continued for an additional half hour, then dichloromethane (100 ml) and ice water (300 ml) are cautiously added. After separation of the layers, two extractions with CH_2Cl_2 are carried out. The combined organic solutions are washed with dilute hydrochloric acid and dried over $MgSO_4$. Careful distillation of the liquid remaining after removal of the solvent gives the ethylation product, b.p. 75 °C/12 mm, n_D^{23} 1.5582, in 92 % yield.

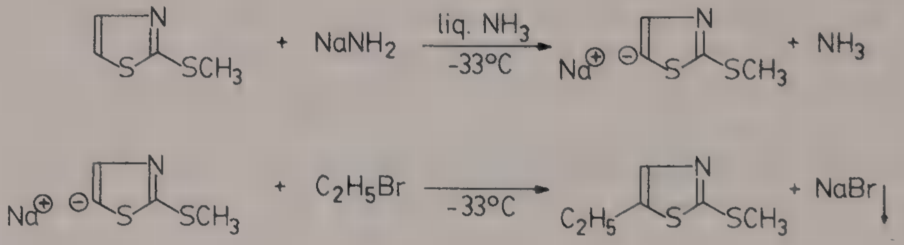
In the reaction with oxirane, a mixture of 0.20 mol (8.8 g) of oxirane (Note 2) and 40 ml of Et_2O is added over 15 min. The grey suspension is stirred for an additional half hour (Note 3), after which 15 g of powdered ammonium chloride is added in small portions (the dropping funnel and vent having been removed). The work-up is carried out as described above. After thorough removal of the solvent and other volatile components (first at 10–20 mmHg, subsequently at 1 mm or lower pressure), the pure alcohol is obtained in an almost quantitative yield.

Notes

1. The excess is used to compensate for small losses in the filtering operation of Chap. I, Exp. 8 and to guarantee a complete deprotonation.

2. Part of the volatile bromoethane and oxirane may be swept along with the evaporating ammonia.
3. In view of the possibility of a further reaction of the primarily formed alcoholate with oxirane (formation of —$CH_2CH_2OCH_2CH_2OK$) it is advisable to limit the period of additional stirring.

5.10 5-Ethyl-2-(Methylthio)Thiazole

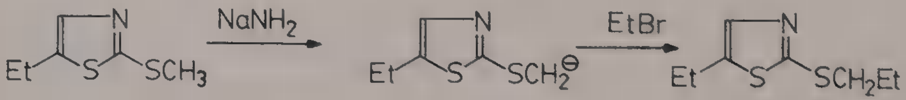


Scale: 0.10 molar.

Apparatus: 1-l round-bottomed, three-necked flask, equipped with a dropping funnel, a mechanical stirrer and a vent (see Exp. 9).

Introduction

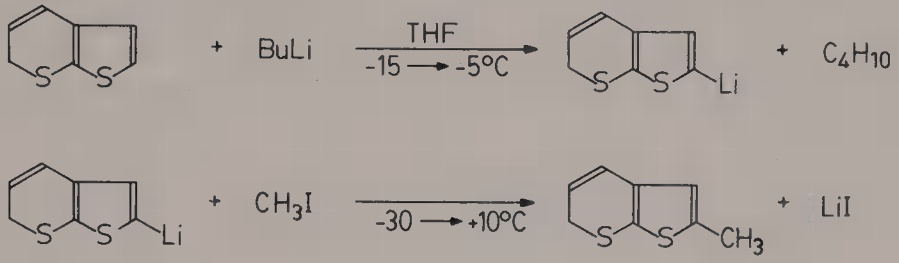
The acidity of the 2- and 5-protons in 1,3-thiazole is considerably higher than that of the corresponding protons in thiophene. If no substituents are present at the positions 2 and 5, the 2-proton is specifically abstracted by strongly basic organometallic reagents. The excellent yield of 5-ethyl-2-(methylthio)-thiazole from the reaction of 2-(methylthio)thiazole with sodamide in liquid ammonia and subsequent addition of bromoethane suggests that the 5-proton in the substrate is removed to a considerable extent. A similar procedure with thiophene gives at best only traces of 2-ethylthiophene. The anion of 2-(methylthio)thiazole appears to be very reactive in the polar liquid ammonia (much more reactive than acetylides $RC{\equiv}C^-$), and thus alkylations with less soluble higher alkyl bromides might also give good results. If a too large excess (2 or more equivalents) of sodamide is used, the primary alkylation product is deprotonated in the CH_3S-grouping, which gives rise to the formation of small amounts of 5-ethyl-2-(propylthio)thiazoles:



Procedure

A suspension of 0.15 mol of sodamide in 175 ml of liquid ammonia is prepared as described in Chap. I, Exp. 7. A mixture of 0.10 mol (13.1 g) of 2-methylthio-thiazole (see Exp. 52) and 30 ml of Et_2O is added dropwise over 5 min. Subsequently 0.25 mol (27.3 g) of ethyl bromide is introduced over 20 min and stirring is continued for an additional 30 min. The remainder of the ammonia is then removed by placing the flask in a water bath at 35 °C. Water (200 ml) is added and three extractions with Et_2O are carried out. The combined organic solutions are dried over potassium carbonate and then concentrated *in vacuo*. Distillation of the remaining liquid gives the desired product, b.p. 110 °C/15 mm, n_D^{19} 1.5782, in 92 % yield.

5.11 2-Methyl-2H-Thieno-[2.3-b]-Thiopyran



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

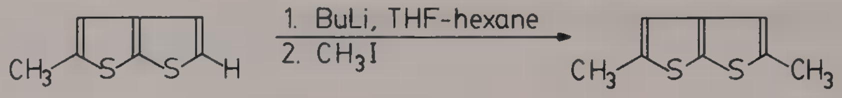
Introduction

The most acidic hydrogen atoms in thienothiopyran are the 2H-protons in the thiopyran ring and the α-proton in the thiophene ring. The kinetically preferred process in the interaction with a strong base in a non-polar or sligthly polar solvent is abstraction of the thiophene proton. With BuLi in Et_2O or THF the deprotonation is irreversible. If LDA is used, however, the diisopropylamine formed in the deprotonation can reprotonate the thiophene ring, after which the LDA can attack the thiopyran ring. The final result is the deprotonated thiopyran ring. Under strongly polar conditions (e.g. with alkali amides in liquid ammonia) deprotonation of the thiopyran ring is probably not preceded by the formation of an α-thienyl-anion. This procedure gives reaction conditions for alkylation in THF with methyl iodide, and is representative for methylations with (dissolved) organolithium compounds of basicity corresponding to pK values in the region of 35, e.g. lithiated thienothiophene, benzothiophene, benzofuran, selenophene, tellurophene. Methylations with methyl iodide proceed at much lower temperatures than alkylations with all of the other alkyl halides.

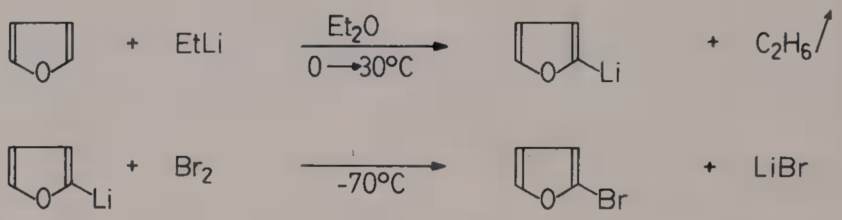
Procedure

A mixture of 0.06 mol of butyllithium, 40 ml of hexane and 45 ml of THF (see Exp. 2) is cooled to −15 °C and 0.05 mol (7.7 g) of thienothiopyran (exp. 50) is added over 5 min. After this addition the cooling bath is removed and the temperature is first allowed to rise to −5 °C, then the solution is cooled to −30 °C, and 0.07 mol (9.9 g) of methyl iodide is finally added over 2 min. The temperature is kept at −30 °C for an additional 10 min, after which the cooling bath is removed. When the temperature has reached +10 °C, 100 ml of water is added. The aqueous layer is extracted twice 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 methylated product, b.p. 70 °C/0.1 mm, n_D^{20} 1.6595, in 95 % yield.

2-Methylthienothiophene is methylated in an essentially similar way to give the symmetrical dimethyl derivative. Crystallization from pentane at −20 °C gives a m.p. 78.5–79 °C. The yield is almost quantitative.



5.12 2-Bromofuran



Scale: 0.5 molar.

Apparatus: Chap. I, Fig. 1, 1 l. The outlet is connected *via* a plastic tube with a trap, cooled at −78 °C.

Introduction

Although furan is lithiated much more easily in THF than in Et_2O, the latter solvent is chosen in this procedure for 2-bromofuran because of its volatility (b.p. 102 °C). Distillative separation from THF would be very troublesome. Since furan itself reacts (addition) rapidly with bromine even at very low temperatures, no excess of this compound should be used in the metallation reaction. Butyllithium in hexane and Et_2O is an unsuitable base for the lithiation, because any unconverted BuLi would react with bromine to give butyl bromide, this having the same volatility as 2-bromofuran. Moreover, separation of 2-bromofuran from hexane would be just as difficult as from THF. These considerations led to the choice of ethyllithium in Et_2O. The metallation of furan can be brought to completion by using an excess of EtLi. The excess is converted by Br_2 into the volatile ethyl bromide (b.p. 38 °C). The yield of 2-bromofuran is modest (~60 %), probably because part of the bromine adds to this product.

Introduction of a bromine atom by reaction of a lithium derivative with free bromine is probably not limited to the case of 2-lithiofuran. In other cases the use of the less aggressive complex of bromine and dioxan could be considered.

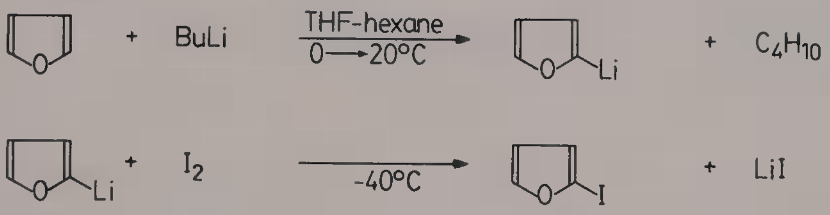
Procedure

A solution of ethyllithium in 500 ml of Et_2O is prepared from 70 g (0.64 mol) of ethyl bromide and 12 g (1.7 mol) of lithium (see Chap. I, Exp. 1). The excess of lithium is separated off and the solution is transferred into the reaction flask. Freshly distilled furan (37.4 g, 0.55 mol) is added at 0 °C keeping the temperature of the mixture between 5 and 10 °C for the first half hour (occasional cooling). After this period the temperature is allowed to rise to ca. 25 °C in 1 h. The liquid in the cold trap is then added to the reaction mixture, and the solution is stirred for an additional period of 2 h. The solution is then cooled down to −80 °C and 0.50 mol (80 g) of bromine is added over 30 min with vigorous stirring. The temperature is initially maintained between −70 and −80 °C (occasional cooling with liquid nitrogen), but is allowed to rise to −30 °C in the last stage of the addition. A rather thick suspension is formed in a light-brown solution. The mixture is poured into 200 ml of an aqueous solution of 20 g of potassium hydroxide and 40 g of ammonium chloride. After vigorous shaking for 2–3 min, the light-brown organic layer is separated off and dried over potassium carbonate. The aqueous layer is extracted twice with small portions of Et_2O. The dried solutions are transferred into a 1-l round-bottomed flask, 30 g of *N,N*-diethylaniline is added (Note 1) and the ether is slowly distilled off through a 40-cm Widmer column. The bath temperature is gradually raised to 70 °C. When the distillation has stopped (using this bath temperature) the condenser is connected to a single receiver (500 ml flask), cooled in a bath at −50 °C. The bromofuran and a small amount of Et_2O are distilled off from the high-boiling products and *N,N*-diethylaniline in a water-pump vacuum (10–20 mmHg). During this operation the bath temperature is gradually raised from 30 to 80 °C. The contents of the receiver are carefully distilled through a 40-cm Vigreux column. 2-Bromofuran, b.p. 102 °C/760 mm, n_D^{20} 1.4912, is obtained in 60% yield (Note 2).

Notes

1. Some side-products may eliminate HBr during the distillation. In the absence of $PhNEt_2$ this HBr may induce a vigorous decomposition of the residue.
2. This preparation has been carried out only once.

5.13 2-Iodofuran



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

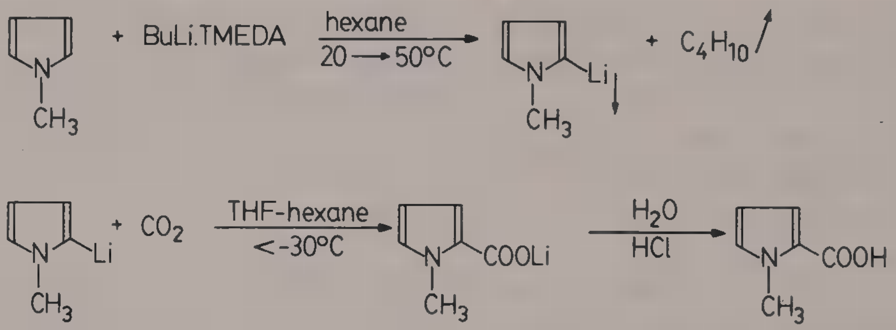
Introduction

The procedure for 2-iodofuran is typical for the introduction of iodine *via* an organolithium intermediate. In contrast to bromine, iodine does not react with furan at temperatures up to at least 20 °C. This allows the use of an excess of furan to shorten the reaction time of the lithiation and to be sure that all butyllithium has reacted. This is absolutely necessary in connection with the fact that 2-iodofuran and butyl iodide can not be separated by distillation.

Procedure

A solution of 0.10 mol of 2-lithiofuran in 70 ml of hexane and 70 ml of THF is prepared as described in Exp. 6 (20 % excess of furan is used). The solution is cooled to −50 °C and a solution of 0.12 mol (30.5 g) of iodine in 40 ml of THF is added dropwise with vigorous stirring, while keeping the temperature of the mixture between −30 and −50 °C. After stirring for an additional minute a solution of 10 g of sodium thiosulfate ($Na_2S_2O_3 \cdot 5\,H_2O$) in 100 ml of water is added with vigorous stirring. The light-yellow organic layer is separated off, and the aqueous layer is extracted twice with small portions of Et_2O. After drying over $MgSO_4$ most of the solvent is distilled off at normal pressure through a 40-cm Vigreux column. After cooling to 20 °C, the remaining liquid is distilled through the same column at 30 mmHg. 2-Iodofuran (b.p. ~50 °C (at 30 mmHg) n_D^{21} 1.5618) is obtained in 88 % yield.

5.14 1-Methylpyrrole-2-Carboxylic Acid

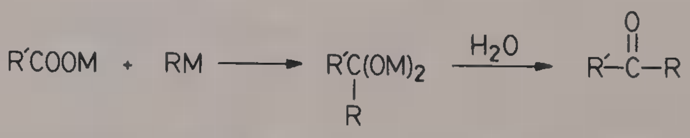


Scale: 0.10 molar.

Apparatus: For the metallation: Chap. I, Fig. 1, 500 ml. For the carboxylation: 1-l round-bottomed flask, equipped with a gas-inlet tube, a mechanical stirrer and a rubber stopper with a hole of 5 mm diameter. For the addition of the solution of the lithiated pyrrole: 50 to 100 ml syringe.

Introduction

For carboxylations with carbon dioxide reversed-order addition is generally carried out, i.e. the solution or suspension of the metallated compound is poured on the powdered "dry ice", which may be covered with an organic solvent. The reason for applying this technique is that alkali salts of carboxylic acids can undergo an attack by the organometallic derivative:



$$R'COOM + RM \longrightarrow R'\underset{\displaystyle R}{\underset{|}{C}}(OM)_2 \xrightarrow{H_2O} R'-\overset{\displaystyle O}{\overset{\|}{C}}-R$$

Reversed-order addition is also applied in the alternative procedure for 1-methylpyrrole-2-carboxylic acid. In this way the chance of introduction of moisture is minimized. This method is generally applicable if the organometallic intermediate is a solution or thin suspension. If no α-hydrogen atoms are present in RCOOM and RM is a weaker base than phenyllithium, good yields of the acids may be obtained even if the normal order of addition is applied, i.e. if CO_2 is introduced at sufficiently low temperatures. Thiophene-2-carboxylic acid and 3-bromothiophene-2-carboxylic acid, for example, have been obtained by us in excellent yields by introducing gaseous CO_2 into the solutions of the lithium compounds. In the case of the preparation of allenic carboxylic acids, however, (see Chap. IV) this manner of addition leads to low yields. In general THF is a better solvent than Et_2O for the preparation of carboxylic acids by carboxylation. Some organometallic intermediates have a slight solubility in Et_2O, which may give rise to incomplete reaction with CO_2. The same holds for Grignard compounds, which often form oily or viscous products with CO_2.

The metallation of 1-methylpyrrole proceeds considerably less easily than that of thiophene and furan. With the butyllithium · TMEDA complex in hexane, however, this pyrrole derivative can be lithiated in a short time. Since THF is attacked very readily by BuLi · TMEDA, it cannot be used as a co-solvent during the metallation. It is added when the metallation in hexane is complete.

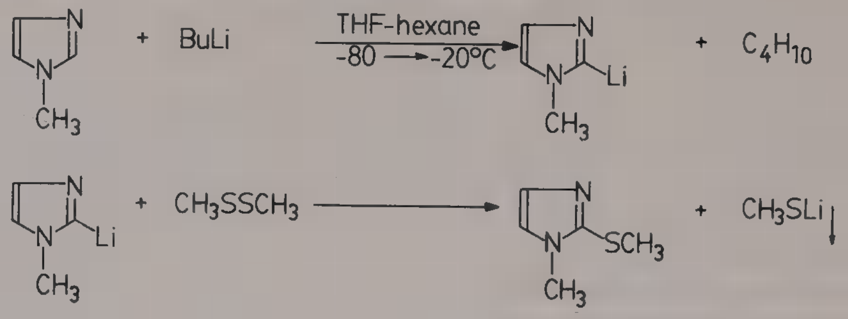
Procedure

A solution of 0.10 mol of butyllithium in 70 ml of hexane (Note 1) is added at 20 °C to a mixture of 0.11 mol (8.1 g) of 1-methylpyrrole and 0.11 mol (12.8 g) of TMEDA. The temperature rises in a few min to 50 °C or higher. The mixture is then kept for an additional period of 15 min at this temperature. After cooling to room temperature 70 ml of THF is added and most of the suspended material dissolves. In the second (1-l) flask a fast stream of carbon dioxide (ca. 2 l/min) is led (with vigorous stirring) through 100 ml of THF, cooled to −60 °C. The solution of 2-lithio-1-methylpyrrole is cooled to ca. −20 °C, and subsequently transferred over 4 to 5 min into the reaction flask using a syringe. During this operation the temperature of the mixture is kept between −60 and −30 °C by efficient cooling (occasional cooling in a bath with liquid nitrogen is better than cooling with dry ice and acetone) and vigorous stirring. After this addition the cooling bath is removed and the introduction of carbon dioxide is continued for another 2 min. The solution is warmed up to −10 °C and 100 ml of water is cautiously added with vigorous stirring. After separation of the layers, the organic layer is shaken with 30 ml of water and the resulting aqueous layer is added to the other aqueous solution. The combined aqueous solutions are extracted twice with Et_2O (in order to remove "neutral" products). The turbid aqueous layer is acidified to pH 3 (Note 2) by cautious addition (with manual swirling) of 4N hydrochloric acid. The carboxylic acid is extracted with Et_2O (5 extractions). After drying the combined organic solutions over $MgSO_4$, the ether is removed under reduced pressure. Pure (^{1}H-NMR) carboxylic acid is obtained in 94% yield. Crystallization of a sample from Et_2O gives a m.p. of 136 °C.

Notes

1. 1-Methylpyrrole is used in excess to be sure that no butyllithium is present during the reaction with CO_2: the pentanoic acid formed from BuLi might give rise to difficulties in the purification of the pyrrole carboxylic acid.
2. Pyrrole derivatives are not stable under strongly acidic conditions.

5.15 1-Methyl-2-(Methylthio)Imidazole



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

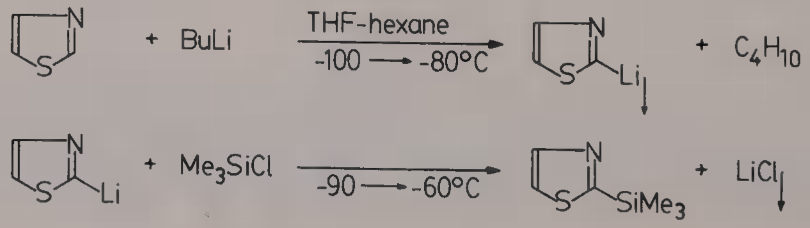
Introduction

N-substituted imidazole derivatives are metallated much more easily than the analogous pyrrole derivatives. Although inductive electron-withdrawal by the additional nitrogen atom will be an important factor, coordination of the lithium base to this nitrogen atom may also contribute in facilitating the deprotonation at carbon atom 2. The 2-lithio derivative is much more stable than that of 1,3-thiazole. Many derivatives of imidazole have a good solubility in water, which might give rise to some problems in their isolation. To demonstrate that the metallation with BuLi in THF is a fast and clean reaction, we have carried out the derivatization with dimethyl disulfide.

Procedure

1-Methylimidazole (8.2 g, 0.10 mol) is added in one portion to a solution of 0.11 mol of butyllithium in 77 ml of hexane and 77 ml of THF cooled to −90 °C. The cooling bath is removed, and an immediate rise of the temperature to about −40 °C is observed. Hereafter the temperature is allowed to rise to −20 °C. The light-yellow solution is then recooled to −60 °C and 0.12 mol (11.3 g) of dimethyl disulfide is added in one portion. The temperature may rise to −30 °C or higher, while a white suspension is formed. After stirring an additional 5 min, 50 ml of water is added with vigorous stirring. After separation of the layers, ten(!) extractions with small portions of Et_2O are carried out. The combined organic solutions (washing with water is omitted!) are dried over potassium carbonate and subsequently concentrated under reduced pressure. Distillation of the remaining liquid gives the methylthio derivative, b.p. 98 °C/15 mm, n_D^{18} 1.5532, in 94 % yield.

5.16 2-Trimethylsilyl-1,3-Thiazole



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

The great facility with which the 2-proton in thiazoles and imidazoles (Exp. 15) is removed by organolithium bases resembles the situation with terminal acetylenes RC≡CH [6, 7]. This is fortunate in view of the low stability of metallated thiazoles, since it allows the metallation to be carried out quatitatively in a very short time. The subsequent silylation reaction of lithiated thiazole is not only relevant, because the good result is a reflection of the successful metallation, but also because the silyl derivative is a potentially useful intermediate. A silyl function in the 2-position can be removed quantitatively in a few minutes by treatment with dilute mineral acid at 0–10 °C [9]. On the other hand it is not attacked by butyllithium, so that the 5-position can be metallated and subsequently functionalized. Acid treatment of this derivative results in the formation of a 5-substituted thiazole. The silyl group in the 2-position thus has the function of a protecting group. In analogy with (trimethylsilyl)benzothiazole [192] it may be expected that the Me_3Si group can be readily exchanged for acyl groups: reaction of 2-(trimethylsilyl)thiazoles with acid chlorides or chloroformates ClCOOR thus may result in the corresponding ketones and esters, which probably are not easily accessible in a direct reaction *via* the lithio-intermediate.

Procedure

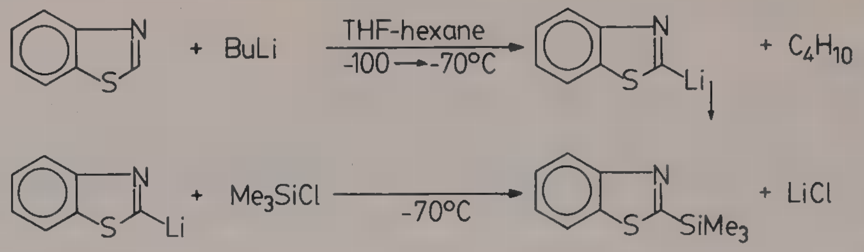
Thiazole (8.5 g, 0.10 mol, Exp. 53) is added over 5 min to a solution of 0.11 mol of butyllithium in 77 ml of hexane and 77 ml of THF with cooling to −100 °C (occasional cooling in a bath with liquid nitrogen). The cooling bath is then removed and the temperature allowed to rise to −80 °C. After stirring for an additional 5 min at this temperature, the thick white suspension is cooled to −90 °C and 0.10 mol (10.9 g) of trimethylchlorosilane (Note 1) is added over 5 min. The temperature is then allowed to rise to −60 °C over 15 min (occasional cooling) after which time the suspension disappears almost completely. The solution is then allowed to warm up to −20 °C whereupon a much thinner suspension of lithium chloride appears. Water (100 ml) is then added with vigorous stirring. After separation of the layers, the aqueous layer is extracted three times with Et_2O. The unwashed organic solutions are dried over sodium sulfate, after which the greater part of the solvent is distilled off at normal pressure through a 40-cm Vigreux column. The remaining liquid is carefully distilled through the same column to give the expected silyl derivative, b.p. 53 °C/15 mm, n_D^{18} 1.4929, in 84 % yield.

Addition of $t\text{-}C_4H_9\text{—}CH\text{=}O$ (at −80 °C) to the suspension of 2-lithiothiazole gives a clear solution. Aqueous work up, followed by extraction with Et_2O, drying over K_2CO_3, concentration of the (unwashed) extracts *in vacuo* gives the carbinol, m.p. 84 °C, in ~95 % yield.

Notes

1. The ratio 0.11:0.10 with respect to BuLi and Me_3SiCl is a good guarantee that no acid is produced during the addition of water, which might cause removal of the silyl group.

5.17 2-(Trimethylsilyl)Benzothiazole



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

This procedure is another example (compare Exp. 16) of the generation of an unstable lithio-intermediate and subsequent functionalization at low temperatures with a reactive reagent. The decomposition of the lithio-derivative at temperatures higher than −50 °C (formation of a dark-brown solution) was not investigated further, but possibly there is some relation with the reaction of benzothiazole with alkali amide in liquid ammonia (Exp. 18). The reaction with trimethylchlorosilane gives the expected product in a good yield, but a small amount of a higher boiling side-product is formed, which possibly results from an initial addition of butyllithium to the azomethine double bond.

Procedure

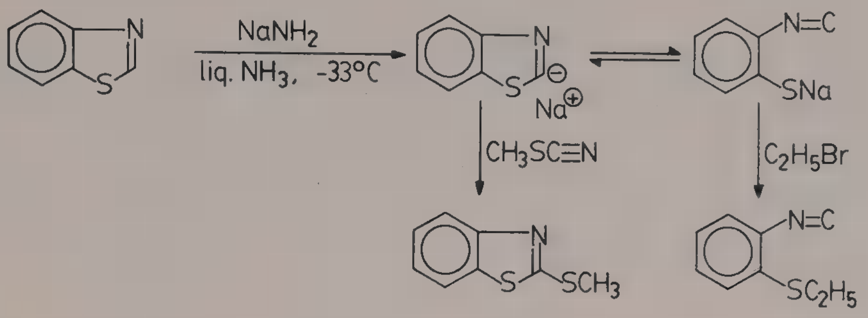
THF (150 ml, Note 1) is added to a solution of 0.11 mol of butyllithium in 70 ml of hexane with cooling to below 0 °C. The mixture is cooled to −100 °C and a mixture of 0.10 mol (13.5 g) (Note 2) of benzothiazole and 20 ml of THF is added over 10 min. During this addition the temperature of the yellowish suspension is kept between −90 and −100 °C (occasional cooling in a bath with liquid nitrogen). The cooling bath is then removed and the temperature allowed to rise to −70 °C. Trimethylchlorosilane (10.8 g, 0.10 mol, Note 2) is then added dropwise over 10 min, while maintaining a temperature of −70 to −75 °C. The suspension disappears almost completely and a brown solution is formed. After an additional period of 20 min (at −70 °C) the mixture is hydrolyzed with 200 ml of water. The organic layer and three ethereal extracts are dried over sodium sulfate and subsequently concentrated under reduced pressure. Careful distillation of the remaining liquid through a 30-cm Vigreux column gives (after a small fraction of benzothiazole) the silyl derivative, b.p. 134 °C/15 mm, n_D^{19} 1.5752, in 72 % yield. There is 3–4 g of high-boiling residue (consisting partly of the silyl derivative).

Notes

1. If the usual (compare other experiments) amount of 80 ml is added, the suspension of the lithium compound becomes very thick, making stirring difficult.
2. See Note 1 of Exp. 16.

5.18 Reaction of Benzothiazole with Sodamide in Liquid Ammonia and Subsequent Ethylation and Methylthiolation

Formation of 2-ethylthio-phenyl isocyanide and 2-(methylthio)benzothiazole.



Scale: 0.10 molar.

Apparatus: 1-l round-bottomed flask, equipped with a dropping funnel, a mechanical stirrer and a vent (rubber stopper with a hole of 7 mm diameter.

Introduction

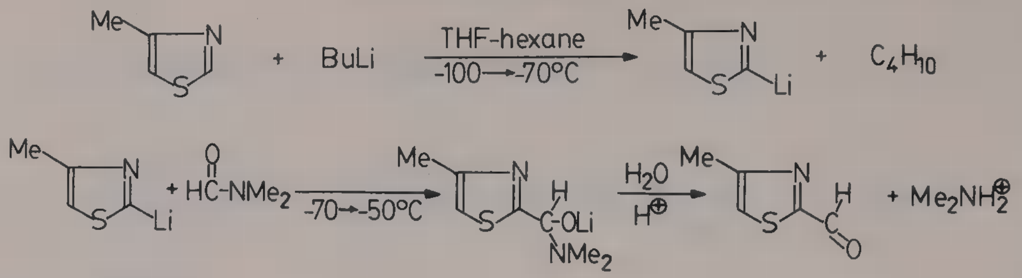
Metalated thiazoles are only stable at low temperatures. The formation of an isonitrile in the procedure below clearly shows this poor stability (compare Ref. [189]). On the other hand the methylthio derivative of benzothiazole is formed in good yield upon addition of a methythiolation reagent to the solution resulting from the interaction between benzothiazole and sodamide in liquid ammonia. This situation may be analogous to the ambident behaviour of 2-lithio-4,5-diphenyl-oxazole [193].

Procedure

A suspension of sodamide is prepared from 3.5 g (excess) of sodium in 250 ml of liquid ammonia (compare Chap. I, Exp. 7). A mixture of 0.10 mol (13.5 g) of benzothiazole and 50 ml of Et_2O is added over 10 min. After an additional period of 10 min 0.20 mol (22 g) of ethyl bromide is added over 10 min. Stirring is continued for another half hour, then the greater part of the ammonia is evaporated by placing the flask in a water bath at 35 °C. Water (150 ml) is added to the remaining mass, after which three extractions with Et_2O are carried out. The organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Distillation of the remaining liquid through a 20-cm Vigreux column gives the isonitrile, b.p. 80 °C/0.5 mm, n_D^{18} 1.5892, in 90 % yield.

If, instead of ethyl bromide, methyl thiocyanate (11.0 g, 0.15 mol, see Exp. 55) is added, pure 2-methylthio-benzothiazole is obtained in more than 90 % yield.

5.19 4-Methyl-2-Thiazolecarboxaldehyde

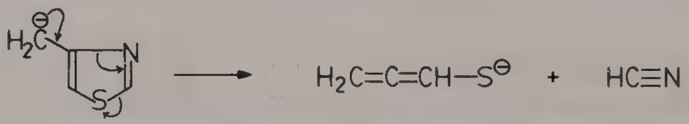


Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

The kinetically most acidic protons in thiazole are the 2H and 5H. If 4-methylthiazole is allowed to interact with a strong base, abstraction of a methyl proton could be imagined to occur also, this could induce a fragmentation.



Under the conditions of procedure 19, however, this process does not occur, and the 2-proton is abstracted specifically. This is apparent from the isolation of a pure aldehyde in excellent yield from the lithio intermediate with dimethylformamide. This formylation is a very general reaction for organolithium or Grignard compounds. The counter ion needs not necessarily be Li or MgX, for some experiments in the course of the preparation of this book suggest that potassio derivatives can also be applied successfully. "Anions" with a low basicity (corresponding to pK values lower than 20) do not give aldehydes, possibly because the equilibrium is on the side of the reactants. Strongly basic organometallic reagents (derived from compounds with pK values higher than 25) react in general at temperatures of $-50°$ or lower. In the case of organometallic derivatives with a slight solubility or with a high aggregation state, higher temperatures may be required. The addition of RM to the C=O group is in most cases very fast and reaction times of 30 minutes or longer mentioned in some papers are not rational. The yields are in most cases high. The best way to hydrolyze the reaction mixtures is by adding the mixture to a slight excess of dilute mineral acid. This can be done by pouring the reaction mixture into the stirred solution of acid (if it is a rather thick suspension) or by slowly transferring it into the acid by means of a syringe (if the reaction mixture is a solution or thin suspension and if there is the danger of subsequent addition of the liberated dimethylamine to the aldehyde).

Procedure

THF (80 ml) is added to a solution of 0.11 mol of butyllithium in 77 ml of hexane with cooling to below 0 °C. The mixture is cooled to -100 °C and a mixture of

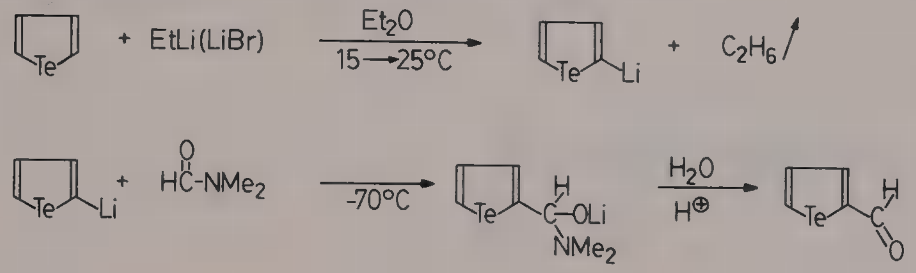
0.10 mol (9.9 g) of 4-methylthiazole (Exp. 53) and 20 ml of THF is added dropwise over 20 min, while keeping the temperature between −90 and −100 °C (occasional cooling in a bath with liquid nitrogen). After an additional 10 min (at −70 °C) 0.15 mol (11.0 g) of DMF is added over 1 min. The yellowish suspension disappears and a light-yellow solution is formed. During this addition the temperature is kept below −50 °C. After 5 min the cold solution is poured with manual swirling into a mixture of 25 g of 36 % hydrochloric acid and 300 ml of water. The aqueous layer is then brought to pH 9 by controlled addition of a concentrated aqueous solution of potassium carbonate (Note 1). After separation of the layers, four extractions with Et_2O are carried out. The combined organic solutions are dried (without washing) over $MgSO_4$ and then concentrated *in vacuo*. Distillation through a 30-cm Vigreux column gives the aldehyde, b.p. ca. 55 °C/0.5 mm, in 84 % yield.

Notes

1. In view of the liberation of dimethylamine the amount of HCl required is three times that of BuLi. The excess of HCl keeps part of the aldehyde in solution (formation of $=\overset{+}{N}H$) Cl^- and the addition of base serves to liberate the aldehyde from the thiazolium salt.

   5-Formyl-2(methythio)thiazole is obtained from 2-(methylthio)thiazole (Exp. 52) by a similar procedure. The residue remaining after removal of the solvent under reduced pressure is not distilled, but is crystallized from Et_2O and pentane (at −20 °C) to give the pure aldehyde as light-yellow needles, m.p. 82.4 °C, in 70 % yield.

5.20 2-Tellurophenecarboxaldehyde



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

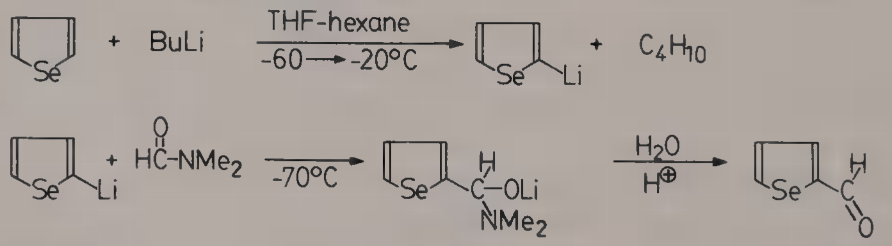
The metallation and derivatization of tellurophene has been described in only a few reports [1] and yields are often modest. A possible reason for the limited amount of data about the chemistry of tellurophene is that chemists have to overcome the barrier of making it from diacetylene, a compound which has the reputation of being dangerous. Furthermore tellurium compounds are disliked because of the stench, a strong garlic odour. Preliminary experiments in which tellurophene was allowed to interact with butyllithium (commercial) in mixtures of THF or Et_2O and hexane showed us that there are two side-reactions, one leading to the formation of dibutyl telluride and one affording lithium telluride (elimination induced by abstraction of a proton in the *3*-position). Particularly the non-volatile dibutyl telluride may give rise to difficulties in the purification of derivatives. The use of *ethyllithium* (prepared from ethyl bromide and lithium in Et_2O) has two advantages. The more important one is that by the association with lithium bromide the base is less reactive and therefore more selective. Further attack on tellurium affords the more volatile diethyl telluride. It appears that both side-reactions do occur with $EtLi \cdot LiBr—Et_2O$, but only to a slight extent, so that derivatives of tellurophene can be prepared in high yields. This is exemplified in procedure [20] by the isolation of 2-tellurophenecarboxaldehyde in 82 % yield.

Procedure

Tellurophene (9.0 g, 0.05 mol, see Exp. 54) is added in one portion to a solution of 0.065 mol of ethyllithium in about 70 ml of Et_2O (compare Chap. I, Exp. 1). The temperature (initially 10 °C) rises to about 25 °C within 15 min (occasional cooling may be necessary). The brown solution is kept for an additional half hour at 25 °C, then cooled to −75 °C and 0.08 mol (5.9 g) of dimethylformamide is added in one portion. Five min later the solution is poured (with manual swirling) into a mixture of 15 g of 36 % hydrochloric acid and 150 ml of water. After separation of the layers, three extractions with Et_2O are carried out (the formation of a black precipitate of tellurium may give rise to some difficulty in the separation of the layers). After drying over $MgSO_4$ and concentration of the solutions *in vacuo*, the remaining brown liquid is distilled through a 20-cm Vigreux column, giving the aldehyde, b.p. ~80 °C/0.5 mm, $n_D^{20} > 1.71$, in 82 % yield.

2-(Trimethylsilyl)tellurophene is prepared in ca. 75 % yield by adding 0.07 mol (7.6 g) of Me_3SiCl to a solution of lithiotellurophene at −30 °C and allowing the temperature to rise to 20 °C. A small volatile fraction of diethyl telluride precedes the main fraction, which has b.p. 83 °C/15 mm, n_D^{20} 1.566.

5.21 2-Selenophenecarboxaldehyde



Scale: 0.05 molar.

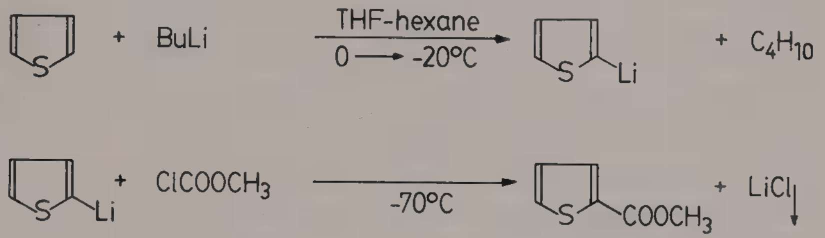
Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

The metallation of (non-substituted) selenophene has not been investigated extensively. Butyllithium in Et_2O has been used as metallating reagent. The procedure below shows that the metallation can be carried out in high yields, using BuLi in a THF-hexane mixture. There is no indication for the occurrence of side-reactions during the metallation.

Procedure (compare Exp. 20)
Selenophene (6.6 g, 0.055 mol, see Exp. 54) is added in one portion to a solution of 0.06 mol of BuLi in 42 ml of hexane and 40 ml of THF, cooled at −60 °C. The temperature is allowed to rise to −20 °C, after which the solution is kept for an additional 10 min at this temperature. The solution is then cooled to −70 °C, and 0.07 mol (5.1 g) of DMF is added in one portion. Ten min after this addition the mixture is treated with dilute acid. The aldehyde, b.p. 87 °C/15 mm, n_D^{18} 1.6222, is obtained in 80 % yield as is described in Exp. 20.

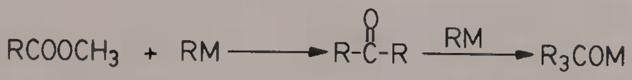
5.22 Methyl 2-Thiophenecarboxylate



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, contents 500 ml for the lithiation, 1 l for the reaction with chloroformate.

Introduction
In principle, it is possible to introduce an ester grouping directly by reaction of the organometallic intermediate with a chloroformic ester. For solubility reasons lithiumcompounds in general seem more promising. The results may be disappointing because of the possibility of subsequent reactions, the primarily introduced ester group may undergo an attack by the organometallic reagent, ultimately resulting in a carbinol:



$$RCOOCH_3 + RM \longrightarrow R\text{-}\overset{\overset{O}{\|}}{C}\text{-}R \xrightarrow{RM} R_3COM$$

If the group R contains a double bond directly linked to the metal, conjugate addition of RM to the α,β-unsaturated ester may occur as well. Finally the ester $RCOOCH_3$ may undergo deprotonation under the influence of RM if one or two α-protons are available in R. Acetylenic esters $R'C{\equiv}C{-}COOCH_3$ can be obtained in excellent yields by adding the THF solution of the lithium acetylide $R'C{\equiv}CLi$ to a mixture of THF and a large excess of methyl chloroformate. This inversed-order addition technique turns out to be successful also in the case of the much more strongly basic and hence much more reactive 2-thienyllithium!

Comparative experiments with aryllithium compounds (phenyllithium and *para*-fluorophenyllithium), however, resulted in low yields of the methyl esters in spite of the fact that a 300 % excess of chloroformic ester had been used. Reactions of ClCOOR′ with lithio derivatives of heterocycles containing an azomethine function (e.g. lithiated thiazole, imidazole, pyridine) cannot succeed, since the excess of chloroformate will react with the basic nitrogen atom. A comparable situation arises if the organolithium intermediate has been generated by means of LDA: reaction of ClCOOR′ with the diisopropylamine liberated in the metallation will provide HCl which will of course inactivate the organolithio compound.

Procedure

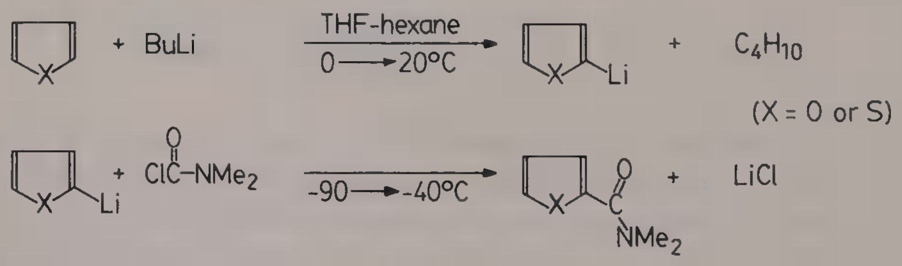
A solution of 0.05 mol of 2-thienyllithium in THF and hexane is prepared as described in procedure 5.3. The solution is cooled to −20 °C and is transferred into the dropping funnel of a second reaction flask, containing a mixture of 0.20 mol (18.9 g, 300 % excess!) of methyl chloroformate and 30 ml of THF. The solution of thienyllithium is added dropwise over 15 min, while keeping the reaction mixture between −70 and −60 °C. The cooling bath is removed and the temperature is allowed to rise to 0 °C. The solution is almost colourless. After addition of 50 ml of water, shaking, and separation of the layers, two extractions with Et_2O are carried out. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated under reduced pressure. The remaining liquid is first distilled at 1 mmHg or lower pressure (Note 1) and the distillate redistilled at water-pump pressure. The ester, b.p. 85 °C/15 mm, n_D^{21} 1.5347, is obtained in 78 % yield.

Notes

The first distillation is carried out at low pressure to avoid strong heating, which might give rise to decomposition of the residue.

The *methyl ester* of *1-methylpyrrole-2-carboxylic acid* can be prepared in a similar way from 2-lithio-1-methylpyrrole (prepared as described in Exp. 8) and $ClCOOCH_3$. The boiling point of the ester is ca. 50 °C/0.5 mm, n_D^{22} 1.5132, the yield is 65 %.

5.23 *N*,*N*-Dimethyl-2-Furancarboxamide and *N*,*N*-Dimethyl-2-Thiophenecarboxamide



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1; contents of the flask 500 ml for the metallation, 1 l for the acylation.

Introduction

Direct introduction of a *N*,*N*-disubstituted carboxamide group can be achieved by adding an organometallic derivative to a dialkylcarbamoyl chloride. The possible side-reactions are analogous to those in the case of carboxyalkylation with chloroformic esters (see Exp. 22). Reactions with carbamoyl chlorides have been reported only incidentally, so that little is known about the scope and limitations. Formation of ketones by subsequent attack of the organometallic reagent on the product can be minimized if an excess of carbamoyl chloride is used and inversed-order addition is carried out. This gives good results, even in the case of the more reactive *aryllithium* derivatives. A possible explanation for the difference with carboxymethylation may be that the NR_2 group is a poorer leaving group than OCH_3.

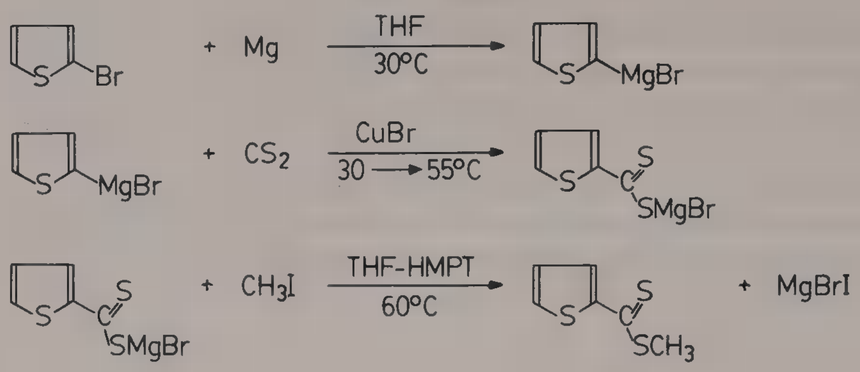
Procedure

A solution of 0.10 mol of 2-furyl- or 2-thienyllithium in THF and hexane is prepared as described in Exps. 6 and 4. The cold solution (−20 °C) is transferred into the dropping funnel and is added over 10 min to a mixture of 0.20 mol (21.5 g, 100 % excess) of dimethyl carbamoyl chloride and 100 ml of THF. During this addition the temperature of the solution or thin suspension is kept between −70 and −90 °C (occasional cooling in a bath with liquid nitrogen). The temperature is then allowed to rise to −30 °C and a solution of 7 g of potassium hydroxide in 70 ml of water is added with vigorous stirring. The mixture is warmed up to room temperature and the layers are separated. The aqueous layer is extracted ten times with small (2 × 40, 8 × 20 ml) portions of THF. The combined organic solutions are dried (without previous washing, Note 1) over 50 g of $MgSO_4$ (vigorous shaking during a few minutes, Note 2). After filtration through sintered glass and rinsing of the desiccant with THF, the solvent is removed under reduced pressure. Careful distillation of the remaining liquid through a 30-cm Vigreux column gives (after a fraction of the carbamoyl chloride) the acid amide. The furan derivative, b.p. 115 °C/15 mm, is obtained in 73 % yield, the thiophene derivative, b.p. 130 °C/15 mm, in 80 % yield. The latter compound solidifies upon standing at room temperature; the m.p. after crystallization from a mixture of Et_2O and pentane is 45–46 °C.

Notes

1. Washing is not carried out in view of the good solubility of the acid amide in water.
2. Caution! The solution still contains the carbamoyl chloride, which is a cancer-suspect compound.

5.24 Methyl-2-Thiophenecarbodithioate

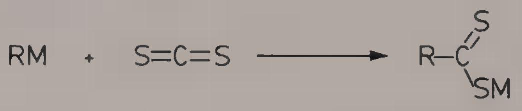


Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

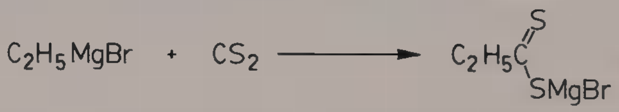
Introduction

Dithioates are the primary products from a carbophilic attack of an organometallic reagent on carbon disulfide:



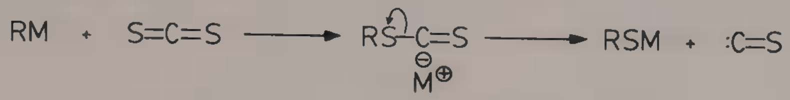
$$RM + S{=}C{=}S \longrightarrow R{-}C({=}S){-}SM$$

In this general scheme RM can also represent a "trivial" organometallic reagent, e.g. CH_3SNa, NaN_3, CH_3ONa. The product can be readily alkylated to give a dithioester RCSSR′. Primary (and most secondary) alkylmagnesium halides react with CS_2 to give the Grignard-"salts" of the dithioacids, e.g.:



$$C_2H_5MgBr + CS_2 \longrightarrow C_2H_5C({=}S)SMgBr$$

In diethyl ether yields are poor, but in THF the results are mostly quite good. The reaction of *vinylic* Grignard compounds C=C—MgX with CS_2 is not very successful, possibly because the primary product C=C—CSSMgX undergoes conjugate addition of the starting Grignard reagent. During the interaction of aromatic and hetero-aromatic Grignard- and alkali compounds with CS_2 this consequtive reaction cannot occur. The Grignard derivatives, however, react sluggishly with CS_2 and require the assistance of copper(I) bromide. With aromatic and hetero-aromatic *alkali* compounds the reaction is unpredictable. Some hetero-aromatic lithium derivatives (e.g. 1-methyl-2-imidazolyllithium) give intractable tars in the reaction with CS_2 and after subsequent alkylation. In the case of 2-thienyllithium thiophilic attack is suspected to be a serious side-reaction, whereas 2-furyllithium gives the dithioate moderately cleanly. With aryllithium (e.g. PhLi) thiophilic attack seems to be the dominant process. Reaction of phenyllithium with carbon disulfide and subsequent addition of methyl iodide gives significant amounts of $PhSCH_3$ and much tar. This result might be explained by assuming a thiophilic attack with primary formation of $(PhS—\overline{C}{=}S)Li^+$, which decomposes to PhSLi and carbon monosulfide. Further reaction of the latter species might give rise to the formation of tars:

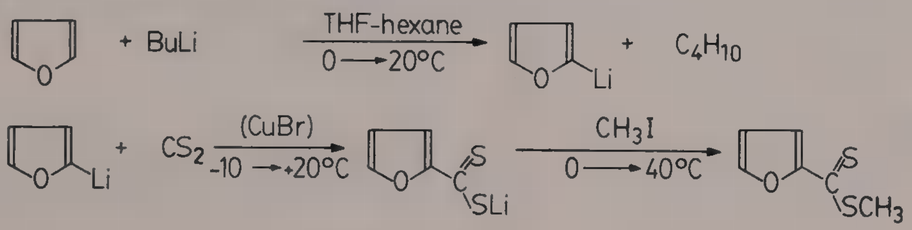


If 2-thienyl*potassium* is allowed to react with CS_2, and CH_3I is added, appreciable quantities of 2-thienyl-SCH_3 can be isolated. On the other hand, the conversions of 2-thienyl-MgBr and PhMgBr with CS_2 (the former in the presence of a catalytic quantity of CuBr) give almost quantitatively the dithioates, as shown by the isolation of the methyl esters in excellent yields after addition of methyl iodide. The procedure below for methyl 2-thiophenecarbodithioate and also the next experiment are two successful preparations of dithioesters in the hetero-aromatic field. The procedure further demonstrates the preparation of an hetero-aromatic Grignard compound.

Procedure

Magnesium turnings (0.21 mol, 5 g) are covered with 40 ml of THF and 4 g of 1,2-dibromoethane is added. The evolution of ethene starts after a few minutes and soon ceases. An additional volume of 70 ml of THF is then added and 0.10 mol (16.3 g) of 2-bromothiophene is introduced dropwise over 30 min, while keeping the temperature of the mixture between 30 and 35 °C (at lower temperatures salt may separate). After warming for an additional half hour at this temperature, the greyish solution is poured into another flask, the excess of magnesium being rinsed with 20 ml of THF. The solution is cooled to 20 °C and 0.5 g of copper(I) bromide is added, followed by 0.14 mol (10.6 g) (excess) of carbon disulfide. After warming to ca. 30 °C, a weakly exothermic reaction starts, during which the temperature may rise by some 15°. Thirty min after the addition, the mixture is warmed to 50 °C and held at that temperature for an additional half hour. Methyl iodide (21.3 g, 0.15 mol) and HMPT (40 ml) are then added and the mixture is heated for 3 h at 60 °C. The dark solution is then poured into 200 ml of an aqueous solution of 4 g of potassium cyanide and 30 g of ammonium chloride (for removal of the copper salt). After vigorous shaking and separation of the layers, the aqueous layer is extracted four times with Et_2O. The combined organic solutions are washed four times with water (to remove HMPT) and are subsequently dried over $MgSO_4$. The residue remaining after removal of the solvent *in vacuo* is distilled through a 20-cm Vigreux column, affording the dithioester, b.p. ~100 °C/0.5 mm, in more than 90 % yield.

5.25 Methyl-2-Furancarbodithioate



Scale: 0.10 molar.

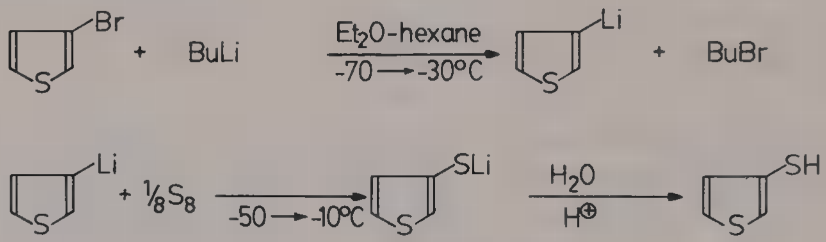
Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction: see Exp. 24.

Procedure

Copper(I)bromide (0.5 g) is added to a solution of 0.10 mol of 2-furyllithium in THF and hexane (see Exp. 6). Carbon disulfide (10.6 g, 0.14 mol) is then added over 10 min at −20 °C. The temperature of the dark-brown solution is allowed to rise to 20–25 °C. After stirring for an additional 20 min (at room temperature) the solution is cooled to 0 °C and 0.15 mol (21.3 g) of methyl iodide is added in one portion. A moderately exothermic reaction ensues and the temperature rises to ca. 20 °C within 15 min. The reaction is brought to completion by stirring for an additional half hour at 35 °C. After a work-up similar to that in Exp. 24 the dithioester, b.p. 120 °C/15 mm, is obtained as a red liquid in 85 % yield.

5.26 3-Thiophenethiol



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l; the dropping funnel is replaced by a stopper, which is temporarily removed during the addition of sulfur.

Introduction

The introduction of Exp. 2 gives detailed comments concerning the reaction conditions for the bromine-lithium exchange in 3-bromothiophene. In the procedure for 3-thiophenethiol Et_2O is used as solvent, since this minimizes the chance of a subsequent reaction of 3-thiophenethiolate with butyl bromide produced in the exchange reaction. The preparation of thiols from lithium compounds and elemental sulfur is particularly successful in the aromatic and hetero-aromatic series. Potassium compounds were found by us to react very sluggishly to give brown reaction mixtures. 3-Thiophenethiol is very sensitive towards oxygen, so that careful working is required during the stage of isolation. The 2-isomer is much more stable: its preparation is described in Organic Synthesis [164].

Procedure

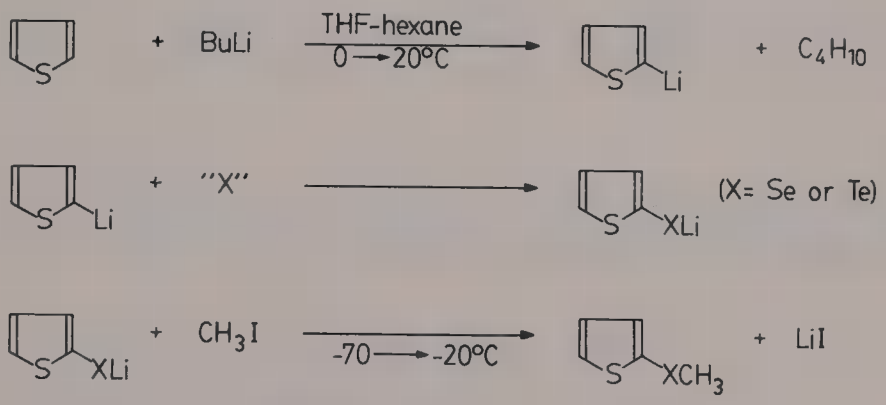
A solution of 0.11 mol of butyllithium in 77 ml of hexane is mixed with 80 ml of Et_2O and the mixture is cooled to −70 °C. 3-Bromothiophene (16.3 g, 0.10 mol) is added dropwise over 15 min, during which time the temperature is allowed to rise gradually to −30 °C. Stirring is continued for an additional 15 min, then the solution is cooled to −50 °C and 0.10 at (3.2 g) of dry, powdered sulfur is added over a few seconds. An exothermic reaction starts and (without external cooling) the temperature rises to −15 °C. Stirring at this temperature is continued for an additional 30 min, until all sulfur has disappeared. To the light-yellow or colourless solution is then added a solution of 10 g of potassium hydroxide (Note 1) in 70 ml of water. The organic layer is separated from the light-yellow aqueous layer and is discarded. The aqueous layer is extracted once with Et_2O to remove traces of organic side-products. After separation of the layers, the aqueous layer is cooled to −5 °C and 5N hydrochloric acid is added with stirring (or manual swirling) (Note 2) until a pH of 2 is reached. An oily under-layer is formed. The product is extracted four times with small portions of dichloromethane. The combined organic solutions are washed twice with water and subsequently dried over $MgSO_4$. Concentration of the solution *in vacuo* gives almost pure 3-thiophenethiol (n_D^{15} 1.6162) in ca. 90 % yield (Note 3). The compound is not distilled.

Notes

1. The KOH serves to suppress hydrolysis of the thiolate to thiol.
2. All operations with the free thiol must be carried out under nitrogen in view of the sensitivity to oxygen.
3. When kept under inert gas at low temperatures the product remains unchanged for at least 24 h; if air is admitted, however, the refractive index soon rises, and attempts to distill the compound result in decomposition and formation of high-boiling material.

General note: Use rubber gloves: the thiol has a very persisting stench.

5.27 2-(Methylseleno)Thiophene and 2-(Methyltelluro)Thiophene



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

Reaction of aryl- and hetero-aryllithium compounds with elemental selenium and tellurium proceeds smoothly and cleanly; addition of methyl iodide to the resulting solutions of the selenolates and tellurolates gives the corresponding selenides and tellurides in high yields. Grignard derivatives also give good results, however, potassium compounds do not react well (c.f. the reaction with sulfur). We have not studied what actually happens. The only thing which is clear is that they are not the proper intermediates for making selenolates and tellurolates. Selenolations and tellurolations proceed most smoothly with the red and grey (respectively) powders. Black selenium ("selenium nigrum") often reacts slowly and yields may be disappointing. Black tellurium powder ("precipitated") appears to be practically inert; a possible explanation is that the very small particles are covered by a layer of oxide, which makes them inaccessible for interaction with the organometallic reagent.

Procedure

A solution of 0.05 mol of 2-lithiothiophene in about 40 ml of THF and 40 ml of hexane is prepared as described in Exp. 3. The solution is cooled to −60 °C and 0.05 mol (4.1 g) of red selenium ("precipitated") powder is added over a few s. After removal of the cooling bath the powder dissolves within 15 min, while the temperature rises by 20 to 30° (powders from bottles with an other batch number or from other suppliers, also indicated as "red selenium", dissolved at considerably higher temperatures, giving comparable yields of the methyl selenides). When all powder has dissolved, the slightly coloured (brown) solution is cooled to −60 °C and 0.10 mol (14.2 g) of methyl iodide is added in one portion. The reaction is very fast and a white suspension is formed immediately. After allowing the reaction mixture to warm up to room temperature, 100 ml of water is added under vigorous stirring. The aqueous layer is extracted twice with ether. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated under reduced pressure. Distillation of the remaining oil trough a 20-cm Vigreux column gives the selenide, b.p. 75 °C/15 mm, n_D^{20} 1.6183, in 87 % yield.

2-(Methyltelluro)thiophene, b.p. 97 °C/12 mm, n_D^{20} 1.6737, is obtained in 82 % yield as a brown oil. The procedure is similar to that described for the selenide. The Te powder (grey!) is added at 0 °C and dissolves after stirring for about 1 h at 5–10 °C. Like other tellurides the compound is sensitive to oxygen.

5.28 Reaction of Metallated Hetero-Aromates with Methyl Isothiocyanate, Phenyl Isothiocyanate, Phenyl Isocyanate and Phenyl Sulfinylamine

$$\mathrm{RLi} + \mathrm{CH_3N{=}C{=}S} \longrightarrow \mathrm{R\text{-}C(SLi){=}NCH_3} \xrightarrow{H_2O/H^{\oplus}} \mathrm{R\text{-}C({=}S)NHCH_3}$$

$$\mathrm{RLi} + \mathrm{PhN{=}C{=}S} \longrightarrow \mathrm{R\text{-}C(SLi){=}NPh} \xrightarrow{H_2O/H^{\oplus}} \mathrm{R\text{-}C({=}S)NHPh}$$

$$\mathrm{RLi} + \mathrm{PhN{=}C{=}O} \longrightarrow \mathrm{R\text{-}C(OLi){=}NPh} \xrightarrow{H_2O/H^{\oplus}} \mathrm{R\text{-}C({=}O)NHPh}$$

$$\mathrm{RLi} + \mathrm{PhN{=}S{=}O} \longrightarrow \mathrm{R\text{-}S(OLi){=}NPh} \xrightarrow{H_2O/H^{\oplus}} \mathrm{R\text{-}S({=}O)NHPh}$$

Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

The addition reaction depicted in the general scheme seems to be general in the hetero-aromatic series. The structures of the heterocumulenes suggest a high reactivity and indeed the additions of the lithiated hetero-aromatics proceed quickly at temperatures far below 0 °C. Reactions with Grignard- and potassium compounds have not been carried out by us, but there is no reason to suspect that any serious deviation would be obtained. Yields of the adducts, obtained after aqueous work-up, are mostly excellent. We have not, however, investigated reactions with lithiated hetero-aromatics having more than one nitrogen.

Since part of the product may remain in solution as the lithium thiolate or alcoholate, it is advisable to carry out the hydrolysis of the reaction mixtures in the presence of an equivalent amount of mineral acid. If the metallated hetero-aromatic compound has been obtained *via* lithiation with LDA, or with BuLi · TMEDA, an additional amount of acid is required to neutralize the amine. Purification in many cases can be carried out by crystallization from an organic solvent.

General Procedure

A solution of 0.055 mol of the lithiated heterocyclic compound in about 40 ml of THF and 40 ml of hexane (prepared as described in the preceding experiments) is cooled to ca. −80 °C. A mixture of 0.05 mol of the heterocumulene (Note 1) and 25 ml of THF is added dropwise over 5–10 min, then the cooling bath is removed and the temperature allowed to rise. A precipitate often appears during or after the addition. Most reactions are quickly completed at temperatures below −20 °C. A mixture of 6 g of 36 % (fuming) hydrochloric acid and 100 ml of water is then added with vigorous stirring and, after separation of the layers, the aqueous layer is extracted three times with Et_2O (if good solubility in water is suspected, dichloromethane or chloroform may be used, whereby washing is not carried out in this case). After washing, the combined solutions are dried over $MgSO_4$, and the solvent is removed under reduced pressure (the last traces in a high-vacuum with moderate heating). In some cases the residue is almost pure, as shown by ^1H-NMR, although the colour may be very dark.

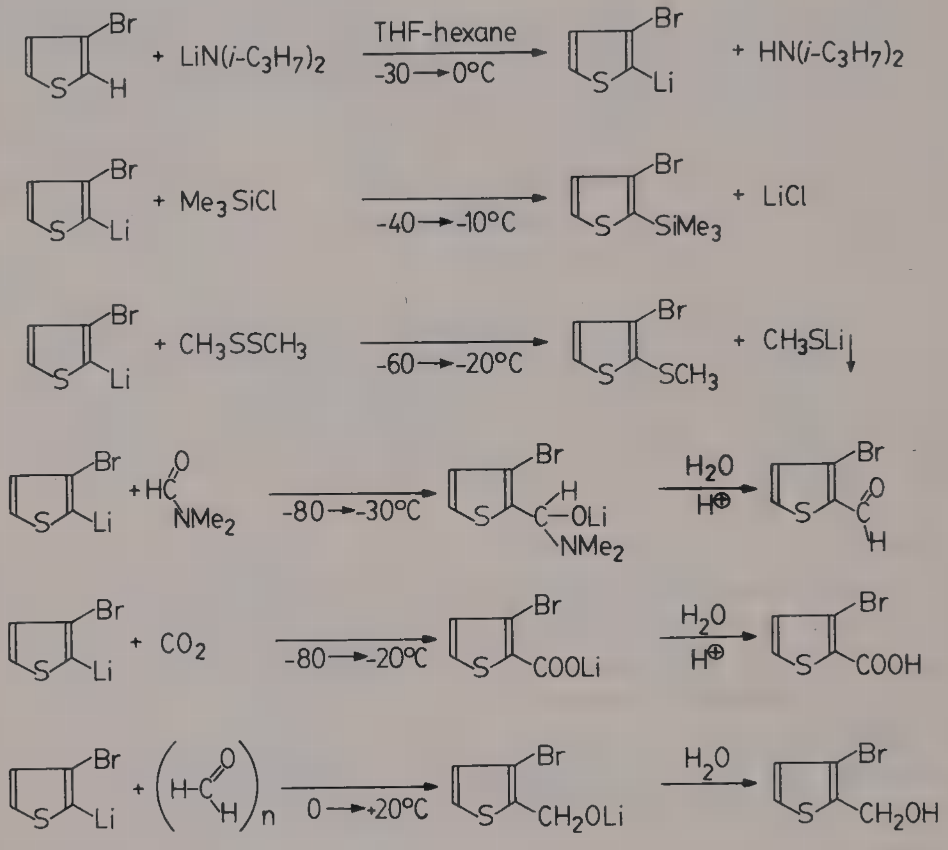
The following compounds were prepared by us:

2-thienyl $C(=S)NHCH_3$, m.p. 90.0 °C (after crystallization from Et_2O-pentane 1:2).
3-thienyl $C(=S)NHCH_3$, crystalline, no m.p. determined.
2-furyl $S(=O)NHPh$, crystalline, no m.p. determined.
2-furyl $C(=O)NHPh$, crystalline, no m.p. determined.
4-methyl-2-thiazolyl-$C(=S)NHCH_3$, liquid at room temperature.
4-methyl-2-thiazolyl-$C(=S)NHPh$, crystalline, no m.p. determined.
2-thienyl-$S(=O)NHPh$, crystalline, no m.p. determined.
Yields of these derivatives were higher than 80 %.

Notes

1. The isothiocyanates and phenyl isocyanate are commercially available, PhN=S=O is prepared as described in Ref. [194].

5.29 Regiospecific Vicinal Metallation of 3-Bromothiophene and Preparation of Derivatives



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

Addition of 3-bromothiophene to a solution of butyllithium in THF or Et_2O gives exclusively replacement of bromine by lithium (see Exp. 2). With dialkylamides this reaction is thermodynamically unfavourable (low energy of the Br—N bond). The vicinal 2-position is particularly activated and interaction between 3-bromothiophene and lithium dialkylamide results in a specific abstraction of the 2-proton under mild conditions (compare also the reaction with KNH_2 in liquid ammonia, Exp. (9). The remarkable stability of 2-lithio-3-bromothiophene (and presumably also of the furan analogue) allows successful derivatization at temperatures around +20 °C, and contrasts with the facile ring opening of 3-lithiothiophene and the elimination of alkali halide from *ortho*-metallated halogenopyridines and -benzenes.

Procedure

A solution of 0.06 mol of LDA is prepared from HDA (7.1 g, 0.07 mol) and butyllithium (0.06 mol) in about 45 ml of hexane and 45 ml of THF (see Chap. I, Exp. 5). 3-Bromothiophene (8.2 g, 0.05 mol, see Exp. 47) is added over 5 min with cooling to between −20 and −30 °C. The cooling bath is then removed and the temperature is allowed to rise to 0 °C. The following derivatization reactions can be carried out with the obtained solution:

a) Trimethylchlorosilane (8.7 g, 0.08 mol) is added over 5 min with cooling to between −30 and −40 °C. The temperature is allowed to rise to −10 °C and the reaction mixture is poured into a mixture of 10 g of concentrated hydrochloric acid and 150 ml of ice water. After vigorous shaking, the layers are separated and two extractions with Et_2O are carried out. The combined solutions are dried over $MgSO_4$, concentrated *in vacuo* and the residue distilled through a short column.

Trimethylsilyl-3-bromothiophene, b.p. 95 °C/15 mm, n_D^{23} 1.5253, is obtained in 88 % yield.

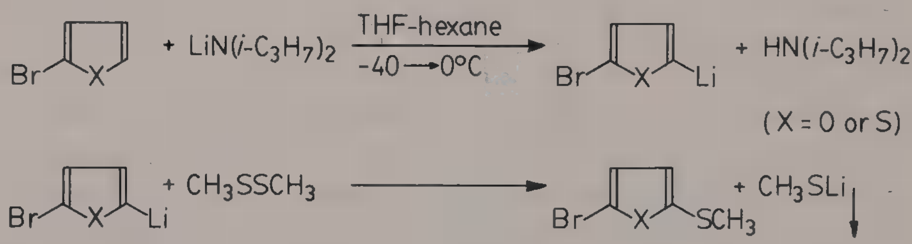
b) Dimethyl disulfide (7.5 g, 0.08 mol) is added in one portion at −50 °C, the cooling bath is removed and after 15 min 100 ml of water is added with vigorous stirring. The layers are separated and the aqueous layer is extracted three times with Et_2O. The combined organic solutions are washed with 50 ml of water and dried over $MgSO_4$. Evaporation of the solvents followed by distillation gives 2-methylthio-3-bromothiophene, b.p. ~70 °C/0.3 mm, n_D^{23} 1.6333, in 86 % yield.

c) Dimethyl formamide (5.8 g, 0.08 mol) is added in one portion at −80 °C. The initial white precipitate dissolves, when the cooling bath is removed and the temperature is allowed to rise to −30 °C. The clear solution is poured with swirling into a mixture of 22 g of 36 % (fuming) hydrochloric acid (slightly more than the amount required to bind the HDA, LiOH and Me_2NH liberated) and 150 ml of ice water. After vigorous shaking and separation of the layers, three extractions with Et_2O are carried out. The combined solutions are washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. Distillation of the remaining oil gives 2-formyl-3-bromothiophene, b.p. ~80 °C/0.3 mm, n_D^{23} 1.6344, in 84 % yield.

d) The solution is cooled to −80 °C and carbon dioxide is introduced (2 l/min) with vigorous stirring (the dropping funnel is replaced by an inlet tube) keeping the temperature below −30 °C. After 3–4 minutes the introduction of the gas is stopped and the temperature is allowed to rise to −20 °C. The solution is poured into a mixture of 15 g of concentrated (36 %) hydrochloric acid and 200 ml of water. After vigorous shaking and separation of the layers four extractions with Et_2O are carried out. The organic solution is dried over $MgSO_4$ and then concentrated *in vacuo*. The last traces of volatile components are removed by evacuating at 0.5 mm or lower pressure. A yield of 11 g of white solid residue corresponding to more than 90 % yield, is obtained. The ^1H—NMR spectrum (hexadeuteroacetone) indicated pure carboxylic acid.

e) Dry, powdered paraformaldehyde (2.5 g, corresponding to an excess) is added without external cooling at 0 °C to the solution. The temperature rises gradually to 20 °C or higher. The conversion is completed by warming at 30 °C for an additional 45 minutes after which the turbid solution is then poured into a mixture of 12 g of 36 % hydrochloric acid and 100 ml of water. After vigorous shaking and separation of the layers, three extractions with Et$_2$O are carried out. The combined solutions are washed one time with brine. After drying over MgSO$_4$ the solvents are evaporated. High-vacuum distillation gives the alcohol, b.p. ~90 °C/0.4 mm, n_D^{24} 1.6050, in 90 % yield.

5.30 Lithiation of 2-Bromofuran and 2-Bromothiophene in the 5-Position; Preparation of 2-Bromo-5-(Methylthio)Furan and -Thiophene



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

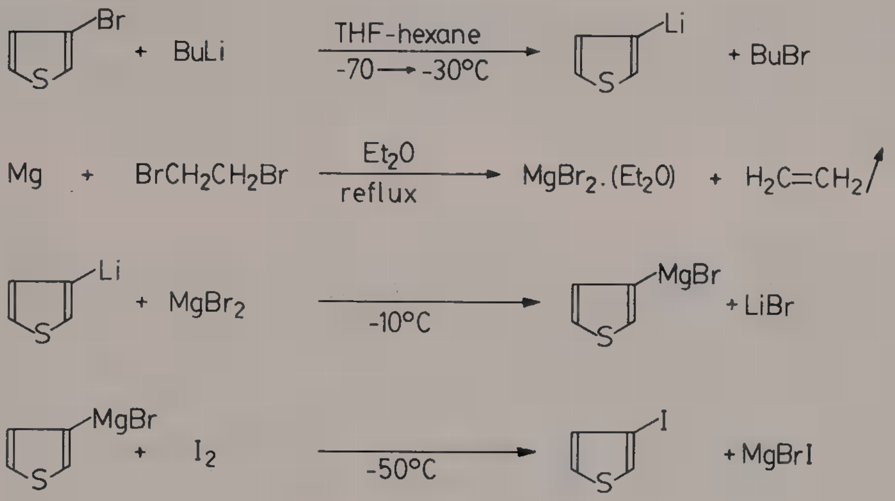
As mentioned in section V-1, reaction of 2-substituted furans and thiophenes with metallating reagents in organic solvents, in nearly all cases leads to the introduction of the metal into the 5-position. This regiospecific behaviour is accounted for by the activating influence of the hetero atom, which is felt most strongly in the α-position. If the 2-substituent is alkyl or another group having no or only weak electron-withdrawing properties, a strong base like butyllithium presumably will be required for complete deprotonation at carbon atom 5. The procedures below suggest that LDA is sufficiently basic to generate the 5-lithiated intermediates in high concentrations. It is undoubtedly the inductive effect of bromine which is responsible for the increased thermodynamic acidity of the proton at carbon atom 5. Attack of the lithium amide on bromine does not occur, since this reaction has no "driving force". The formation of 2-bromo-5-methylthio-derivatives in excellent yields reflects the efficiency of the metallation with LDA.

Procedure

2-Bromothiophene (8.2 g, 0.05 mol, see Exp. 48) or 2-bromofuran (7.4 g, 0.05 mol, see Exp. 12) is added to a solution of 0.06 mol of LDA in about 45 ml of THF and 45 ml of hexane (prepared from 0.06 mol of BuLi and 0.07 mol (7.1 g) of HDA as described in Chap. I, Exp. 5) cooled to −40°. After the addition, which takes about 5 min, the cooling bath is removed and the temperature is allowed to rise to 0 °C.

The resulting solution is then cooled to −50 °C and 0.07 mol (6.6 g) of dimethyl disulfide is added in one portion and the temperature is allowed to rise (without cooling) to −10 °C. Water (100 ml) is then added to the suspension with stirring. The layers are separated and three extractions with Et_2O are carried out. After washing the combined solutions with brine and drying over $MgSO_4$, the solvents are removed *in vacuo*. Careful distillation through a 30 cm Vigreux column gives 2-bromo-5-(methylthio)furan, b.p. 50 °C/1 mm, n_D^{20} 1.5632, in 86 % yield, and 2-bromo-5-(methylthio)thiophene, b. p. 65 °C/0.2 mm, n_D^{23} 1.6303, in 92 % yield.

5.31 3-Iodothiophene



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

3-Substituted thiophenes are generally obtained via the readily available 3-bromo-compound. The usual procedure involves bromine-metal exchange by reaction with butyllithium, followed by addition of the derivatization reagent. In most cases yields are quite good. Addition of iodine, (dissolved in THF), however, gave a moderate yield of 3-iodothiophene. The main product was a (high-boiling) di-iodo-compound, probably the 2,3-isomer. This result may be explained by assuming that part of the initially formed 3-iodothiophene is metallated by 3-lithiothiophene after which the metallated 3-iodothiophene reacts with iodine. This undesired reaction does not occur with the kinetically less basic 3-thienylmagnesium bromide, which can be obtained by simple addition of magnesium bromide etherate to 3-lithiothiophene.

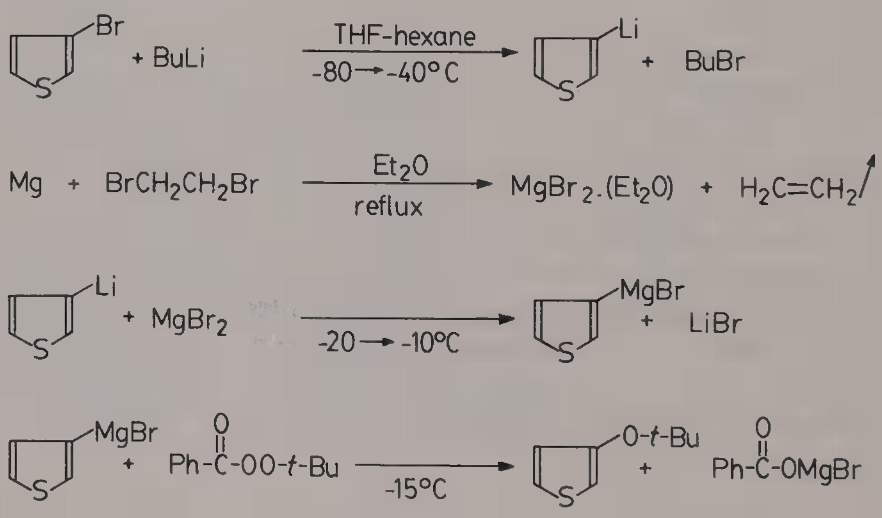
Procedure

A solution of 0.11 mol of butyllithium in about 75 ml of hexane is mixed with 75 ml of THF cooled to below −40 °C. The solution is cooled to −80 °C and 0.10 mol (16.3 g) of 3-bromothiophene (see Exp. 47) is added over 15 min with cooling to between −80 and −60 °C. After this addition the cooling bath is removed and the temperature is allowed to rise to −30 °C. A mixture of magnesium bromide (~0.15 mol) and Et_2O (~40 ml) (Note 1) is poured into the vigorously stirred solution of 3-lithiothiophene, while keeping the temperature between −40 and −20 °C. The resulting suspension is subsequently cooled to about −50 °C and a solution of 31 g (0.12 mol, slight excess) of iodine in 50 ml of THF is added over 10 min with vigorous stirring and cooling to between −50 and −30 °C. The greater part of the iodine reacts almost immediately, but in the last stage of the addition the brown colour persists. A solution of 15 g of sodium thiosulfate ($Na_2S_2O_3 \cdot 5aq$) in 150 ml of water is then cautiously added with vigorous stirring and cooling at 0 °C. After separation of the layers the aqueous phase is extracted twice with Et_2O. The combined solutions are dried over $MgSO_4$ and subsequently concentrated in a water-pump vacuum. Careful distillation of the remaining oil gives 3-iodothiophene, b.p. 75 °C/15 mm, n_D^{20} ~1.650, (Note 2) in 86 % yield. The product may have a brown colour, due to formation of traces of iodine towards the end of the distillation.

Notes

1. The magnesium bromide is prepared by dropwise addition of 0.16 mol of 1,2-dibromoethane to a mixture of 0.30 mol (7.2 g) of magnesium (excess) and 60 ml of Et_2O. During this addition and also for an additional period of 30 min thereafter, the ether is allowed to reflux. The oily, grey underlayer of $MgBr_2 \cdot Et_2O$ and the supernatant ether are decanted from the excess of magnesium and added to the solution of 3-lithiothiophene.
2. Traces of impurities having a much lower n_D^{20} may give rise to a considerably lower value.

5.32 3-*t*-Butoxythiophene

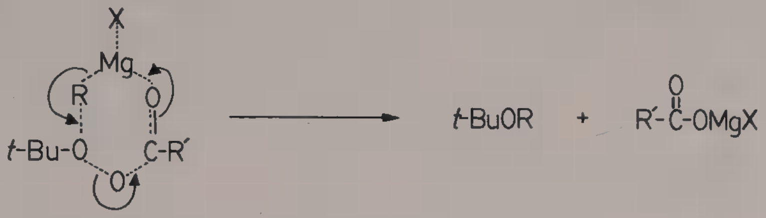


Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

t-Butyl ethers can be obtained in reasonable yields by reaction of per-esters with alkyl- or arylmagnesium halides. The formation is assumed to proceed *via* a six-membered transition state:



Lithium compounds (RLi) do not give good results, possibly because the interaction with Li is not sufficiently strong to give the required cyclic transition state. If the Grignard derivatives cannot be prepared in a direct way from halogen compounds and magnesium, they are accessible by reaction of the lithium compound with magnesium halide.

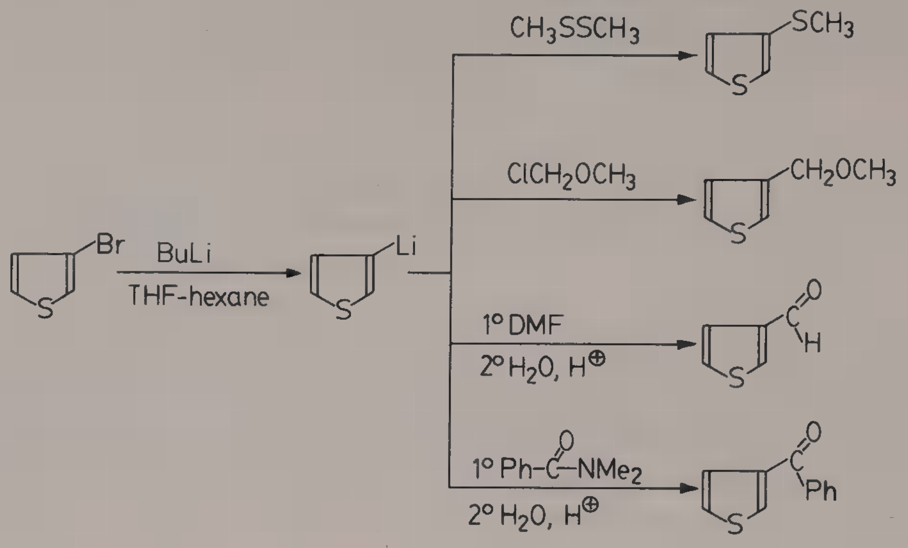
Procedure

THF (80 ml) is added to a solution of 0.11 mol of BuLi in 77 ml of hexane cooled to below −10 °C. 3-Bromothiophene 0.10 mol (16.3 g) (see Exp. 47) is then added over 15 min, while keeping the solution between −60 and −80 °C. After an additional 10 min (∼ −50 °C) a mixture of magnesium bromide etherate and about 40 ml of Et_2O is added (Note 1) with vigorous stirring. During this addition (taking about 3 minutes) the temperature is kept between −30 and −20 °C. *t*-Butyl perbenzoate (19.4 g, 0.10 mol) is subsequently added over 10 min at ca. −20 °C. After an additional period of 30 min of stirring at 0 °C, the white suspension (partly an oil) is poured into 200 ml of an aqueous solution of 30 g of ammonium chloride to which a few ml of triethylamine have been added (Note 2). After vigorous shaking and separation of the layers, three extractions with Et_2O are carried out. The combined solutions are dried over potassium carbonate. After concentration of the extracts *in vacuo*, the remaining liquid is distilled in a high vacuum (after 1 ml of triethylamine has been added). 3-*tert*-Butoxythiophene, b.p. ∼40 °C/0.5 mm, n_D^{21} 1.5009, is obtained in 72 % yield.

Notes

1. Prepared as described in Exp. 31, Note 1 from 0.15 mol of $BrCH_2CH_2Br$.
2. The amine is added to keep the medium sufficiently basic. Acids may induce decomposition of the *tert*-butyl ether.

5.33 3-Substituted Thiophenes from 3-Bromothiophene



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

3-Bromothiophene is an important starting compound for the synthesis of other 3-substituted thiophenes. The very facile bromine-lithium exchange reaction proceeds almost quatitatively and the butyl bromide present in the solution does not interfere in subsequent reactions with reactive "electrophilic" reagents. The following procedures are examples of smooth reactions with the intermediary 3-lithiothiophene.

Procedures

General: A solution of 0.10 mol of 3-lithiothiophene in 80 ml of THF and 80 ml of hexane is prepared from 0.10 mol (16.3 g) of 3-bromothiophene (see Exp. 47) and 0.11 mol of butyllithium, as described in the Exps. 2, 31, 32.

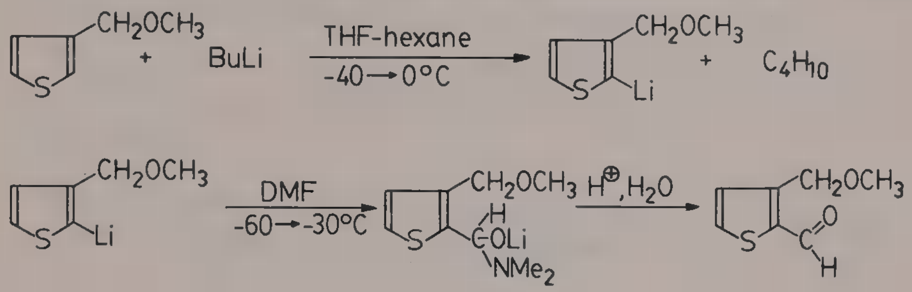
a) Dimethyl disulfide (11.3 g, 0.12 mol) is added over 5 minutes with cooling to between −70 and −20 °C. The reaction is extremely fast and a white suspension of lithium methanethiolate appears. The work-up is carried out by addition of 100 ml of water, separation of the layers, extraction of the aqueous phase with Et_2O and drying of the extracts over $MgSO_4$. After removal of the solvents *in vacuo*, the remaining liquid is carefully distilled, giving 3-(methylthio)thiophene, b.p. 72 °C/15 mm, n_D^{20} 1.6073, in 88 % yield.

b) Chlorodimethyl ether (9.7 g, 0.12 mol) is added over 15 min with cooling to between −40 and −20 °C. The temperature is then allowed to rise to 0 °C and 100 ml of water is added to the white suspension. A work-up and distillation similar to that followed under (a), give the methoxy ether, b.p. 72 °C/15 mm, n_D^{20} 1.5870, in 82 % yield.

c) Dimethylbenzamide (20.9 g, 0.14 mol) is added over 5 min with cooling to between −80 and −60 °C. Five minutes after the addition the reaction mixture is poured into a cold (0 °C) mixture of 30 g of (36 %) hydrochloric acid and 300 ml of water. After vigorous shaking, extraction and frequent washing of the extracts with water (to remove small amounts of dimethylbenzamide) the solution is concentrated *in vacuo*, the last traces of volatile material being evaporated in a vacuum of lower than 1 mm. The remaining liquid (weight ~95 % of the theoretical) appears to be reasonably pure (≥90 %) ketone.

d) 3-Thiophenecarboxaldehyde is prepared in a similar way from 3-lithiothiophene and DMF.

5.34 2-Formyl-3-(Methoxymethyl)Thiophene



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

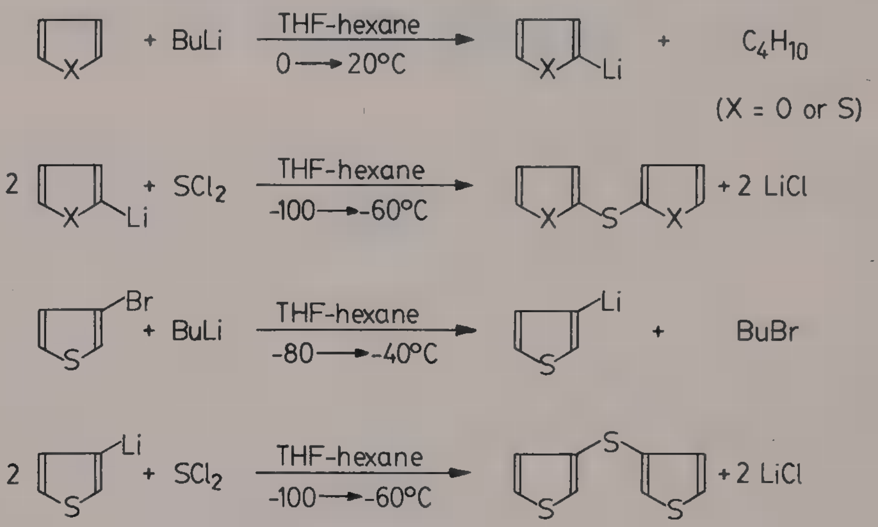
If 3-bromothiophene is metallated with LDA (compare Exp. 29), the metal is introduced exclusively in the 2-position. In contrast to bromine the methoxymethyl group has no inductive, electron-withdrawing properties, so that a stronger base seems to be required for complete deprotonation. Interaction between 3-(methoxymethyl) thiophene and butyllithium in a THF or Et_2O-hexane mixture results in the 2-metallated thiophene, which may be explained by assuming coordinative complexation of the attacking base by the CH_3O-function. This factor, together with the activating action of the sulfur atom, directs the metallation towards the 2-position. There is no indication for the formation of any 3-thienyl-CH(Li)OCH_3 (compare the metallation of $PhCH_2OCH_3$). The reason for the choice of dimethylformamide as functionalization reagent is that the presence of the isomeric product with the formyl group in the 5-position can be easily shown by ^1H—NMR spectroscopy. Preliminary experiments with 3-*t*-butoxythiophene, 3-methylthiothiophene and 3-methoxymethyl-thiophene [9] showed that metallation in the 5-position can occur to an appreciable extent, if the reaction is carried out at room temperature, particularly when THF is used as solvent.

Procedure

THF (40 ml) is added to a solution of 0.06 mol of butyllithium in 42 ml of hexane cooled to below −10 °C. The solution is cooled to −40 °C and 0.05 mol (6.4 g) of 3-methoxymethyl-thiophene (Exp. 33) is added over 10 min at this temperature.

The cooling bath is then removed and the temperature allowed to rise to 0 °C. After stirring for an additional 15 min at 0 °C, the solution is recooled to −60 °C and 0.07 mol (5.1 g) of DMF is added dropwise over 2 min. The temperature is allowed to rise to −40 °C, after which the solution is poured (with swirling) into a mixture of 14 g of 36% hydrochloric acid and 200 ml of water. After vigorous shaking, separation of the layers and extraction, the solutions are washed with water and subsequently dried over $MgSO_4$. Concentration of the solution under reduced pressure followed by distillation through a short Vigreux column gives pure aldehyde, b.p. ca. 85 °C/0.2 mm, n_D^{20} 1.5648, in 76% yield.

5.35 Di(2-Furyl)Sulfide, Di(2-Thienyl)Sulfide and Di(3-Thienyl)Sulfide



Scale: 0.20 molar (RLi).

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

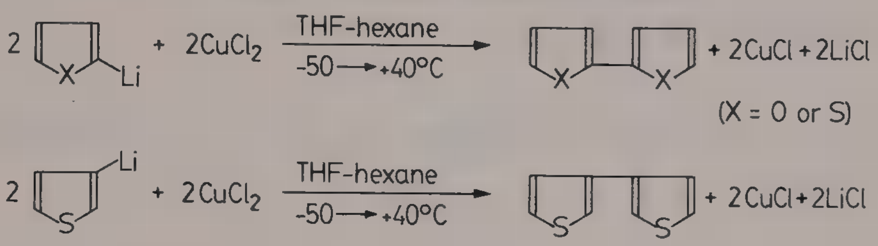
There are no systematic studies on the reaction of sulfur dichloride with polar organometallic reagents. The high reactivity of sulfur dichloride allows the couplings to be carried out at very low temperatures, even at −100 °C the reactions proceed almost instantaneously. The use of an excess of SCl_2 should be avoided, since this reactive molecule may easily add to the hetero-aromatic system or form an (unstable) sulfonium compound with the sulfur between the two heterocyclic units.

Procedure

Solutions of the lithiated heterocycles (0.20 mol) in THF (150 ml) and hexane (150 ml) are prepared as described in the Exps. 2, 3 and 5. The solutions are cooled to −105 °C, (occasional cooling in a bath with liquid nitrogen, avoiding formation of a solid crust on the bottom of the flask), after which 0.105 mol (10.8 g) of freshly distilled sulfur dichloride (Exp. 56) is added dropwise over 5 min with vigorous stirring. Occasional cooling is applied to keep the temperature between −90 and

−100 °C. Towards the end of the addition the suspension becomes slightly yellow or light-brown. The cooling bath is then removed and the temperature allowed to rise to −60 °C. Water (200 ml) is added with vigorous stirring and the mixture is warmed to 0 °C. 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 *in vacuo*. Distillation of the remaining liquids through a 20-cm Vigreux column gives the sulfides:
di(2-furyl)sulfide, b.p. ca. 75 °C/0.5 mm, n_D^{20} 1.5562, in 80 % yield.
di(2-thienyl)sulfide, b.p. ca. 105 °C/0.5 mm, n_D^{20} 1.6562, in 79 % yield.
di(3-thienyl)sulfide, b.p. ca. 105 °C/0.5 mm, n_D^{20} 1.6712, in 70 % yield.

5.36 2,2′-Bifuryl, 2,2′-Bithienyl and 3,3′-Bithienyl



Scale: 0.20 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

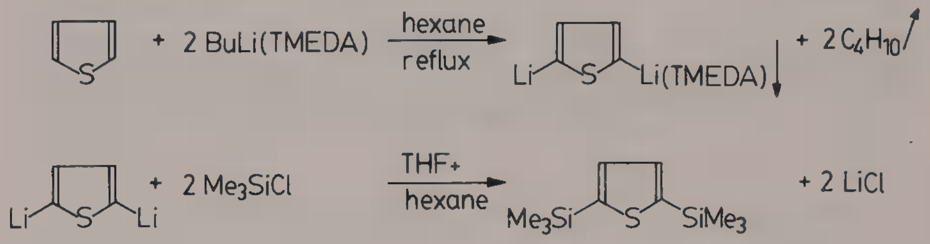
Introduction

Oxidative coupling of lithiated hetero-aromatic compounds to "dimers" with copper(II)halide has only been carried out in a few cases. Copper(I)halide in combination with oxygen has also been used. Another variant involves heating a copper derivative. The reported yields are poor to moderate, with favourable exceptions in the thiophene series [195]. The procedures below describe successful "dimerizations to bi-furyl and two bi-thienyls. Application of the same reaction conditions in the cases of o-CH_3—C_6H_4—Li, o-CH_3O—C_6H_4—Li and p-CH_3O—C_6H_4—Li gave poor results [9].

Procedure

Solutions of the lithiated heterocycles in 150 ml of THF and 150 ml of hexane (0.20 mol) are prepared as described in the Exps. 2, 3 and 5. Powdered anhydrous copper(II)chloride (26.9 g, 0.20 mol) is added over 10 min with cooling at ca. −50 °C. After the addition the cooling bath is removed and the temperature allowed to rise to +20 °C. As considerable heat is evolved at temperatures above −30 °C, occasional cooling may be necessary. The brown suspension gradually changes into a dark-green solution. After warming the mixture for an additional half hour at +30 °C, stirring is stopped. Two layers are formed, a dark under layer and a light-brown upper layer. The contents of the reaction flask are poured into 400 ml of an aqueous solution of 100 g of ammonium chloride and 30 g of alkali cyanide. After shaking for a few minutes, the layers are separated, and the aqueous layer is extracted five times with small portions of Et_2O or (preferably) light petrol of b.p. 40–60 °C. The combined solutions are washed three times with water and subsequently dried over $MgSO_4$. The solvent is removed under reduced pressure, using a heating bath at 35–40 °C. In the cases of bi-furyl and 2,2′-bi-thienyl, the remaining liquids are distilled through a 30-cm Vigreux column. 2,2′-Bi-furyl, b.p. 60 °C/15 mm, n_D^{20} 1.5496, is obtained in 67% yield, 2,2′-bi-thienyl, b.p. 120 °C/15 mm, is obtained in 70% yield. Pure 3,3′-bi-thienyl is obtained in 65% yield after sublimation. The ^{1}H-NMR spectrum (solvent CCl_4) shows one signal for all protons.

5.37 2,5-Dimetallation of Thiophene. Preparation of 2,5-bis(Trimethylsilyl)Thiophene



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml; the thermometer is replaced by a reflux condenser.

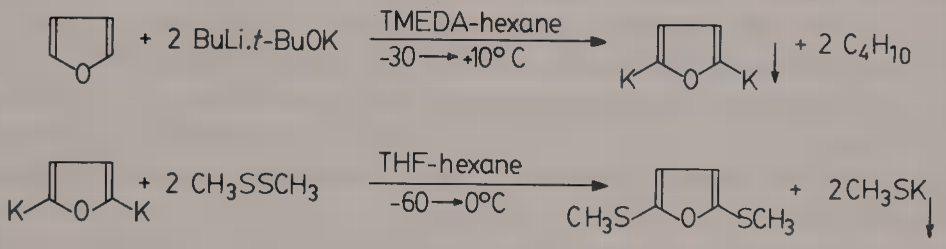
Introduction

Thiophene is readily metallated by buthyllithium in THF or Et_2O. Dimetallation, however, is not possible in these solvents, since under forcing conditions the solvent is attacked. Addition of the strongly polar HMPT (as co-solvent) does not lead to introduction of an additional metal atom, but causes ring-opening *via* deprotonation in the 3-position [128]. In the absence of THF or Et_2O the monomeric BuLi · TMEDA complex is capable of abstracting both the 2- and the 5-proton in thiophene. The first deprotonation occurs at relatively low (−10 °C or lower) temperature, the removal of the second proton is sufficiently fast at elevated temperatures. Quenching with trimethylchlorosilane is used to demonstrate the formation of a dilithio-derivative, since silylation is usually a quantitative reaction. However, the formation of a disilyl derivative is not always a good proof for the existence of a dianion, since formation may also occur stepwise, i.e. formation of a monoanion and its silylation (which may be even faster than that of butyllithium), deprotonation of the carbon atom bearing the silyl group, and reaction of the silyl-stabilized anion with Me_3SiCl. In the present procedure, there is no question of such a sequence of reactions, and the excellent yield of 2,5-bis(trimethylsilyl)thiophene can be considered as a proof for the high efficiency of the preceding dilithiation.

Procedure

Butyllithium (0.12 mol in 85 ml in hexane) is added to a mixture of 0.12 mol (13.9 g) of TMEDA, 30 ml of hexane and 0.10 mol (8.4 g) of thiophene. During this addition, which is carried out at room temperature, a white suspension is formed gradually. The cooling bath is removed, which allows the temperature to rise to 40 °C or higher. The conversion is completed by refluxing the mixture for 30 min. The suspension is cooled to below 0 °C and 40 ml of THF is added. After cooling to −60 °C, 16 g (0.15 mol, excess) or trimethylchlorosilane is added in one portion to the vigorously stirred solution. The temperature may rise to 0° or higher. After stirring at 30 °C for an additional 30 min the mixture is poured into water. After vigorous shaking, the layers are separated and three extractions with light petrol (b.p. 40–60 °C) are carried out. The solutions are washed with water, dried over $MgSO_4$ and then concentrated *in vacuo*. Careful distillation of the remaining liquid through a 30-cm Vigreux column gives the disilyl derivative, b.p. 105 °C/15 mm, n_D^{19} 1.4882, in 90 % yield.

5.38 2,5-Dimetallation of Furan. Preparation of 2,5-bis(Methylthio)Furan



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

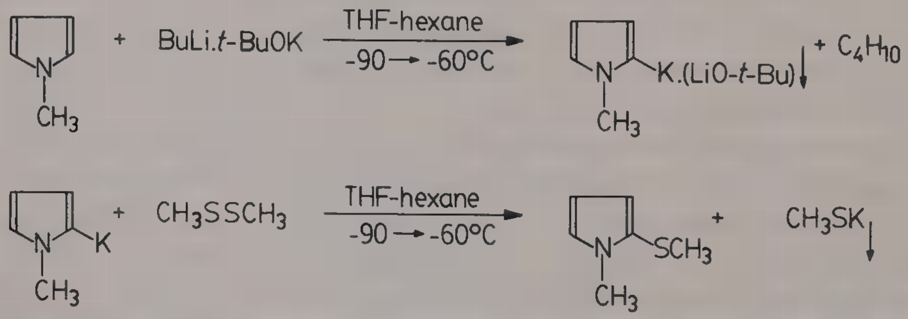
Introduction

In the preceding procedure we have shown that thiophene can be dimetallated quite satisfactorily with BuLi · TMEDA in hexane. The introduction of the second lithium requires elevated temperatures. If the same procedure is followed for furan, the yields of derivatization (quenching) products are moderate. This may be the consequence of decomposition of the metallated furan at higher temperatures. Of course, a large excess of base, in combination with lower temperatures, may be expected to result in better yields but practical chemists may object to "wasting" a relatively expensive reagent. If butyllithium in hexane is combined with potassium *t*-butoxide, a reactive system is formed which is capable of deprotonating kinetically (and thermodynamically) weak carbon acids, such as toluene, isobutene and benzene at room temperature [3]. An important disadvantage of this system ("butylpotassium") is its slight solubility in apolar solvents. The butylpotassium particles may be covered with potassiated carbon acid (which is insoluble), so that only part of the butylpotassium is consumed. If a sufficient amount of HMPT is used as co-solvent, this complication does not occur, since the reactants are in solution. However, the use of BuLi · *t*-BuOK in THF-hexane has the serious limitation that competitive metallation of THF can occur, when the metallation of the carbon acid is not sufficiently fast at low temperatures. This will certainly be the case when a second proton is to be abstracted. The "cocktail" BuLi · *t*-BuOK · TMEDA has a reasonably good solubility in hexane, and is an extremely potent basic system. The most important advantage is that the reactants are in a dissolved state. The procedure for the 2,5-dimetallation of furan is a good example. Although several kinds of reagents may be used to illustrate the dimetallation, we have chosen the reaction with dimethyl disulfide. In many other cases, sulfenylation has shown to proceed cleanly, so that the reaction with CH_3SSCH_3 may be used as a measure of the success of the dimetallation.

Procedure

Powdered potassium *t*-butoxide (13.4 g, 0.12 mol) is suspended in 40 ml of hexane. The mixture is cooled to below −60 °C and a solution of 0.12 mol of butyllithium in 84 ml of hexane is introduced using a syringe. Care should be taken that the temperature does not rise above −30 °C. The suspension is stirred for 10 min at −40 °C, then 0.14 mol (16.3 g) of TMEDA is added over a few min whereupon the suspension becomes much thinner. Freshly distilled furan (3.4 g, 0.05 mol) dissolved in 30 ml of hexane is added at −30 °C, after which the cooling bath is removed. A rather thick suspension is gradually formed. After stirring for 1 h at −20 °C, the cooling bath is removed and the temperature allowed to rise to +10 °C. The suspension is then cooled to −60 °C, and 60 ml of THF is added, followed directly by a mixture of 30 ml of THF and 0.14 mol (13.2 g) of dimethyl disulfide. The temperature of the vigorously stirred suspension may rise above 0 °C. Stirring is continued for 5 min, then 150 ml of ice water is added with vigorous stirring. The light-brown organic layer is separated from the dark aqueous layer. The organic solution is washed four times with water in order to remove the TMEDA and *t*-butylalcohol. The washings are combined with the first aqueous layer, after which two extractions with hexane or light petrol are carried out. These extracts are also washed with water. The combined light-brown organic solutions are dried over $MgSO_4$, concentrated *in vacuo*, and the residue carefully distilled through a 30-cm Vigreux column to give 2,5-bis(methylthio)furan, b.p. 100 °C/15 mm, n_D^{22} 1.5728, in 78 % yield. A small high-boiling residue remains.

5.39 1-Methyl-2-(Methylthio)Pyrrole



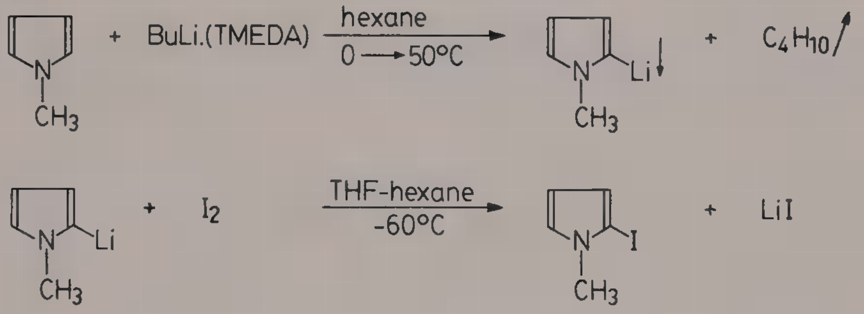
Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction
The deprotonation of 1-alkylpyrroles proceeds considerably less easily than that of furan and thiophene. A large excess of 1-methylpyrrole is required to obtain good results if butyllithium in THF is used (see Exp. 8), in which case the metallation has a synthetically acceptable rate at 20 to 30 °C. Complexation of butyllithium with *t*-BuOK causes an enormous enhancement of the deprotonation rate, as is shown below: it is not necessary to use the pyrrole derivative in excess.

Procedure
THF (40 ml) and 1-methylpyrrole (8.1 g, 0.10 mol) are successively added to a solution of butyllithium (0.105 mol) in hexane (74 ml) cooled to below −10 °C. The mixture is cooled to −90 °C and a solution of 0.105 mol (11.8 g) of potassium *t*-butoxide in 40 ml of THF is added dropwise over 15 min, while maintaining the temperature between −80 and −90 °C (occasional cooling in a bath with liquid nitrogen is sufficient, but care should be taken that none of the solvent solidifies at the bottom of the flask). A white suspension is soon formed. After the addition, the cooling bath is removed and the temperature is allowed to rise to −60 °C. Dimethyl disulfide (12.2 g, 0.13 mol) dissolved in 40 ml of Et_2O is then added over a few seconds with vigorous stirring. Ten minutes after this addition, 100 ml of water is added with vigorous stirring. After separation of the layers, the aqueous layer is extracted three times with Et_2O. The combined organic solutions are dried over $MgSO_4$ and then concentrated under reduced pressure. Distillation of the remaining liquid through a 30-cm Vigreux column gives 1-methyl-2-methylthiopyrrole b.p. 70 °C/15 mm, n_D^{21} 1.5496, in 94% yield.

5.40 2-Iodo-1-Methylpyrrole



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction
N-Methylpyrrole can be lithiated very quickly using BuLi · TMEDA in an apolar solvent (compare Exp. 14). This method is more suitable than the metallation with BuLi · *t*-BuOK described in Exp. 39 if condensations with enolisable carbonyl

compounds are to be carried out. Formation of enolates from ketones may be the predominant reaction with organic *potassium* compounds. Although TMEDA reacts very easily with iodine, this reaction does not seriously compete with the iodination of the 2-lithio compound at low temperatures. THF is added as a co-solvent prior to the reaction with iodine.

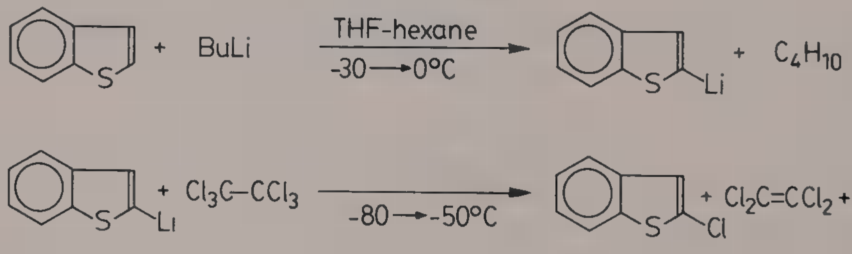
Procedure

A suspension of 2-lithio-1-methylpyrrole in ca. 80 ml of hexane is prepared from 0.11 mol (8.9 g) of 1-methylpyrrole and 0.10 mol of butyllithium (see Exp. 14). THF (90 ml) is added, and the resulting solution is cooled to −80 °C (cooling with liquid nitrogen is necessary). A solution of 30 g (0.12 mol) of iodine in 70 ml of THF is added over about 10 min with vigorous stirring (Note 1), while keeping the temperature between −80 and −60 °C. A brown suspension is formed. The temperature is allowed to rise to −40 °C and a solution of 10 g of sodium thiosulfate ($Na_2S_2O_3 \cdot 5aq$) in 200 ml of water is added with vigorous stirring. The separation of the layers may be difficult because of the dark colour. After four extractions with Et_2O the combined solutions are dried over sodium sulfate. The solvents are removed in a water-aspirator vacuum, after which the remaining liquid is subjected to a rough distillation at a pressure of 1 mmHg or lower. During this distillation the (single) receiver is cooled at −40 °C. Careful redistillation of the contents of the receiver through a 40-cm Vigreux column gives 2-iodo-1-methylpyrrole, b.p. 80 °C/15 mm, n_D^{20} 1.597, in 72 % yield.

Notes

1. Too high local concentrations of iodine may give rise to reaction with TMEDA.

5.41 2-Chlorobenzo[b]Thiophene



Scale: 0.05 molar.

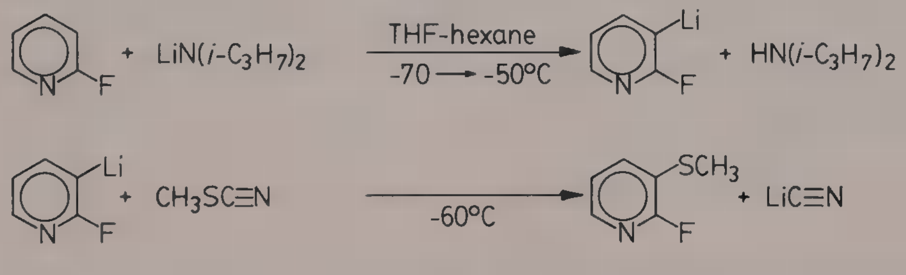
Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

Whereas iodinations of polar organometallic compounds in most cases are carried out with elemental iodine (see for example Exp. 40) the aggressive nature of chlorine may give rise to side and subsequent reactions, or reactions with the organic solvent. However, there are a number of compounds, containing so-called positive chlorine, e.g. N-chlorosuccinimide (NCS), carbon tetrachloride and hexachloroethane, which can be used as a source of chlorine. An important disadvantage of N-chlorosuccinimide is that the initially *N*-metallated succinimide may be attacked by the metal compound (C=O groups!), particularly if the kinetic baisicity is high (alkali acetylides and acetylenic Grignard derivatives can be converted into 1-chloroacetylenes in good yield using NCS [222]). Chlorination with CCl_4 gives the trichloromethyl-"anion": this loses Cl^- to give dichlorocarbene which is likely to interfere. Chlorinations with hexachloroethane proceed smoothly, even at temperatures in the region of −70 °C. The side product is tetrachloroethene, which has a b.p. of ca. 125 °C at normal pressure. This means that the hexachloroethane method cannot be applied if compounds with boiling points close to 125 °C are to be prepared. We found that tetrachloroethene can also react with organometallic intermediates, but the reaction proceeded at considerably higher temperatures than the chlorination with hexachloroethane.

Procedure
THF (40 ml) is added to a solution of 0.06 mol of butyllithium in 40 ml of hexane with cooling to below 0 °C. The mixture is cooled to −50 °C and a solution of 0.05 mol (6.7 g) of benzothiophene in 20 ml of THF is added over one minute. The cooling bath is removed and the temperature is allowed to rise to −10 °C. The white suspension is stirred for an additional 10 min at −10 °C, then cooled to −80 °C and a solution of 0.05 mol (11.9 g) of hexachloroethane in 30 ml of THF is added over 15 min. The temperature of the suspension is kept between −80 and −60 °C during this period. The reaction is very exothermic. After the addition the cooling bath is removed and the temperature allowed to rise to −20 °C. Water (100 ml) is added with vigorous stirring and three extractions with Et_2O are carried out. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo* to give a solid, almost colourless residue. This is subjected to careful distillation at 10–15 mmHg, using a 20-cm Vigreux column. The distillation is stopped as soon as the temperature in the head of the column indicates 100 °C. The solid which has collected in the condenser, is mainly hexachloroethane (1–2 g), the residue in the flask is fairly pure 2-chlorobenzothiophene (yield ~80%). Further purification may be carried out by crystallization from pentane at −20 °C.

5.42 2-Fluoro-3-Methylthio-Pyridine



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

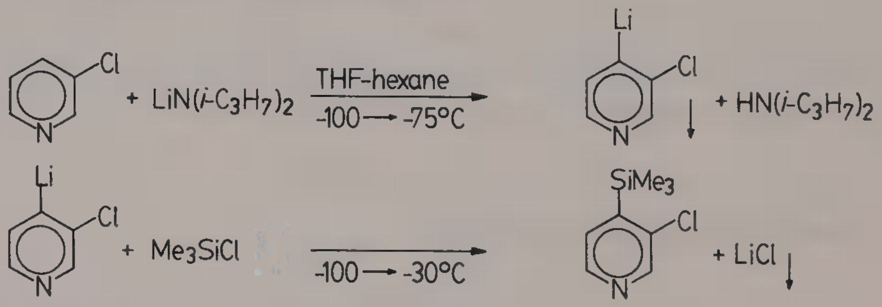
Introduction

2-Halogenopyridines readily undergo displacement of halogen by nucleophilic reagents. The reaction takes place *via* addition across the azomethine double bond. LDA has a strongly decreased tendency to add across multiple bonds or to enter into nucleophilic displacements. It has, however, pronounced "protophilic" properties. The 3-hydrogen atom in 2-fluoropyridine has an increased acidity due to the strong inductive effect of fluorine. LDA is apparently a sufficiently strong base to effect complete removal of the 3-proton. Subsequent addition of methyl thiocyanate gives the expected methylthio derivative in a high yield. We prefer $CH_3SC{\equiv}N$ to CH_3SSCH_3, since there is some chance that the methanethiolate split off will substitute fluorine (with the less polarisable $^-C{\equiv}N$ this danger seems less).

Procedure

A solution of 0.06 mol of LDA is prepared in 60 ml of THF and 42 ml of hexane as described in Chap. I, Exp. 5. After cooling to −70 °C, 0.05 mol (4.9 g) of 3-fluoropyridine, dissolved in 15 ml of THF is added over 10 min, while keeping the temperature between −55 and −70 °C. After an additional 15 min at −50 °C, the mixture is cooled to −60 °C and 0.07 mol (5.1 g) of methyl thiocyanate (see Exp. 55) is added in one portion with vigorous stirring. The suspension becomes much thinner. After an additional 5 min 150 ml of water is added with vigorous stirring. The layers are separated and the aqueous layer extracted five times with Et_2O. The solutions are not washed with water but after drying over anhydrous potassium carbonate the solvents are removed *in vacuo*. Careful distillation of the remaining liquid through a 30-cm Vigreux column gives 2-fluoro-3-methylthiopyridine, b.p. 97 °C/15 mm, n_D^{19} 1.5663, in 82 % yield.

5.43 3-Chloro-4-Trimethylsilyl-Pyridine



Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction (Compare also Exp. 42).

The inductive electron-withdrawal of chlorine in 3-chloropyridine causes an increase in the acidities of the hydrogen atoms in the 2- and 4-positions. It is difficult to predict which proton will be preferentially abstracted by a given base. The experimental facts show that with LDA in THF deprotonation at C-4 is very selective. With BuLi · TMEDA, however, we found a remarkable influence of the solvent on the regioselectivity, yields of the derivatization products being low probably as a consequence of competitive addition of BuLi to the azomethine double bond. In Et_2O 2-lithiation seems to be preferred, but in THF predominant abstraction of the 4-H atom occurs. In Et_2O the ring-nitrogen atom may have an assisting function in that it complexes with the base, thus creating a situation which is favourable for attack on the 2-proton. In the following procedure we describe the reaction conditions for the metallation in the 4-position and the subsequent trimethylsilylation. For comparison our observations with BuLi · TMEDA in Et_2O or THF are also mentioned.

Procedure

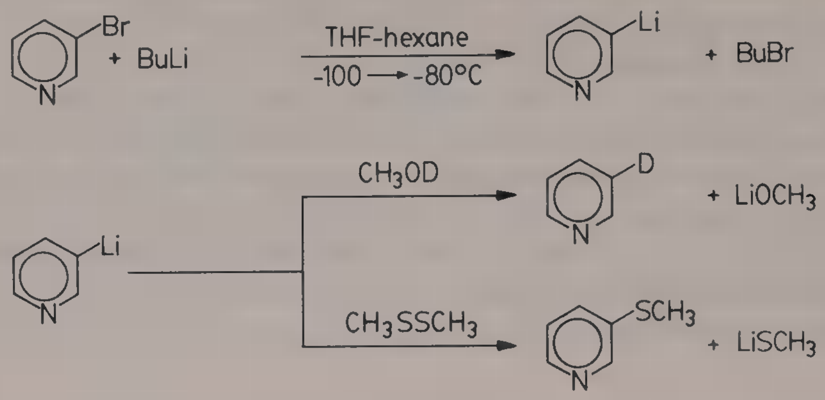
A solution of 0.07 mol of LDA is prepared in 65 ml of THF and 50 ml of hexane (see Chap. I, Exp. 5). The solution is cooled at −100 °C and a mixture of 0.05 mol (5.7 g) of 3-chloropyridine and 20 ml of THF is added in one portion. The reaction mixture is stirred for 40 min at −70 °C (Note 1), then recooled to −100 °C and 0.10 mol (10.8 g) of trimethylchlorosilane is added over a few seconds and is stirred for 20 min at −80 °C. The initial thick suspension disappears almost completely. After removal of the cooling bath, the temperature is allowed to rise to −30 °C and a new suspension (less thick) appears. Water (100 ml) is added with vigorous stirring after which the layers are separated and five extractions with Et_2O are carried out. The solutions are dried over anhydrous potassium carbonate and subsequently concentrated *in vacuo*. Careful distillation through a 30-cm Vigreux column gives 3-chloro-4-(trimethylsilyl)pyridine, b.p. 100−110 °C/15 mm, n_D^{20} 1.5133, in 79% yield. A small higher-boiling fraction (b.p. 125–130 °C/15 mm) consists mainly of 3-chloro-2,4-bis(trimethylsilyl)pyridine. There is no residue. In a comparative experiment with BuLi · TMEDA in Et_2O, TMEDA (7.0 g, 0.06 mol) is added to a solution of 0.055 mol of BuLi in 38 ml of hexane and 40 ml of Et_2O cooled to below −20 °C. The mixture is cooled to −90 °C and 0.05 mol (5.7 g) of 3-chloropyridine in 20 ml of Et_2O is added dropwise over 10 min. After stirring for an additional 15 min at −75 °C, 0.07 mol (6.6 g) of dimethyl disulfide is added in one portion with vigorous stirring, giving rise to a dark-brown solution. After 10 min 100 ml of water is added, causing the colour to change into yellow. The usual work-up gives 3-chloro-2-methylthiopyridine (purity ~90%), b.p. ~60 °C/0.1 mm, n_D^{21} 1.5816, in a yield of only 33%. A considerable viscous residue is left behind.

If the same experiment is carried out in a THF-hexane mixture, the product obtained by distillation (low yield) consists predominantly of 3-chloro-4-methylthiopyridine.

Notes

1. Stirring should be carried out at a moderate rate to prevent splashing of the reaction mixture into the relatively warm upper part of the flask, where decomposition can occur (brown colour).

5.44 3-Deuterio- and (3-Methylthio)Pyridine

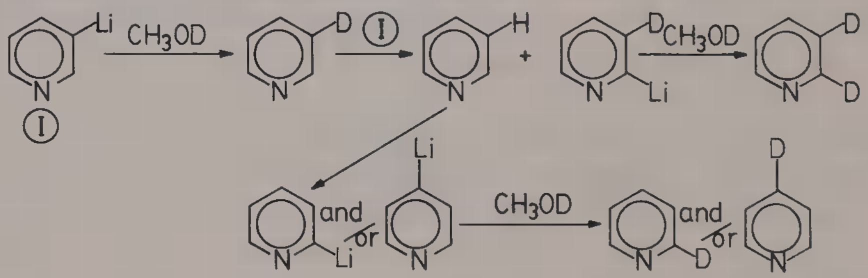


Scale: 0.10 molar for the deuteration; 0.05 molar for the thiomethylation.

Apparatus: Chap. I, Fig. 1, 1 l for the deuteration, 500 ml for the methylthiolation.

Introduction

At very low temperatures 3-bromopyridine and butyllithium react cleanly, and 3-(methylthio)pyridine can be obtained in almost quantitative yield after addition of dimethyl disulfide. To minimise the danger of side-reactions (e.g. addition of BuLi across the azomethine double bond, removal of a proton vicinal to bromine) a low temperature is maintained during the halogen-metal exchange reaction. The reversed-order addition is applied to introduce deuterium, since the normal way of addition may give rise in principle to scrambling of D or introduction of more than one D; e.g.:



The possibility of such undesired processes is considerable if the medium is strongly polar (e.g. if HMPT is present as a co-solvent) and/or the neutral compound has other protons which are easily abstractable. We prefer to use CH_3OD rather than the cheaper D_2O because CH_3OD is completely soluble in the organic solvent, D_2O dissolves incompletely and the undissolved D_2O may solidify at the temperatures normally applied in quenching reactions so that it does not react or reacts incompletely.

Procedure

a) Deuteration

THF (120 ml) is added to a solution of 0.11 mol of butyllithium in 80 ml of hexane with cooling to below 0 °C. The mixture is cooled to −100 °C and a mixture of 0.10 mol (15.8 g) of 3-bromopyridine and 30 ml of THF (Note 1) is added dropwise over 10 min. During this addition the temperature is kept carefully at ca. −100 °C. Cooling with liquid nitrogen should be applied only occasionally and care should be taken that no part of the solution solidifies at the bottom of the reaction flask. After the addition the temperature is allowed to rise to −80 °C and stirring at that temperature is continued for an additional 15 min. The green solution obtained is then cautiously poured into a vigorously stirred mixture of 0.4 mol (13.2 g) of deuteriomethanol (CH_3OD) and 50 ml of Et_2O, maintained at ~ −30 °C. The solution of 3-lithiopyridine is poured through an open neck of the 1-l flask containing the CH_3OD solution over 2 to 3 min. Five minutes after the addition a mixture of 15 g of concentrated (36%) hydrochloric acid and 30 ml of water is added. After warming up to room temperature, stirring is stopped and all volatile compounds are removed by means of the rotary evaporator. The small residue is shaken twice with pentane and the upper layers are decanted. The aqueous solution is then heated (~40 °C) in a water-pump vacuum for a few minutes. After cooling to 0 °C, 40 g of KOH pellets are introduced in small portions with manual swirling and cooling in an ice-water bath. The 3-deuterated pyridine is then distilled off (b.p. 20–40 °C) from the concentrated KOH solution at 10–20 mmHg. It is collected in a *single* 100-ml receiver, which is cooled at −20 °C. During the distillation the flask is heated at 50–60 °C. The distillation is stopped when 10 to 15 ml of liquid have collected in the receiver. The contents of the receiver are vigorously shaken with 10 g of powdered KOH for a few minutes and subsequently subjected to a final distillation to obtain pure 3-deuteriopyridine. The yield may depend upon the experimental skill, but 70–80% seems attainable.

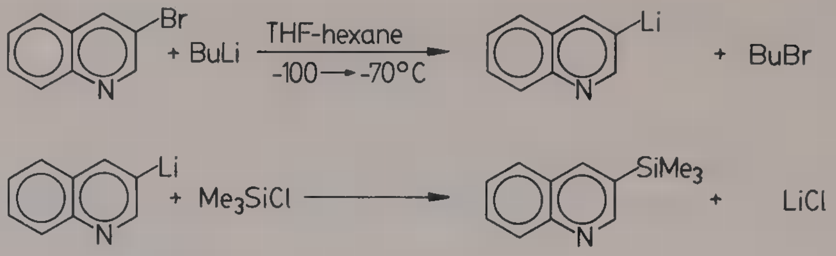
b) Methylthiolation

A mixture of 0.05 mol (7.9 g) of 3-bromopyridine (Note 1) and 20 ml of THF is added over 15 min to a solution of 0.06 mol of butyllithium in 60 ml of THF and 40 ml of hexane maintaining the temperature between −95 and −100 °C. After an additional 15 min period 0.07 mol (6.6 g) of dimethyl disulfide is added in one portion with vigorous stirring. After warming to −20 °C, 100 ml of water is added to the suspension. After separation of the layers three extractions with Et_2O are carried out. The solutions (washing is not carried out) are dried over anhydrous potassium carbonate and subsequently concentrated *in vacuo*. Distillation through a 20-cm Vigreux column gives (3-methylthio)pyridine, b.p. 85 °C/15 mm, n_D^{19} 1.5833 in 95% yield.

Notes

1. Addition of undiluted 3-bromopyridine may give rise to the formation of a brown precipitate and yields of the products are considerably lower.

5.45 3-Trimethylsilyl-Quinoline



Scale: 0.05 molar.

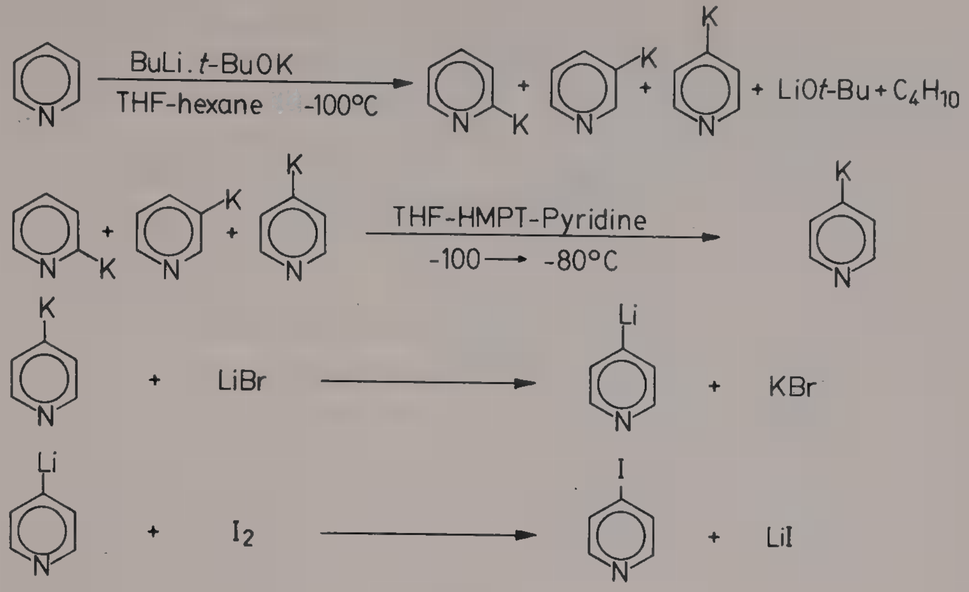
Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction (see introduction to Exp. 44).

Procedure
A mixture of 0.05 mol (10.4 g) of 3-bromoquinoline (Exp. 49) and 20 ml of THF is added over 10 min to a solution of 0.06 mol of butyllithium in 40 ml of THF and 42 ml of hexane maintaining the temperature between −95 and −105 °C. A red-brown suspension may be formed. Stirring is continued at −70 °C for an additional 20 min, then the suspension is cooled to −90 °C and 0.065 mol (7 g) of trimethylchlorosilane is added in one portion. The cooling-bath is removed and the temperature allowed to rise. At about −45 °C (Note 1) the reaction becomes more exothermic and the suspension disappears. After warming to 0 °C, the reaction mixture is treated with 100 ml of water. The organic layer and one ethereal extract are dried over anhydrous potassium carbonate, concentrated under reduced pressure, and carefully distilled through a 20-cm Vigreux column to afford (3-trimethylsilyl)quinoline, b.p. 145 °C/15 mm, n_D^{19} 1.5707, in 85% yield.

Notes
1. Normally strongly basic organoalkali compounds react at much lower temperatures with Me_3SiCl. The relatively low reactivity of 3-quinolinyllithium is probably due to its slight solubility.

5.46 3-Iodopyridine



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

Although pyridine can be metallated directly using the very strongly basic 1:1 complex of butyllithium and potassium *tert*-butoxide, a mixture of 2-, 3- and 4-potassiopyridine is formed, so that the synthetic utility is very limited. Addition of a sufficient amount of HMPT and pyridine to the metallation mixture can bring about a change in the ratio of the three species in favour of the 4-potassio compound: a relative percentage of 85–90 % is attainable. Subsequent functionalization gives a corresponding relative amount of the 4-isomer. In the case of iodination the circumstances for obtaining pure 4-iodopyridine are particularly favourable, since this compound can be purified by crystallization. The yield of pure product obtained by our laborious procedure is modest, but this method is the shortest route to this potentially useful compound. Prior to carrying out the iodination, potassium is exchanged for lithium to minimise the chance of vicinal metallation of 4-iodopyridine by unconverted 4-metallated pyridine. 4-lithiopyridine is kinetically less basic than the potassium compound.

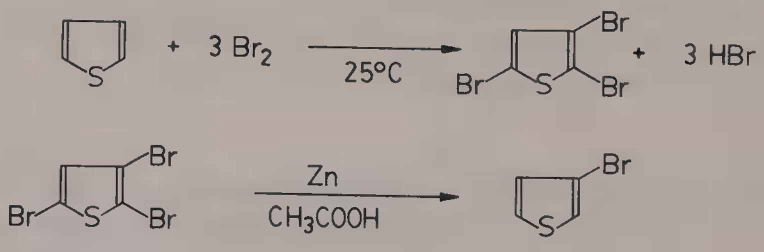
Procedure

A solution of 0.11 mol of butyllithium in 80 ml of hexane is cooled to −105 °C and a solution of 0.12 mol (13.4 g) of *t*-BuOK in 110 ml of THF is added with efficient stirring, carefully keeping the temperature between −95 and −105 °C (if a solid crust is formed at the bottom of the flask due to too strong cooling with liquid nitrogen, the addition should be interrupted until the solid has disappeared). A mixture of 0.10 mol (7.9 g) of pyridine and 20 ml of THF is added over 15 min. The reaction mixture is stirred for 1 h at −90 °C (Note 1) then a mixture of 30 ml of dry HMPT (see Chap. I–2), 10 ml of THF and 4 g of pyridine is added over 10 min with cooling to −95 °C. This temperature is maintained for 90 min. A solution of 0.17 mol (15 g) of anhydrous lithium bromide in 40 ml of THF (Note 2) is then added with cooling to between −80 and −90 °C. A rather viscous suspension is formed. After 10 min a solution of 0.12 mol (30 g) of iodine in 50 ml of THF is added with vigorous stirring (Note 3), while keeping the temperature between −50 and −90 °C. Five minutes after this addition a solution of 10 g of sodium thiosulfate ($Na_2S_2O_3 \cdot 5aq$) in 200 ml of water is added. The mixture is warmed up to 0 °C with vigorous stirring. The light-yellow organic layer is separated from the dark aqueous layer and is washed four times with 50 ml portions of water, the washings being added to the original aqueous layer. The combined aqueous layers are extracted 7 times with small portions of ether. Each ethereal layer is washed twice with 30 ml portions of water and the washings are returned to the bulk aqueous solution before the next extraction with Et_2O is carried out. The combined solutions are dried by stirring (or shaking) with 50 g of anhydrous potassium carbonate. After filtration and subsequent rinsing of the desiccant with Et_2O, the solvents are removed in a water-pump vacuum, using a heating bath of 30–35 °C (Note 4). About 17 g of a brown residue remains, mainly solid. After a rough distillation through a 10-cm Vigreux column (b.p. ~80–100 °C/15 mm) using an air condenser, 14 g of crystalline material is obtained. Recrystallization from a mixture of Et_2O and pentane gives pure (^{1}H-NMR) 4-iodopyridine in 50 % yield.

Notes

1. Too vigorous stirring gives rise to splashing of the solution in the upper part of the flask, where decomposition (brown colour) can occur. It is advisable to insulate this part of the flask with cotton wool.
2. The commercial salt (~50 g), which may contain small amounts of water, is placed in a 1-l round-bottomed flask and evacuated at 1mmHg. The flask is then heated for 30 min at 150 °C.
3. Vigorous stirring means that not only the stirrer but also the reaction mixture is rotating fast.
4. A too rapid distillation of the solvents may give rise to a loss of product.

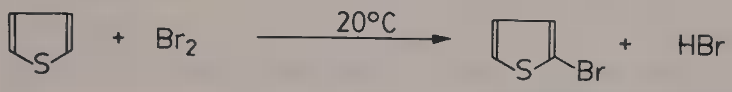
5.47 3-Bromothiophene



Remarks concerning the literature procedure:
The published procedure [142] uses chloroform as a solvent for the bromination. We used a small amount of dichloromethane, which can be easily removed by evaporation *in vacuo*. The authors heat the reaction mixture with alcoholic potassium hydroxide without having removed the solvent chloroform: this reacts

very vigorously with the base. The reason for the treatment with base is not mentioned but it may serve to destroy some adduct of Br_2 and thiophene. We carried out the synthesis with six moles of thiophene and treated the reaction mixture (after removal of the dichloromethane) for 1–2 h with a solution of 3 mol of KOH in 500 ml of ethanol. Our yield and purity were similar to the ones in the organic synthesis procedure. It seems to be essential to purify the tribromothiophene by distillation.

5.48 2-Bromothiophene



Scale: 2 molar.

Apperatus: Chap. I, Fig. 1, 1 l; the thermometer and outlet are replaced by a reflux condenser. The escaping hydrogen bromide is absorbed by water.

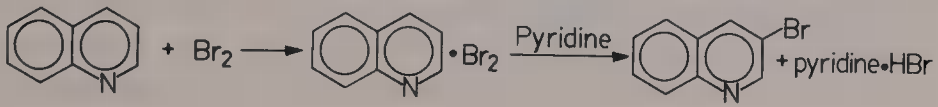
Introduction

Thiophene undergoes electrophilic substitution much more readily than benzene. The initial substitution product is 2-bromothiophene, but the rate of further substitution in the 5-position is comparable to that for the mono-substitution. It is therefore not possible to prevent formation of 2,5-dibromothiophene. The *addition* of Br_2 to the double bond, which leads to a decrease of the number of molecules (negative entropy) becomes more favourable at lower temperatures and we found that at −100 °C thiophene reacts very rapidly with two moles of bromine to give the adduct. Cooling should therefore not be applied if electrophilic substitution is the intended reaction.

Procedure

Bromine (2.0 mol, 320 g) is added to a mixture of 2.0 mol (168 g) of thiophene and 150 ml of dichloromethane without external cooling over 2 h. After an additional 10 minutes (the reaction is very fast) a solution of 30 g of sodium hydroxide in 200 ml of water is added with vigorous stirring. The layers are separated, after which one extraction with 50 ml of dichloromethane is carried out. After drying over $MgSO_4$ the solvent is removed *in vacuo* and the remaining liquid carefully distilled through a 40-cm Widmer column to give 2-bromothiophene, b.p. 44 °C/15 mm, n_D^{20} 1.5862, in 42 % yield. The residue consists mainly of 2,5-dibromothiophene.

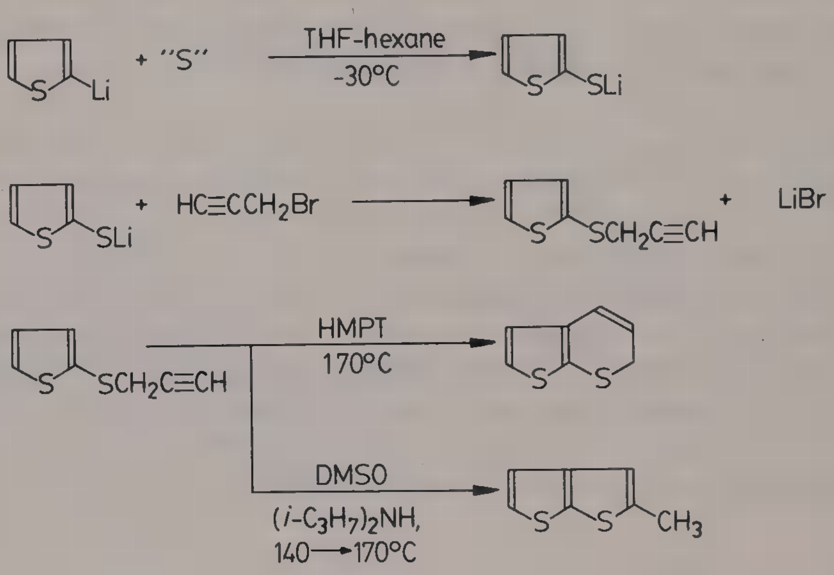
5.49 3-Bromoquinoline



The procedure of Eisch [156] for 3-bromoquinoline makes it possible to prepare this compound in "convenient" quantities. An addition period of 3 h for pyridine, followed by reflux for some 20 h, is prescribed. We added pyridine at a temperature close to the b.p. of CCl_4 and observed a weakly exothermic reaction. After a period of 1 h reflux the reaction mixture was worked up. The light-yellow CCl_4 solution was decanted from the brown viscous mass. This was rinsed twice with hot CCl_4 (50–60°). Careful distillation gave 3-bromoquinoline, b.p. 140–5/15 mm, n_D^{20} 1.6628, in 72 % yield. Our period of reflux may have been somewhat short, but in any case we believe that it is not necessary to heat the mixture for 20 h. Also the pyridine can be added in a shorter time.

5.50 2-Thienyl Propargyl Sulfide, 2H-Thieno(2,3-b)Thiopyran and 2-Methylthienothiophene

(compare Refs. [155] and [157])



Scale: 0.3 molar for propargylthiothiophene; 0.2 molar for the thermal rearrangements.

Apparatus: Chap. I, Fig. 1: 1 l for propargylthiothiophene, 250 ml for the rearrangements.

Procedure

A solution of 0.30 mol of 2-thienyllithium in 210 ml of hexane and 160 ml of THF is prepared from 0.30 mol of BuLi and 0.33 mol (27.7 g) of thiophene (Exp. 2). The solution is cooled to −40 °C and 0.3 at, (9.6 g) of dry, powdered sulfur is introduced in small portions over 15 min, while keeping the temperature between −30 and −40 °C. After an additional 20 min (at −20°) 50 ml of methanol is added to the light-yellow solution, then propargyl bromide (41.7 g, 0.35 mol) is added over 15 min. During this addition the temperature is allowed to rise from about 0° to 40 °C and is kept at that level for an additional half hour. The reaction mixture is then poured into 1 l of ice water and the product is isolated by extraction with Et_2O, washing of the extracts with water, drying over $MgSO_4$, followed by distillation through a short Vigreux column (whereby the temperature of the heating bath is maintained at less than 100 °C). Propargylthiothiophene, b.p. ca. 50 °C/0.5 mm, n_D^{20} 1.605, is obtained in 88 % yield.

To prepare *thienothiopyran*, a mixture of 0.08 mol (12.3 g) of propargylthiothiophene and 50 ml of purified HMPT (chap. I-2) is heated to 170 °C and stirring is carried out at a low rate (ca. 20 r.p.m.). An exothermic reaction starts and occasional cooling (temporarily stirring at a higher rate, or dipping the reaction flask for a few seconds in a water bath may be sufficient) is necessary to keep the temperature below 180 °C. When the reaction has subsided, another portion of 5 g is added. The remainder of the 0.20 mol is added at intervals of about 5 min. The mixture is heated for an additional 15 min at 170 °C to complete the rearrangement. After cooling to room temperature, the mixture is diluted with 300 ml of water and the product is extracted with Et_2O. The organic solutions are washed five times with water to remove the HMPT. After drying over $MgSO_4$, the ether is removed under reduced pressure and the remaining liquid distilled through a 20 -cm Vigreux column to give thienothiopyran, b.p. ca. 130 °C/15 mm, n_D^{20} 1.678, in 90 % yield.

2-Methylthienothiophene is prepared as follows. Propargylthiothiophene (30.8 g, 0.20 mol) is dissolved in 150 ml of dry DMSO (chap. I-2) and 2 ml of diisopropylamine is added. The mixture is heated for 45–60 min at 140 °C, stirring being carried out at a low (10–15 r.p.m.) rate. Continuous monitoring of the temperature is required! After this period the mixture is gradually heated to 170 °C, then it is cooled to room temperature and 15 g of *t*-BuOK is added to destroy the thienothiopyran which is present in relatively small amounts. During this operation (ca. 5 min), the temperature of the reaction mixture is kept between 35 and 40 °C. After an additional 20 min the very dark mixture is poured into 1 l of ice water and at least five extractions with a mixture of Et_2O and pentane are carried out (separation may be rather difficult). The combined organic solutions are washed three times with water and are subsequently dried over anhydrous potassium carbonate.

After concentration of the solution *in vacuo*, the remaining dark liquid is distilled through a 30-cm Vigreux column to give 2-methylthienothiophene, b.p. 118 °C/15 mm, n_D^{20} 1.639, in 55 % yield.

5.51 Methyl Dithiocarbamate

$$2\,NH_3 + CS_2 \xrightarrow[40\,°C]{THF} NH_2CSSNH_4\downarrow$$

$$NH_2CSSNH_4 + (CH_3)_2SO_4 \xrightarrow[20\,\rightarrow\,55\,°C]{H_2O} NH_2CSSCH_3 + CH_3NH_3{}^+HSO_4{}^-$$

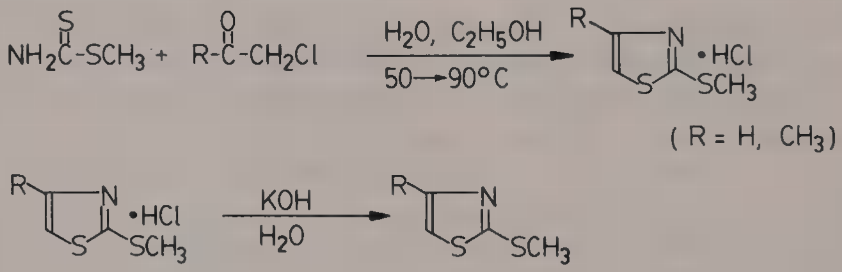
Scale: 1.0 molar.

Apparatus: 2-l three-necked round-bottomed flask, gasinlet tube, mechanical stirrer and thermometer-outlet combination.

Procedure

Ammonia (dried by passing the gas through a 40 cm long tube, filled with KOH pellets) is led through a mixture of 400 ml of dry THF and 1.2 mol (91.2 g) of carbon disulfide with vigorous stirring. The flow of gas is continuously adjusted so that a weak flow leaves the flask. The temperature rises gradually and a yellowish-white precipitate is formed after a few minutes. Occasional cooling is applied to keep the temperature between 40 and 50 °C. After 1 and 1.5 h no more heat is evolved and the temperature begins to drop. The introduction of ammonia is continued for another half hour. The excess of ammonia dissolved in the THF is then removed by distilling off ca. 150 ml of this solvent on the rotary evaporator. Water (200 ml) is added to the remaining suspension. Dimethyl sulfate (126 g, 1.0 mol) is then added with vigorous stirring, while allowing the temperature to rise to 50 °C and stirring at this temperature is continued for another half hour. The layers are then separated and the aqueous layer extracted four times with Et_2O. The organic layer and the extracts are dried (without previous washing) by shaking or stirring during 5 min with about 100 g of $MgSO_4$. After filtration, and rinsing of the dessicant with Et_2O the solvents are removed *in vacuo*, the last traces by evacuation with the oil pump (0.5–1 mmHg). A light-yellow liquid remains, which may solidify on standing at 20 °C. The yield of relatively pure methyl dithiocarbamate (based upon dimethyl sulfate) is at least 95 %.

5.52 2-Methylthio-Thiazole and 4-Methyl-2-Methylthio-Thiazole



Scale: 1.0 molar.

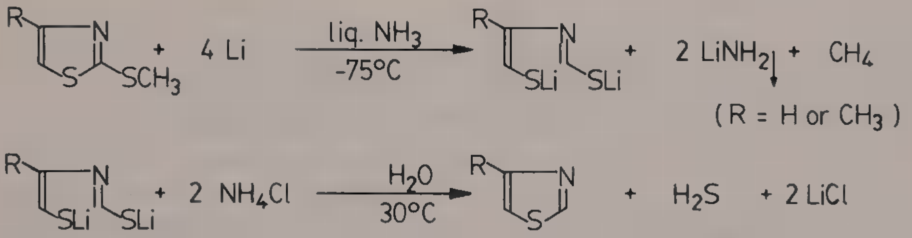
Apparatus: 1-l round-bottomed, three-necked flask, stopper, mechanical stirrer and thermometer-vent combination: in the last stage of the reaction this is replaced with a reflux condenser.

Procedure

1.0 mol (107 g) of methyl dithiocarbamate (see Exp. 51), 1.1 mol of chloroacetaldehyde (as a 40 to 50 % aqueous solution) or chloroacetone (freshly distilled) and 200 ml of 96 % ethanol are placed in the flask. After addition of 3 ml of concentrated hydrochloric acid the mixture is warmed to 58 °C and stirring is then continued at a very low rate (5–10 rpm). A weakly exothermic reaction may be observed and the temperature rises gradually: if a level of 70 °C is reached within 5–10 min, occasional cooling may be necessary. After ca. 30 minutes the alcohol may start boiling, at this point the thermometer is replaced by a reflux condenser. When spontaneous refluxing has stopped (or if it does not occur at all), the light-brown solution is heated under moderate reflux for 15 min. After cooling to 40 °C, the greater part of the ethanol is distilled off on the rotary evaporator, the distillation is stopped when ca. 200 ml of liquid have been collected in the receiver. The brown viscous solution is cooled to 0 °C and a solution of 70 g of KOH in 150 ml of water is added in portions, while keeping the mixture between 0 and 15 °C. A brown lower layer is formed as soon as the stirring is stopped. The product is extracted five times with dichloromethane (40-ml portions are sufficient). The combined solutions (no washing is carried out) are dried over anhydrous potassium carbonate and subsequently concentrated *in vacuo*. Distillation of the remaining oil through a 30-cm Vigreux column gives 2-methylthio-thiazole, b.p. ca. 50 °C/0.5 mm, n_D^{20} 1.6080, in 87% yield and 4-methyl-2-methylthio-thiazole, b.p. ca. 55 °C/0.5 mm, n_D^{20} 1.5824, in 90% yield.

5.53 Thiazole and 4-Methylthiazole

(compare Ref. [162])



Scale: 0.4 molar.

Apparatus: Chap. I, Fig. 1, 2 l.

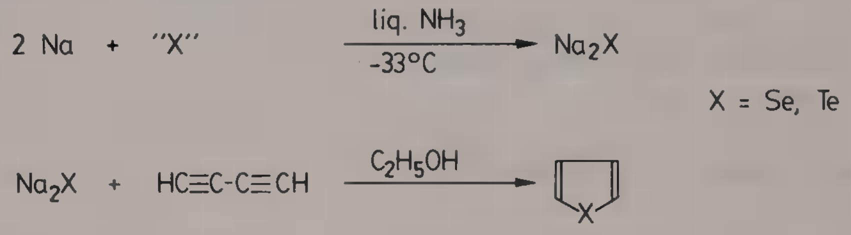
Procedure

A flask containing 700 ml of liquid ammonia, 0.40 mol (52.4 or 58.0 g) of the methylthio-thiazoles (Exp. 52) and 150 ml of Et_2O are cooled (occasional cooling with liquid nitrogen, care being taken that the ammonia does not solidify on the bottom of the flask) to −75 °C. The thermometer is removed and lithium is directly cut into the flask (precut Li reacts sluggishly, because the surface is covered by oxide and nitride) while nitrogen is introduced. The reaction is very vigorous so that the metal has to be introduced in amounts of not more than 3 g, at intervals of ca. 10 min. During the addition of the metal the temperature of the reaction mixture is kept between −70 and −78 °C. When, after addition of slightly more than the stoichiometric amount (11.2 g) of metal, the blue colour persists, the temperature is allowed to rise. The greater part of the ammonia is removed by placing the flask in a water bath at 35 °C. The last traces of ammonia are removed by evacuating the flask (water pump) while continuing the heating. After this operation nitrogen is admitted to the flask and 150 ml of water is added to the remaining solid mass.

Vigorous stirring is necessary to effect dissolution of the solid crust in the flask. Ammonium chloride (70 g), dissolved in 200 ml of water is then added and stirring is continued for 1.5 h at ca. 35 °C. The thiazoles are then extracted with Et_2O; frequent extraction (at least 15 times in the case of thiazole) with small portions is necessary, because the thiazoles are completely soluble in water. After drying the solutions over potassium carbonate, the ether is carefully distilled off through a 40 -cm Widmer column. Distillation of the remaining liquids gives thiazole, b. p. ca. 40 °C/40 mm, n_D^{20} 1.5398, in 79 % yield, and 4-methylthiazole, b. p. ca. 55 °C/40 mm, n_D^{20} 1.5243, in 87 % yield.

5.54 Tellurophene and Selenophene

(compare Refs. [130, 158, 216])



Scale: 0.50 molar (Na_2X).

Apparatus: For the preparation of Na_2X: 2-l three-necked, round-bottomed flask with mechanical stirrer; for the further equipment see below.

Procedure

Diacetylene (35 g, 0.7 mol) is made from 1,4-dichloro-2-butyne and a mixture of potassium hydroxide, water and DMSO, as is described in Refs. [6, 7]. The gas is condensed in 50 ml of cold (−30 to −40 °C) absolute ethanol. For this amount of diacetylene about 1 mol (123 g) of 1,4-dichloro-2-butyne (see Refs. [6, 7]) is required. Sodium (23 g, 1.0 mol. added in 0.5–1 g pieces) is dissolved in 1 litre of liquid ammonia. Ten minutes after the addition, red selenium powder or grey tellurium powder (Note 1) is added through the third neck (Note 2) in portions of 0.5–1 g at intervals of about 5 seconds while purging with nitrogen (0.5 l/min). The blue colour of the dissolved sodium disappears when the stoichiometrical amount (39.5 g Se or 63.8 g Te) of the elements has been added. The flask is then placed in a water bath at 35–40 °C and the white suspension is concentrated to a volume of ca. 100 ml. During this evaporation procedure the suspension is stirred at a moderate rate and the introduction of nitrogen is continued (200–300 ml/min). Absolute ethanol (300 ml) is added to the remaining thick suspension and the flask is fitted with a thermometer-outlet combination. The resulting brown solution is heated on a bath at 50–55 °C, while continuing the introduction of nitrogen (Note 2). The heating bath is removed as soon as the temperature of the suspension has risen to 30 °C (Note 3). In the case of the preparation of selenophene the suspension is cooled to −20 °C (with temporary increase of the rate of introduction of nitrogen,) and the solution of diacetylene is added over 30 min in five equal portions. The cooling bath is then removed and the temperature allowed to rise to 20 °C or higher.

The conversion is completed by heating the reaction mixture for an additional period of 1 h at 40 °C.

The reaction of sodium telluride with diacetylene is carried out at 10 to 20 °C (occasional cooling, addition of diacetylene solution in 5 portions over 15 min). DMSO (40 ml) is then added and stirring is continued for an additional hour while heating the mixture to 30–40 °C. In both cases the work-up is carried out by adding 1.5 l of ice-water to the reaction mixtures and extracting six times with 3:1 mixture of pentane and ether (portions as small as possible). Some difficulties may be encountered in the separation of the layers because of the formation of some polymeric substance or elemental tellurium. The combined organic solutions are washed three times with water and then dried over $MgSO_4$. In the case of selenophene the solvents are distilled off at normal pressure through a 40-cm Widmer column. When (at a bath temperature of 80 °C) the distillation has practically stopped, the remaining brown liquid is cooled to about 40 °C and then subjected to vacuum distillation at 40–50 mmHg. Selenophene, b.p. ~40–55 °C, n_D^{20} 1.5645, is obtained in 48–55 % yields.

In the case of tellurophene, the organic solution is concentrated *in vacuo* and the remaining liquid distilled through a 40-cm Vigreux column. Tellurophene, b.p. 45 °C/20 mm, n_D^{20} 1.680, is obtained in 64 % yield.

Notes

1. The black modification of selenium ("selenium nigrum") reacts much less smoothly. Black tellurium powder reacts very slowly: a possible explanation for this inert behaviour is that this Te, obtained by precipitation from solutions of tellurium salts, is readily inactivated by formation of oxide on the particles.
2. The reaction with the elements is very vigorous and the stream of escaping ammonia together with the flow of N_2 minimizes the entrance of air. Traces of oxygen cause formation of a blue to purple colour of disodium ditelluride, which persists after the sodium has reacted.
3. The suspension re-appears when all ammonia has evaporated from the mixture.

5.55 Methyl Thiocyanate (compare Ref. [6])

$$(CH_3)_2SO_4 + KSCN \xrightarrow{H_2O} CH_3SCN + K(CH_3)SO_4$$

Procedure

Potassium thiocyanate (116.4 g, 1.2 mol) is dissolved in a minimum of water (ca. 50 ml), while heating at 50–60 °C. Dimethyl sulfate (126 g, 1.0 mol) is added with vigorous stirring over 15 min. After the addition, the mixture is heated for 30 min at 80 °C. After cooling to room temperature, a small (ca. 30 ml) amount of Et_2O is added and the upper layer is separated as completely as possible. After drying over $MgSO_4$, the product is distilled: b.p. 40 °C/15 mm, n_D^{20} 1.4681, yields are between 70 and 85 %. Yields are considerably lower when too much water is added for the dissolution of KSCN.

5.56 Sulfur Dichloride (compare Ref. [159])

$$2\,''S'' + Cl_2 \rightarrow S_2Cl_2$$

$$S_2Cl_2 + Cl_2 \xrightarrow{Fe} 2\,SCl_2$$

Procedure

A mixture of 96 g (3 at) of powdered sulfur and 5 g of iron powder is placed in a 500-ml one-necked round-bottomed flask. After mixing the powders, the inlet tube is placed about 0.5 cm under the surface of the powder. Chlorine is introduced at such a rate that it is directly absorbed. After a few min the powder has changed into a heavy yellowish liquid. The end of the inlet tube is then placed at the bottom of the flask, which is cooled in a water bath at 10 to 15 °C. The introduction of gas is continued until the weight of the flask + contents has increased by about 210 g. To the red liquid is then added 3 ml of phosphor trichloride. The flask is then fitted with a 40-cm Vigreux column connected to a condenser and a receiver. After a volatile fraction (a mixture of chlorine and sulfur dichloride) the product distilling between 58 and 65 °C (760 mmHg) is collected separately in a receiver cooled at 0 °C. The high-boiling residue is mainly sulfur *mono*chloride. The yield of sulfur dichloride varies between 60 and 70 %. The compound must be stored in thoroughly dried and well-closed bottles. Paraffin-based grease (no silicone) should be used for the glass stopper. During storage disproportionation into Cl_2 and S_2Cl_2 occurs. It is therefore necessary to distill the compound from a small amount of PCl_3 prior to use. Only the fraction between 58 and 65 °C is used. During work the same handling precautions as in the case of bromine should be taken.

Chapter VI

Metallated Aromatic Compounds

1. Metallated Aromatic Hydrocarbons

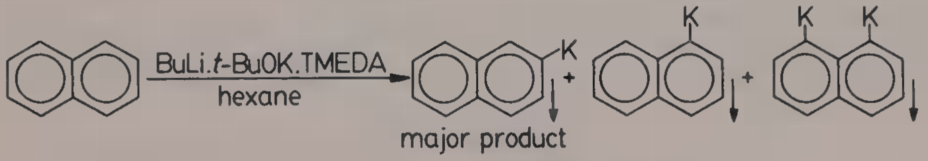
1.1 Deprotonation by Strongly Basic Reagents

The parent hydrocarbons benzene and naphthalene have a poor kinetic acidity and attempts at metallation using alkyllithium in THF or Et_2O result only in attack on the solvent. Quantitative conversion into phenyllithium can be effected however, if a large excess of benzene is allowed to react with BuLi · TMEDA in hexane at reflux temperature [9, 167]. In the case of naphthalene this metallation procedure has no practical importance, because 1- and 2-naphthyllithium are produced in comparable amounts, along with some dimetallated naphthalene ([9], compare also [160]).

A convenient way to prepare phenylpotassium consists of reacting an equimolar mixture of BuLi · *t*-BuOK and TMEDA with an excess of benzene in hexane. The metallation is complete within 1 hour at −20 °C [9].

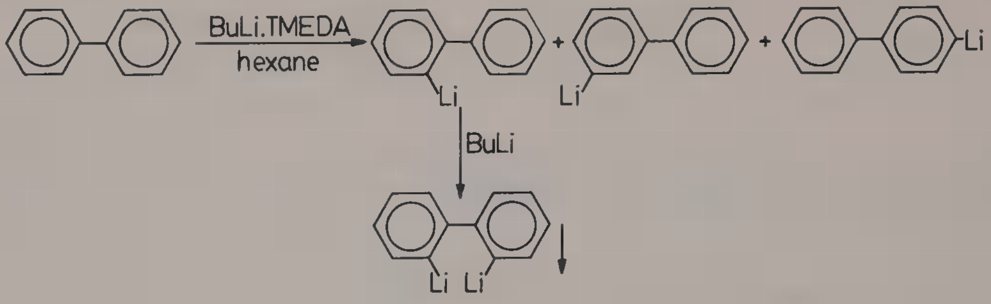
$$\text{Ph—H} \xrightarrow[\text{hexane}]{\text{BuLi}\cdot t\text{-BuOK}\cdot\text{TMEDA}} \text{Ph—K}$$

This ternary mixture gives more satisfactory results than the binary mixture of *t*-BuOK and BuLi, which is insoluble in alkanes and therefore requires the use of a very large excess of benzene [235]. Naphthalene and the cocktail of the three bases produce a 85:15 mixture of 2-naphthylpotassium and the 1-isomer in a reasonable yield, together with some 1,8-dipotassionaphthalene [9]. As 2-naphthyl derivatives in general are not easily accessible by the other methods, the metallation with BuLi · *t*-BuOK · TMEDA has some practical importance.

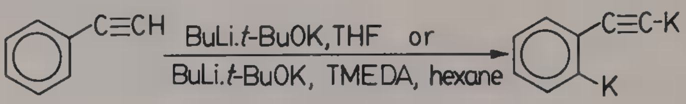


Metallation of naphthalene with BuLi in THF and Et_2O has been reported to give comparable amounts of the two mono-lithium compounds in a modest yield [160].

The metallation of biphenyl with BuLi or BuLi · TMEDA, as reported in an early paper [163], leads to mixtures of comparable amounts of *o*-, *m*- and *p*-lithiobiphenyl. A recent paper dealing with the *o*,*o*-dilithiation of biphenyl [165] reports synthetically useful results. Although the initial mono-metallation presumably affords a mixture of the three mono-metallated biphenyls, the excess of BuLi may select the *ortho*-isomer as the substrate for attack in the second ring:

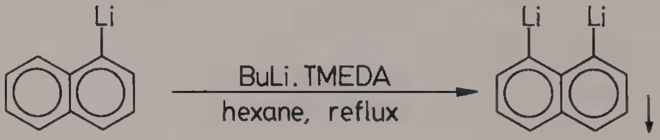


A similar triggering mechanism might explain the unexpectedly easy ring metallation of metallated phenylacetylene with BuLi · *t*-BuOK or BuLi · *t*-BuOK · TMEDA [21, 46]:



The ring metallation is completely regiospecific.

1,8-Dilithionaphthalene has been obtained in a good yield by heating 1-lithionaphthalene with BuLi · TMEDA in hexane [166]:



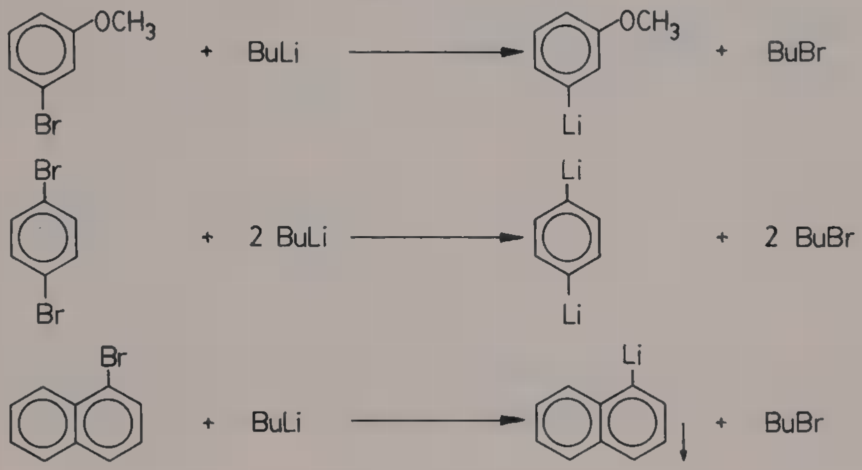
1.2 Bromine-Lithium Exchange

Treatment of bromoarenes with butyllithium generally proceeds smoothly and quantitatively [4, 168]. The halogenated arenes are accessible by electrophilic substitution or diazotation. The exchange reaction can be carried out in Et_2O as well as in THF but in the latter solvent the reaction is considerably faster. However, Et_2O may be preferred in some syntheses, since in this solvent the undesired alkylation reaction between ArLi and butyl bromide is relatively slow.

$$\text{Ar—Br} + \text{BuLi} \xrightarrow{\text{THF or } Et_2O} \text{ArLi} + \text{BuBr}$$

This circumstance offers the possibility for subsequent coupling of the lithiated arenes with paraformaldehyde (introduction of a CH_2OH group) or with oxiranes (introduction of a C—C—OH function). Reaction of organolithium derivatives RLi with paraformaldehyde in most cases proceeds at acceptable rates only at temperatures in the region of +20 °C, irrespective of whether the solvent is THF or

Et_2O, and also irrespective of the nature of R. In THF most aryllithium compounds react smoothly with butyl bromide at about +20 °C. Consequently Et_2O is the solvent of choice, if the aryllithium, produced in the exchange reaction with BuLi, is to be reacted with paraformaldehyde. The same holds for subsequent reactions with epoxides, which in this less polar solvent are assisted by interaction between lithium and the oxygen in the ring. In THF the rates of butylation and hydroxyalkylation with the epoxide are comparable [9]. The exchange reaction with BuLi provides access to aryllithium derivatives, that cannot be generated specifically by deprotonation. The following examples are illustrative:



1.3 Reaction of Arene Derivatives with Metals

Solutions of phenyllithium in Et_2O and of phenylmagnesium bromide in Et_2O or THF can be obtained by reaction of bromobenzene with lithium chips (containing 1–2 % of Na) or magnesium turnings. The efficiency with respect to bromobenzene may be at least 90 to 95 %, if the reactions are carried out carefully, using pure and dry reagents and solvents. The usual by-product is biphenyl. Grignard- and lithium derivatives of substituted bromoarenes (e.g. bromotoluene) may be obtained in a similar way.

2. Metallated Hetero-Substituted Arenes

2.1 Deprotonation by Strongly Basic Reagents

A number of hetero atoms or hetero-atom containing substituents can exert a directing influence during interaction with a basic reagent, giving rise to a predominant or even specific deprotonation of a carbon atom that is vicinal to the one bearing the substituent. This selectivity or specificity may be either the consequence of some activating or coordinating effect of the substituent, or of a combination of both effects. The sequence of this *ortho*-metallation and reaction with an electrophilic reagent constitutes one of the most versatile synthetic operations in the chemistry of aromatic compounds. Since excellent reviews [1, 171, 186–188] on this subject have been published, we suffice in giving a brief survey of the most important metallations in this section. It is possible to distinguish two kinds af activating substituents:

a) Substituents that exert their influence through coordination with the metal atom of the base. In the complex so formed the base is in the vicinity of the *ortho*-proton, which is abstracted in the next step.
b) Substituents with an electron-withdrawing inductive effect. This effect is felt most strongly by the *ortho*-proton.

Very characteristic examples of type *a* are —$CH_2N(alkyl)_2$ and CH_2O^- groups, and of type *b* F and CF_3. Many substituents, however, possess both coordinating and electron-withdrawing capacities: if both are pronounced, as in *N*,*N*-disubstituted acid amide groups $C(=O)NR^1R^2$ and 2-oxazolines, the *ortho*-metallation is particularly smooth. Thioether (RS) functions do not have a strong inductive effect, neither is there a strong tendency to coordinate with the base through the alkali metal. The perfectly specific, and relatively smooth *ortho*-metallation of *t*-butyl phenyl sulfide [169] by BuLi · TMEDA in hexane is not satisfactorily explainable on the basis of inductive or coordinating effects. The good polarizability of sulfur might be invoked to explain the somewhat surprising results with the phenyl sulfide.

On the basis of literature data [171–173] and our own experience [9] we can subdivide the *ortho*-directing substituents as follows:

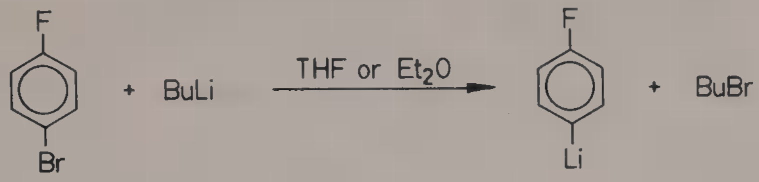
1. Strong activators: —C≡N, —SO_2NR_2, —$OCONR_2$, —$CONR_2$, 2-oxazoline.
2. Moderate activators: —CH_2NR_2, —F, —CF_3, —OCH_3, —OCH_2OCH_3, —SR.
3. Weak activators: —CH_2OLi, —$CH(OLi)NR_2$ (protected formyl groups), —NR_2.

This summary relates to kintic effects, but also corresponds roughly to thermodynamic effects (pK) [170]. Although the lowering of the pK value caused by some groups (e.g. —C≡N, —$OCONR_2$) may be significant, the obvious bases for *complete* deprotonation are alkyllithium reagents.

The metallation of naphthalene derivatives has been studied much less extensively than that of phenyl compounds [1]. It has appeared that treatment of the 1-substituted derivatives with alkyllithium bases can result in metallation on C-atom 8 as well as on C-atom 2. Amino groups direct the metallation predominantly towards the 8-position, while treatment of 1-methoxynaphthalene with BuLi gives mainly 2-naphthyllithium. 2-Substituted naphthalenes in general afford mixtures of 1- and 3-metallated intermediates.

2.2 Halogen-Lithium Exchange

Until about 1960 the reaction between aryl halides (in particular bromo compounds) and alkyllithium was the most important method of generating aryllithium intermediates [4]. Although many metallated derivatives are easily obtainable *via* *ortho*-deprotonation, the bromine-lithium exchange method has not lost its significance: it is the only way to generate a lithium derivative having one or more substituents and the metal in a relative position other than *ortho*, e.g.:



Some specially substituted lithiated aryl compounds, not accessible by deprotonation, e.g. *ortho*-lithionitrobenzene [36] and *ortho*-lithiochlorobenzene [175], have been generated by Br—Li exchange at very low temperatures.

3. Experimental Procedures

All temperatures are internal, unless indicated otherwise.

3.1 General Procedure for Bromine-Lithium Exchange

$$\text{Ar—Br} + \text{BuLi} \xrightarrow{\text{THF or Et}_2\text{O}} \text{Ar—Li} + \text{BuBr}$$

Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction
A number of lithiated arenes can be conveniently prepared by replacement of bromine in the corresponding bromoarenes by lithium. The most frequently applied reagent for this exchange reaction is *n*-BuLi, and Et_2O or THF are generally used as solvents. In THF the reactions proceed more smoothly than in Et_2O, and for this reason it may be preferable to use the former solvent. In some cases, however, Et_2O is the solvent of choice: reactions with epoxides and paraformaldehyde are relatively slow, and in THF the butyl bromide formed in the exchange reaction seriously competes with the epoxide and reacts much faster than paraformaldehyde. Also for thiolations with elemental sulfur Et_2O seems more suitable than THF, since the chance of subsequent reaction of the arenethiolate with BuBr is less great.

Procedure
a) Et_2O as solvent (examples 1-bromonaphthalene, *o*-, *m*- and *p*-$BrC_6H_4OCH_3$, *p*-F—C_6H_4Br).
The bromoarene (0.10 mol) is added to a solution of 0.105 mol of butyllithium in 74 ml of hexane and 80 ml of Et_2O, cooled to ca. −25 °C. After this addition, which

is carried out over 10 min, the solution (suspension in the case of bromonaphthalene) is stirred for an additional 20 min at +10–15 °C (Note 1).

b) THF as solvent (examples 1-bromonaphthalene, *o*-, *m*- and *p*-$BrC_6H_4OCH_3$, *o*- and *p*-FC_6H_4Br, *p*-dibromobenzene, *o*-$BrC_6H_4CH_3$).

THF (75 ml) is added to a solution of 0.11 mol of butyllithium in 77 ml of hexane with cooling to below 0 °C. The mixture is cooled to −90 °C and 0.10 mol of bromoarene (or 0.05 mol (11.8 g) of *p*-dibromobenzene dissolved in 15 ml of THF) is added over 5 min with cooling to between −80 and −90 °C. The cooling bath is removed and the temperature is allowed to rise to −50 °C (Note 1) and stirring is continued (−50 °C) for 15 min. Clear solutions or fine suspensions are formed, in the case of bromonaphthalene however, a thick yellowish suspension is obtained, while 1,4-dilithiobenzene also forms a (white) suspension.

To prepare *p*-LiC_6H_4Br, a solution of 0.10 mol of butyllithium in 70 ml of hexane is added over 10 min to a solution of 0.10 mol (23.6 g) of *p*-dibromobenzene in 90 ml of THF. During this addition the temperature is kept between −80 and −90 °C. After removing the cooling bath, the temperature is allowed to rise to −50 °C. A white suspension is formed (Note 2). This reaction has also been carried out in Et_2O at room temperature [168, 220].

Notes

1. It is advisable to carry out derivatization reactions as soon as possible: particularly in THF too much delay may give rise to reduced yields owing to reaction of butyl bromide with aryllithium. In most cases this alkylation causes an observable heat effect when the temperature is allowed to reach −10 °C; in the case of *o*-$LiC_6H_4OCH_3$, however, this reaction is markedly slower. *o*-LiC_6H_4F eliminates lithium fluoride at temperatures above −40 °C [221].
2. In general this inversed-addition procedure in THF seems to involve the risk of a "Würtz"-coupling when the temperature is not kept sufficiently low:

$$BuLi + C_4H_9Br \rightarrow C_8H_{18} + LiBr$$

3.2 Derivatization Reactions with Aryllithium Obtained by Br—Li Exchange

Reaction of the aryllithium compounds of Exp. 1 with reactive electrophiles such as CH_3SSCH_3, SCl_2, $Me_2N{-}C({=}O)Cl$ and $CH_3N{=}C{=}S$ are carried out under conditions similar to those prescribed for the derivatization of furyllithium and thienyllithium (Chap. V, Exp. 23, 28, 35, 38). The desired products are obtained in good (SCl_2, $Me_2NC({=}O)Cl$) to excellent (CH_3SSCH_3, $CH_3N{=}C{=}S$) yields. Some of the carboxamides and thioamides can be purified (after distillation) by crystallization from Et_2O-pentane mixtures.

3.3 Reaction of Aryllithium with Carbon Disulfide and Subsequent Methylation [9]

$$p\text{-Li—C}_6\text{H}_4\text{—F} + \text{CS}_2 \xrightarrow[\text{CuBr, LiBr}]{\text{THF-hexane}} p\text{-F—C}_6\text{H}_4\text{—CSSLi} \xrightarrow{\text{CH}_3\text{I}}$$

$$p\text{-}F\text{—C}_6\text{H}_4\text{—CSSCH}_3$$

$$o\text{-Li—C}_6\text{H}_4\text{—OCH}_3 + \text{CS}_2 \xrightarrow{\text{id.}} o\text{-CH}_3\text{O—C}_6\text{H}_4\text{—CSSLi} \xrightarrow{\text{CH}_3\text{I}}$$

$$o\text{-CH}_3\text{O—C}_6\text{H}_4\text{—CSSCH}_3$$

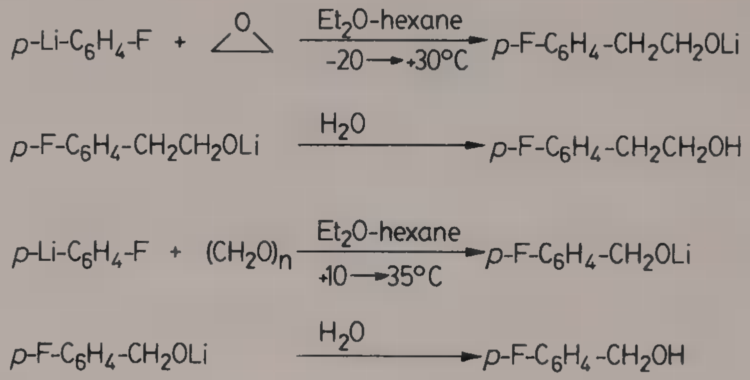
Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction (compare also Exp. 24 of Chap. V).
Whereas interaction between 2-thienyllithium and 2-furyllithium and carbon disulfide in THF affords the corresponding dithioates RCSSLi as the predominant products, aryllithium compounds seem to attack mainly on sulfur with formation of arenethiolates and tarry products [9]. If during the addition of carbon disulfide copper bromide is present in the solution, however, the desired formation of Ar—CSSLi does take place and subsequent addition of methyl iodide affords the dithioesters in good yields. Good results are also obtained when using less than stoichiometric amounts of CuBr. We therefore presume that carbon disulfide reacts more easily with the arylcopper intermediate than with aryllithium: copper is subsequently transmitted from the copper dithioate to aryllithium.

Procedure
A solution of 2 g of copper(I)bromide and 4 g of anhydrous lithium bromide in 15 ml of THF is added to a solution of 0.05 mol o-Li—C_6H_4—OCH_3 or p-Li—C_6H_4—F in 38 ml of hexane and 40 ml of THF (prepared as described in Exp. 1), cooled at ca. −50 °C. An almost colourless solution is formed and after an additional 15 min (−45 °C) a mixture of 0.06 mol (4.6 g) of carbon disulfide and 10 ml of THF is added dropwise over 15 min, while maintaining the temperature between −30 and −45 °C. The colour of the mixture becomes very dark. Ten minutes after the addition of carbon disulfide 0.08 mol (11.4 g) of methyl iodide is introduced in one portion. The cooling bath is removed and the temperature is allowed to rise to 15–20 °C. After an additional 15 min the dark mixture is poured into 100 ml of an aqueous solution of 20 g of ammonium chloride and 6 g of alkali cyanide. After vigorous shaking for a few min the solution turns light-brown to red. The aqueous layer is extracted twice with Et_2O. The combined organic solutions are washed with aqueous ammonium chloride and are subsequently dried over $MgSO_4$. After concentration *in vacuo*, the remaining liquid is distilled through a short Vigreux column to give p-F—C_6H_4—$CSSCH_3$, b.p. ca. 90 °C/0.6 mm, n_D^{20} 1.652, and o-CH_3O—C_6H_4—$CSSCH_3$, b.p. ca. 125 °C/0.6 mm, n_D^{20} 1.662, in yields between 75 and 80 %.

3.4 Reaction of *p*-Fluorophenyllithium with Epoxyethane and Paraformaldehyde



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 11.

Introduction
Solutions of aryllithium obtained by bromine-lithium exchange with butyllithium contain butyl bromide. In THF the aryllithium compounds are smoothly alkylated by this alkyl halide at temperatures above −10 °C. However, if Et_2O is used as a solvent, this butylation is much slower. This observation permits successful hydroxyalkylation with epoxides (assisted by coordination between lithium and oxygen) and paraformaldehyde at temperatures between −10 and +35 °C.

Procedure
Epoxyethane (6 g, excess) or dry, powdered paraformaldehyde (4 g, excess) is added to a solution of 0.10 mol of p-Li—C_6H_4—F in Et_2O and hexane (see Exp. 1), cooled to between −20 and 0 °C. In the reaction with epoxyethane the temperature rises immediately, and efficient cooling in a bath with dry ice and acetone is necessary to keep the temperature between 0 and +15 °C. After the exothermic reaction has subsided, the mixture is stirred for an additional half hour at 25 to 35 °C. The reaction with paraformaldehyde shows an observable heating effect between 10 and 20 °C. This reaction is completed by stirring for an additional hour at about 30 °C. In both cases the reaction mixture is worked up by adding 200 ml of ice water and extracting the aqueous layer three times with Et_2O. The combined organic solutions are dried (without washing) over $MgSO_4$ and the residue remaining after evaporation of the solvent in a water-pump vacuum is carefully distilled through a 30-cm Vigreux column. The alcohols are obtained in yields of ca. 80%. Other alcohols RCH_2CH_2OH and RCH_2OH can be prepared in a similar way.

3.5 Phenyllithium from Benzene and BuLi · TMEDA in Hexane

$$\mathrm{Ph{-}H + BuLi \cdot TMEDA \xrightarrow[\text{reflux}]{} PhLi \cdot TMEDA + C_4H_{10}\uparrow}$$

Scale: 0.10 molar.

Apparatus: 500 ml round-bottomed flask, equipped with a reflux condenser. A narrow gas outlet connected to a washing bottle filled with hexane is placed on the top of the condenser. The inlet tube should not dip more than 0.5 cm into the hexane.

Introduction

The poor kinetic acidity of benzene is apparent from the fact that at best traces of phenyllithium are formed if a mixture of benzene and butyllithium in Et_2O or THF is allowed to stand at room temperature for several days or is heated under reflux. Addition of an equivalent amount of TMEDA to a solution of butyllithium in hexane causes the hexameric aggregate to break down into monomers, which form a 1:1 complex with this chelating reagent. Compared to uncomplexed BuLi this monomer is extremely reactive, and in fact its reaction with benzene in refluxing hexane is a very convenient way to prepare solutions of phenyllithium, which of course is complexed with TMEDA. Quantitative conversion of butyllithium can be effected in a short time by using an excess of benzene. THF or Et_2O cannot be used in this metallation reaction, because these solvents are readily attacked by BuLi · TMEDA (cyclofragmentation to ethene in the case of THF and elimination of ethanol from Et_2O). An additional unfavourable effect with Et_2O would be the considerable lowering of the reaction temperature. This method cannot be applied to prepare tolyllithium or xylyllithium, since the methyl groups are metallated much more easily than the aromatic nucleus. In the case of naphthalene mixtures of 1- and 2-naphthyllithium are formed.

Procedure

A solution of 0.105 mol of BuLi in 75 ml of hexane (slight excess to compensate for losses due to traces of moisture and oxygen) is added to a mixture of 0.11 mol (12.8 g) of TMEDA and 0.40 mol (31 g) of benzene (a smaller excess could also give good results). The mixture is heated under reflux for 1.5 h. After about 1 h the evolution of butane has become very slow (Note 1). The light-brown solution is cooled to room temperature. A good impression of the efficiency of the metallation is obtained by successively adding 50 ml of THF and (0.13 mol, 12 g, excess) of dimethyl disulfide at −30 °C, subsequently allowing the temperature to rise to 0 °C and isolating the $PhSCH_3$ *via* aqueous work-up, extraction, etc. The yield of pure $PhSCH_3$, b.p. 75 °C/10 mm, is at least 90%.

Notes

1. In view of the possibility of sucking back the hexane in the last stage of the conversion the inlet tube should not dip more than 0.5 cm into the liquid.

3.6 Phenylpotassium from Benzene, BuLi · *t*-BuOK and TMEDA in Hexane

$$\text{Ph—H} + \text{BuLi} \cdot t\text{-BuOK} \xrightarrow[-25\,^{\circ}\text{C}]{\text{TMEDA, hexane}} \text{Ph—K}\downarrow + t\text{-BuOLi} + C_4H_{10}$$

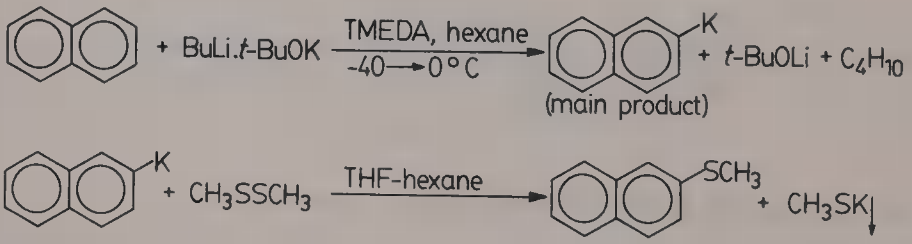
Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 11.

Introduction
It has been reported that benzene is metallated in a very short time by the 1:1-mixture of BuLi and *t*-BuOK using an alkane as solvent [235]. Although this result is a convincing demonstration of the considerable kinetic basicity of the complex, the practical importance is limited. A very large excess of benzene has to be used in order to attain the high rate of conversion. Another unfavourable effect is the insolubility of the basic reagent in the alkane, which might give rise to an incomplete conversion; deposits of phenylpotassium on the reagent (which can be considered as butylpotassium) may render it less reactive. The reagent can be made more soluble by addition of a sufficient amount of THF, or an equivalent amount of TMEDA. A disadvantage of using THF is the fact that this solvent is readily attacked by the strongly basic reagent at temperatures in the region of −60 °C, so that the weakly acidic benzene would experience severe competition from this solvent. The ternary mixture BuLi · *t*-BuOK · TMEDA has a reasonable solubility in alkanes and appears to be stable at temperatures up to about 0 °C. (TMEDA attack starts above 0°), thus providing a long temperature range for the metallation of benzene. Under these conditions the base is used almost quantitatively by benzene (which is present in a moderate excess), as is evident from the excellent yield of $PhSCH_3$ obtained by reaction with CH_3SSCH_3, after addition of THF.

Procedure
To a mixture of 0.3 mol (23.4 g) of benzene, 0.11 mol (12.8 g) of TMEDA, 50 ml of pentane or hexane and 0.11 mol of *t*-BuOK is added over a few minutes a solution of 0.105 mol of BuLi in 74 ml of hexane keeping the temperature below −35 °C. The mixture is stirred for 1 h at −25° and for a further 30 min at −15 °C. A fine suspension is gradually formed. After cooling the suspension to about −50 °C, 60 ml of THF and 0.13 mol (12 g, excess) of dimethyl disulfide are added in sequence. After an additional 10 min the white suspension is treated with water. $PhSCH_3$ is obtained in ca 90% yield (compare Exp. 6).

3.7 Metallation of Naphthalene with BuLi · *t*-BuOK · TMEDA and Subsequent Methylthiolation



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 11.

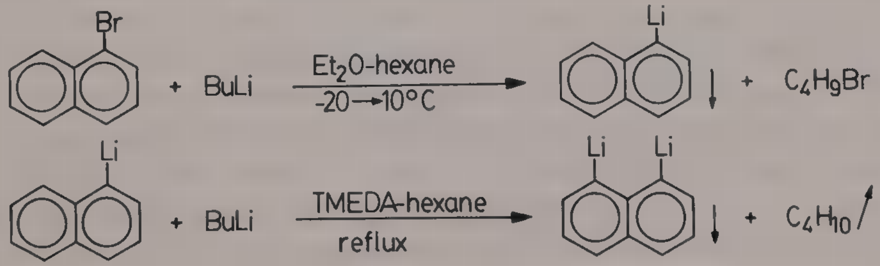
Introduction

Because of its more extended aromatic system naphthalene is expected to be more acidic than benzene, but the difference is hardly observed in synthetic experiments. Treatment of naphthalene with BuLi · TMEDA in hexane results in the formation of comparable amounts of the 1- and 2-lithio compounds and a dilithio derivative (possibly 1,8-) so that this method is not interesting from a synthetic point of view. If the metallation is carried out with the ternary mixture BuLi · *t*-BuOK, TMEDA in hexane at temperatures in the region of −20 °C, subsequent addition of dimethyl disulfide affords a mixture of 1-methylthio-, 2-methylthio- and 1,8-bis(methylthio)naphthalene. The mono- and disubstitution products can be separated by distillation. The favourable ratio of about 15:85, together with the fact that the 2-isomer is solid at room temperature (whereas the 1-isomer is a liquid), permits an easy purification of the predominant product by crystallization. For practical reasons (difficult separation from the products) the use of an excess of naphthalene is avoided (compare the metallation of benzene, Exp. 3), and consequently yields (based on BuLi) are not optimal, since part of the base may react with TMEDA.

Procedure

A solution of 0.11 mol of butyllithium in 77 ml of hexane is added to a mixture of 0.10 mol (11.6 g) of TMEDA, 50 ml of hexane and 0.10 mol (11.2 g) of powdered *t*-BuOK with cooling to below −40 °C. Subsequently a solution of 0.10 mol (12.8 g) of naphthalene in 80 ml of hexane is added with cooling to below −30 °C. The mixture is stirred for 1 h at −25 °C and then for an additional 1.5 h between −10 and −20 °C. The cooling bath is then removed and the temperature is allowed to rise to 0 °C. THF (80 ml) and dimethyl disulfide (12.2 g, 0.13 mol) are successively added with cooling at −40 °C. The yellowish suspension is stirred for an additional 15 min at 0−10 °C, then water (200 ml) is added with vigorous stirring. After separation of the layers two extractions with ether are carried out. The combined organic solutions are washed twice with water and subsequently once with 2N hydrochloric acid. After drying over $MgSO_4$ and concentration of the solution *in vacuo* the remaining liquid is carefully distilled through a 20–30-cm Vigreux column. After a small amount of naphthalene has passed over (b.p. up to ~140 °C/15 mm) and has been collected in the air condenser, the distillation is interrupted and the condenser cleaned. The fraction, distilling between 140 and 160 °C/15 mm (mainly around 150°), and solidifying in the condenser, consists of 2- and 1-(methylthio)-naphthalene in a ratio of ca. 85:15. The yield of this mixture is 65%. The residue (about 4 g) is mainly 1,8-bis(methylthio)naphthalene (compare Exp. 5).

3.8 Preparation of 1,8-Dilithionaphthalene



Scale: 0.10 molar.

Apparatus: For the bromine-lithium exchange Chap. I, Fig. 1, 11; for the introduction of the second lithium atom the flask is equipped with a reflux condenser. The outlet on the top of the condenser is connected with a washing bottle filled with hexane. The inlet tube should not dip more than 0.5 cm into the hexane.

Introduction

The only way to prepare pure 1-naphthyllithium consists in treating 1-bromonaphthalene with BuLi in Et_2O and subsequently removing the butyl bromide formed in the exchange reaction. THF is an unsuitable solvent, because 1-naphthyllithium is readily alkylated by butyl bromide in this solvent. In Et_2O this alkylation is very slow, even at room temperature. This circumstance, together with the slight solubility of 1-naphthyllithium, permits almost quantitative isolation of this intermediate.

Treatment of 1-substituted naphthalenes with butyllithium in a number of cases leads to exclusive introduction of lithium into the 2-position. There are only a few types of substituents that direct the metallation mainly towards the 8-position. The observed regio-preferences have not yet been explained in a satisfactory way. When a mixture of 1-naphthyllithium and BuLi · TMEDA is heated under reflux for 3 hours, 1,8-dilithionaphthalene is formed as the exclusive product in a high yield. The metallation of the 8-position presumably takes place in the 1:1 aggregate of 1-naphthyllithium and BuLi.

Procedure

Et_2O (80 ml) is added to a solution of 0.12 mol of BuLi in 84 ml of hexane with cooling to below 0 °C. Subsequently 0.10 mol (20.7 g) of 1-bromonaphthalene is added over 5 min at −20 °C. The cooling bath is then removed and the temperature allowed to rise to +10 °C and stirring at this temperature is continued for an additional 15 min. The white suspension is cooled to −10 °C and, after standing for about 10 min, as much as possible of the supernatant clear solution is decanted. Dry hexane (250 ml) is then added and, after some swirling, the suspension is recooled to −20 °C. After standing for 10 min the clear solution is decanted. These operations are repeated for another three or four times (Note 1). To the remaining suspension is then added a solution of 0.13 mol of BuLi (Note 2) in 90 ml of hexane and 0.14 mol (16.3 g) of TMEDA. The gas inlet and stirrer are replaced with stoppers and the outlet-thermometer combination with a reflux condenser. The solution is heated under reflux until the evolution of gas has stopped completely (about 3 h). The dilithionaphthalene is a yellowish-brown suspension, which can be used to synthesize 1,8-disubstituted naphthalenes (Note 3). For the preparation of 1,8-bis(methylthio)naphthalene 80 ml of THF is added to the suspension with cooling to below 0 °C. Dimethyl disulfide (23.5 g, 0.25 mol) is then added at −30 °C with vigorous stirring. The temperature is allowed to rise to +10 °C. After an additional 10 min 200 ml of water is added to the yellow suspension with vigorous stirring. The aqueous layer is extracted once with Et_2O. The combined solutions are washed five times with water and subsequently dried over $MgSO_4$. After removal of the solvent in a water-pump vacuum (the last traces at 0.5–1 mm, while heating at 80 °C) the residue is transferred into a 100-ml round-bottom. Distillation through a very short column gives, after a small first fraction consisting mainly of 1-(methylthio)naphthalene, 1,8-bis(methylthio)naphthalene as a yellow solid (Note 4), b.p. ca. 150 °C/0.2 mm, in ~70% yield.

Notes

1. One may find it more practical to separate the precipitate from the solution by filtration through sintered glass (compare Ref. [166]).
2. A larger excess than 0.03 mol of BuLi will be necessary if pure 1,8-dideuterionaphthalene is to be prepared.
3. One should realize that the solution still contains the excess of BuLi.
4. An air condenser has to be used.

3.9 Reaction of PhLi·TMEDA with Elemental Selenium and Tellurium

$$\text{Ph—Li} + \text{"X"} \xrightarrow{\text{THF-hexane}} \text{Ph—XLi} \xrightarrow{CH_3I} \text{Ph—X}CH_3 \quad (\text{X}=\text{Se or Te})$$

Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction (compare Chap. V, Exp. 27)
Reaction of aryllithium with elemental selenium and tellurium leads to insertion of the element with formation of lithium areneselenolates and -tellurolates [227–8]. The reactions can be carried out in Et_2O or THF and often proceed successfully. Selenolates and tellurolates react smoothly with alkyl bromides, even at temperatures below 0 °C to give the corresponding selenoethers and telluroethers. This high reactivity implies that the aryllithium compounds cannot be generated by bromine-lithium exchange with BuLi. We found potassium compounds to react sluggishly with Se and Te, while subsequent methylation gave low yields of the selenides and tellurides. Grignard derivatives react in a satisfactory way [215, 227, 228].

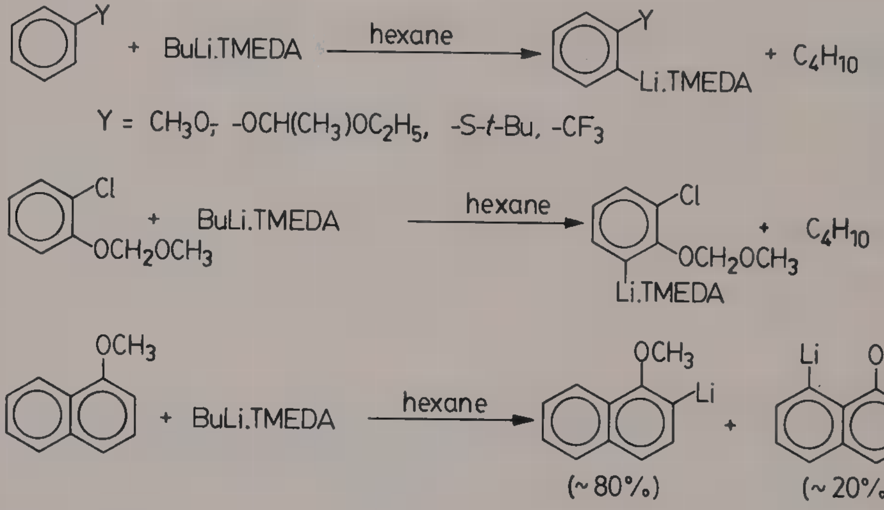
Procedure
THF (50 ml) is added to a solution of 0.05 mol of PhLi·TMEDA (see Exp. 5) in ca. 40 ml of hexane. Red selenium powder (4.2 g, slight excess) or lightgrey (Note 1) tellurium powder (6.5 g) is added over a few min with cooling at −50 °C (Se) and 0 °C (Te), respectively. The cooling bath is removed and the temperature allowed to rise to 0 °C (Se) and +20 °C (Te) (selenium reacts more easily than tellurium). When the powder has dissolved, the brownish solution is cooled to −60° and 0.10 mol (excess) of methyl iodide is added in one portion. A white suspension appears immediately. After stirring the mixtures for an additional 15 min at 0 °C, 100 ml of water is added with vigorous stirring. The aqueous layer is extracted three times with Et_2O (Note 2). After washing the combined organic solutions with water, they are dried over $MgSO_4$. The residue (yellow and brown, respectively) remaining

after removal of the solvents in a water-pump vacuum, is distilled through a 20-cm Vigreux column. PhSeCH$_3$, b.p. 78 °C/12 mm, n_D^{21} 1.5963, is obtained in 92% yield, the yield of PhTeCH$_3$, b.p. 95 °C/12 mm, n_D^{18} 1.6556, is 74%.

Notes

1. *Black* tellurium powder does not react.
2. The use of an inert atmosphere is advisable in the case of the tellurium compound which is very prone to air-oxidation.

3.10 *Ortho*-Metallation of Hetero-Substituted Benzenes and Naphthalenes with BuLi · TMEDA in Hexane



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

A common feature of the metallations described below is the exclusive or predominant introduction of the metal in the *ortho*-position of the substituents. Ether groups are assumed to exert their activating action mainly through their inductive effect. Coordinative effects, however, may also be important, as appears from the specific introduction of lithium into the *ortho*-position of the —OCH$_2$OCH$_3$ group in the reaction of 1-chloro-2-methoxymethoxybenzene with BuLi · TMEDA (second equation). The formation of 20 (rel.)% of 8-lithio-1-methoxynaphthalene from 1-methoxynaphthalene and BuLi · TMEDA may be also the consequence of a "complexation" of the base to the methoxy group. The *ortho*-selectivity (>90%) in the lithiation of (trifluoromethyl)benzene can be accounted for by the —I effect of the CF$_3$ group. We cannot understand why the *t*-butylthio group, which neither strongly coordinates to lithium nor has significant electron-withdrawing properties, directs the lithiation exclusively to the vicinal position.

Procedure

TMEDA (12.8 g, 0.11 mol) is added to a solution of 0.11 mol of butyllithium in 77 ml of hexane between 0 and 20 °C. The solution is then cooled to 0° and 0.10 mol of the substrate (Note 1) is added in one portion; 1-chloro-2-methoxymethoxybenzene, however, is added at −20 °C, and *t*-BuSPh at +20 °C. In the reaction with 1-chloro-2-methoxymethoxybenzene occasional cooling is applied to keep the temperature between 0 and +5 °C. The heating effects of the other reactions are observable in the temperature range of 10 to 25 °C. The conversions are completed by keeping the reaction mixture for an additional half hour at +5 °C (in the case of 1-chloro-2-methoxymethoxybenzene), 40 °C (in the cases of anisole, methoxynaphthalene, $PhCF_3$ and $PhOCH(CH_3)OC_2H_5$), or 50–55 °C (*t*-BuSPh). 1-Chloro-3-lithio-2-methoxymethoxybenzene, lithioanisole and 1-Li-2-*t*-butylthiobenzene precipitate from the solution, either directly or at room temperature, in the other cases no precipitation is observed. As usual a sufficient amount of THF or Et_2O is added to the solutions or suspensions prior to carrying out functionalization reactions. Conversions with carbonyl compounds, trimethylchlorosilane and dialkyl disulfides are very fast and can be carried out at low temperatures. Alkylations of aryllithiums having an ether or CF_3 group in vicinal positions, are slow at room temperature, and heating for an additional hour at 50–60 °C is necessary to bring the conversions to completion; *ortho*-lithiated *t*-butyl phenyl sulfide reacts much more smoothly. Reactions of lithium compounds with dimethylformamide are normally fast at temperatures between −40 and −80 °C; the reaction of 1-chloro-3-lithio-2-methoxymethoxybenzene with DMF in a THF-hexane mixture proceeds at an acceptable rate at about −10 °C; the initial suspension disappears upon addition of DMF (at −10°), but at a somewhat higher temperature (0–10°) a suspension re-appears. After an additional half hour (at 10–20 °C) the reaction mixture is poured into 1 l of ice water and the pH of the aqueous layer is brought at 6–7 by addition of 5N hydrochloric acid. The aldehyde is obtained in ca. 80% yield (compare Ref. [1]).

Notes

a) Preparation of $PhOCH(CH_3)OC_2H_5$

A solution of 0.05 mol (4.7 g) of pure, water-free phenol in 20 ml of Et_2O is added to 14.4 g (0.2 mol, excess) of ethyl vinyl ether. The mixture is cooled to −5 °C and 100 mg of *p*-toluenesulfonic acid is added. The cooling bath (CO_2-acetone) is removed and the temperature is allowed to rise to +10 °C, then the solution is cooled again to 0 °C and the second portion of 0.05 mol of phenol is added. After the exothermic reaction has subsided, the solution is stirred for an additional half hour at +10 °C. A second portion of 100 mg of acid is added. If no evolution of heat is observed, a solution of 5 g of potassium carbonate in 25 ml of water is added with vigorous stirring. The upper layer is separated off, dried over potassium carbonate and concentrated *in vacuo*, giving the protected phenol in almost quantitative yield. The undistilled product is used for the metallation.

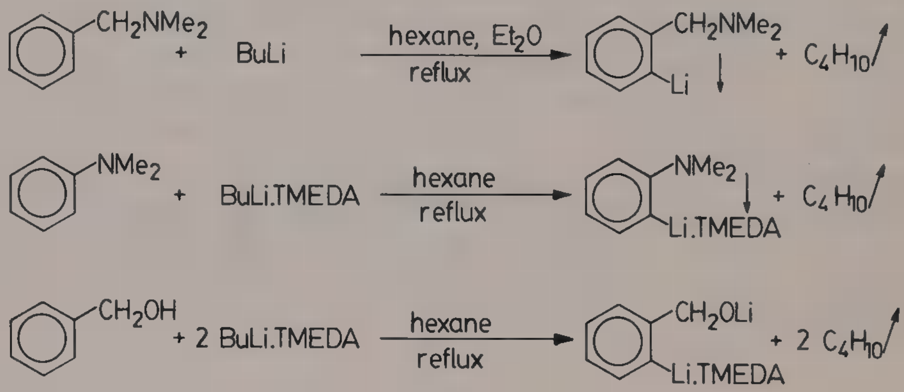
b) 2-Chloro-1-methoxymethoxybenzene.

Ortho-chlorophenol (25.8 g, 0.20 mol) is added at 0 °C to a solution of 0.22 mol (24.6 g) of *t*-BuOK in 150 ml of THF. The solution is cooled to −10 °C and

0.20 mol (16.1 g) of chlorodimethyl ether is added over 10 min, while keeping the temperature between 0 and −10 °C. After an additional half hour (at 0 °C) ice water is added and the product is isolated in the usual way. The protected phenol, b.p. 100 °C/12 mm, n_D^{20} 1.5230, is obtained in a yield of 85%.

c) *t*-Butyl phenyl sulfide.
A mixture of 4 g of 96% sulfuric acid and 100 ml of dichloromethane is saturated with isobutene at +30 °C. Thiophenol (55 g, 0.50 mol) is added dropwise over 45 min with vigorous stirring, while maintaining the introduction of isobutene (at a rate such that most of the gas is absorbed). The reaction is mildly exothermic. After the addition, introduction of gas and heating at about 40 °C are continued for half an hour. The solution is shaken with a dilute aqueous solution of KOH and subsequently dried over $MgSO_4$. The liquid remaining after evaporation of the solvent *in vacuo* is distilled through a 30-cm Vigreux column to give the sulfide, b.p. 90 °C/12 mm, n_D^{18} 1.5305, in 92% yield.

3.11 Ring-Metallation of Benzyl Dimethylamine, *N*,*N*-Dimethylaniline and Benzyl Alcohol



Scale: 0.10 molar.

Apparatus: 500-ml round-bottomed, three-necked flask, equipped with a gas inlet, a mechanical stirrer and a reflux condenser. The top of the condenser is connected to a washing bottle filled with hexane. The inlet tube should not dip more than 0.5 cm into the hexane.

Introduction
The reactions of *N*,*N*-dimethyl benzylamine [176] and benzylalcohol [177] with butyllithium and butyllithium · TMEDA, respectively, result in specific *ortho*-lithiation, and are typical examples of the "coordination only" mechanism [1]. The benzylamine forms a complex with butyllithium, experimentally this is visible by a modest, but significant and promptly occurring heating effect when the amine is quickly added to the solution of butyllithium. Addition of benzylalcohol to two equivalents of BuLi · TMEDA results also in the formation of a complex, *viz.* $PhCH_2OLi \cdot BuLi$ (analogous to the aggregates from alkali alkoxides and BuLi, e.g.

$BuLi \cdot t$-$BuOK$, compare Ref. [3]). This complex presumably is more stable than the complex from $PhCH_2NMe_2$ and BuLi. In the next step the base, which now has a considerable entropy advantage, abstracts the *ortho*-proton which is in the most favourable position. Chemists have an intuitive tendency to use relatively large amounts of Et_2O, in the expectation to promote the metallation of the benzylamine. While Et_2O as such is not harmful, its presence in abundant quantities keeps the attainable temperature relatively low, so that considerably longer reaction times are necessary. THF is likely to compete seriously for the very reactive basic species at the reaction temperature required. The TMEDA assists in the *ortho*-lithiation of benzylalcohol. In the first place it complexes with the aggregate of BuLi and $PhCH_2OLi$, making the Li—C bond in BuLi more polar. Furthermore, it solubilizes the aggregate in a way similar to that in the case of $BuLi \cdot t$-$BuOK$ or $BuLi \cdot t$-$BuONa$ in apolar solvents [22]. Under these conditions the *o*-lithiation of benzylalcohol can be completed in 1–1.5 hour in refluxing hexane. If TMEDA is used in the metallation of the *benzylamine*, comparable amounts of $PhCH(Li)NMe_2$ and *o*-$Li—C_6H_4CH_2NMe_2$ are formed [9]. This result might be explained by assuming that TMEDA forms the monomeric chelation complex with BuLi, which is more stable than the complex $PhCH_2NMe_2 \cdot BuLi$. This kinetically very active chelation complex deprotonates $PhCH_2NMe_2$ at the benzylic carbon atom. The exclusive formation of $PhCH(K)NMe_2$ [9] in the reaction of $PhCH_2NMe_2$ with $BuLi \cdot t$-$BuOK$ in THF at -70 °C may be explained in a similar way.

The metallation of *N,N*-dimethylaniline by $BuLi \cdot TMEDA$ in hexane [178] proceeds less easily than the lithiation of $PhCH_2NMe_2$ and $PhCH_2OH$. The dimethylamino group in this amine has only weak inductive and coordinating properties. Nevertheless a specific *ortho*-lithiation can be effected by heating the solution of $PhNMe_2$ and $BuLi \cdot TMEDA$ in hexane for 3–4 hours under reflux.

Functionalization of the aryllithium intermediates

Derivatization reactions are usually carried out in the presence of a sufficient amount of Et_2O or THF. These solvents are added after completion of the metallations. We have carried out reactions with alkyl halides, dimethyl disulfide, dimethylformamide and iodine. The alkylation with higher alkyl bromides (*n*-butyl bromide was taken as a model) proceeds less easily than those with most of the other aryllithiums, and heating at 50–60 °C, or addition of a small amount of HMPT is necessary to bring the conversions to completion (similar effects can be observed in alkylations of *o*-$Li—C_6H_4—OCH_3$ and *o*-$Li—C_6H_4—CF_3$). The decreased reactivities might be the consequence of a stabilization of the *ortho*-lithiated species (compared with unsubstituted phenyllithium and *m*- and *p*-substituted phenyllithiums), or to the formation of aggregation clusters (making the approach of the reagent more difficult).

The reaction of *o*-$Li—C_6H_4CH_2NMe_2$ with DMF in Et_2O has to be carried out at temperatures in the range of -10 to $+30°$, which is considerably higher than that in most of the other formylation reactions. In this case, the slight solubility of the lithium compound might be responsible for the decreased reactivity.

The iodination of *o*-$Li—C_6H_4CH_2NMe_2$ with iodine in THF can be carried out at low temperatures and a high yield is obtained. The reaction of *o*-$Li—C_6H_4CH_2OLi$ with iodine proceeds less satisfactory, and the expected product is obtained in modest yields. Here, competitive reaction of iodine with TMEDA occurs to a considerable extent [9].

The reaction with dimethyl disulfide gives a good result in all reactions.

Procedure

Lithiation of N,N-dimethyl benzylamine

Et_2O (30 ml) is added to a solution of 0.105 mol of butyllithium in 74 ml of hexane at 20 °C. 0.15 mol (20.3 g) of *N,N*-dimethyl benzylamine is added in one portion (if alkylation with a lower alkyl halide is to be carried out, the use of an excess of the amine presumably will give rise to difficulties with the purification of the product). The temperature of the solution rises to about 30 °C in a few seconds. The introduction of nitrogen is stopped and the stirrer is replaced with a stopper. The solution is heated under reflux until the evolution of gas has completely stopped (about 3 h) during which time a thick, white suspension is gradually formed. If no excess of the amine is used, a longer period of refluxing will be necessary. If the lithiated amine is to be reacted with iodine, 0.10 mol of the amine is added to a mixture of 0.13 mol of BuLi in 91 ml of hexane and 30 ml of Et_2O. The mixture is heated for ~3 h. A 1-l flask is used in that case.

Lithiation of benzylalcohol

TMEDA (12.8 g, 0.11 mol) is added to a solution of 0.11 mol of butyllithium in 77 ml of hexane at ~25 °C. Benzylalcohol (5.4 g, 0.05 mol) is then added dropwise over 5 min without external cooling. The introduction of nitrogen is stopped and the stirrer is replaced with a stopper. The mixture is heated under reflux until no more butane is evolved (1–1.5 h). A dark-brown solution with some solid material is formed.

Lithiation of N,N-dimethylaniline

To a solution of 0.105 mol of butyllithium in 74 ml of hexane is added (at 20–30 °C) 0.105 mol (12.2 g) of TMEDA, and subsequently 0.12 mol (14.5 g) of *N,N*-dimethylaniline. The introduction of nitrogen is stopped and the stirrer is replaced with a stopper. The mixture is heated under reflux until no more butane is evolved (ca. 3 h). A light-brown solution is formed.

Formylation of lithiated N,N-dimethyl benzylamine

Et_2O (80 ml) is added to the suspension of the lithiated amine. The mixture is cooled to −20 °C and 0.15 mol (11.0 g) of DMF is added in one portion. The cooling bath is removed and the temperature allowed to rise. The suspension disappears gradually, but at a later stage a new suspension appears. After the exothermic reaction has subsided, the mixture is warmed for an additional half hour at 30 °C. The suspension is then poured into 1 l of ice water and after vigorous shaking, the layers are separated. The aqueous layer is extracted three times with Et_2O. The combined organic solutions are dried over sodium sulfate and subsequently concentrated *in vacuo*. Careful distillation of the remaining liquid through a 40-cm Vigreux column gives the aldehyde, b.p. 112 °C/12 mm, n_D^{19} 1.5355, in 93 % yield.

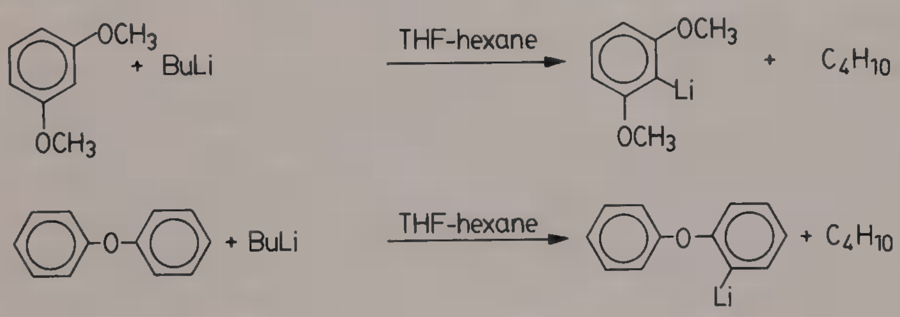
Iodination of lithiated N,N-dimethyl benzylamine

THF (80 ml) is added to the suspension of the lithiated amine. A solution of 0.14 mol (35.6 g) of iodine in 60 ml of THF is added with vigorous stirring and cooling to between −50 and −70 °C. In the last stage of the addition the temperature is allowed to rise to −20 °C. A solution of 10 g of sodium thiosulfate ($Na_2S_2O_3$) in 250 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 dried over potassium carbonate and subsequently concentrated *in vacuo*. Traces of butyl iodide are removed at 0.5 mmHg by heating the remaining liquid in a bath at 30 °C. The undistilled product (yield ca. 95 %) appears to be practically pure according to NMR.

Methylthiolation of lithiated benzylalcohol and lithiated N,N-dimethylaniline

After addition of 80 ml of THF to the solutions of the lithium compounds, the mixtures are cooled to −60 °C and dimethyl disulfide (0.07 and 0.12 mol, 6.6 and 11.3 g, respectively) is added in one portion with vigorous stirring. White suspensions are formed. The cooling bath is removed and the temperature allowed to rise to +20 °C. Water is then added and the products are isolated in the usual way. Careful distillation through a 20-cm Vigreux column gives the desired products, o-$CH_3S—C_6H_4CH_2OH$, b.p. ca. 110 °C/0.5 mm, n_D^{18} 1.6033, is obtained in 76 % yield, the yield of o-$CH_3S—C_6H_4NMe_2$, b.p. 120 °C/12 mm, n_D^{18} 1.5874, is 86 %.

3.12 Metallation of Phenyl Ethers with Butyllithium in THF



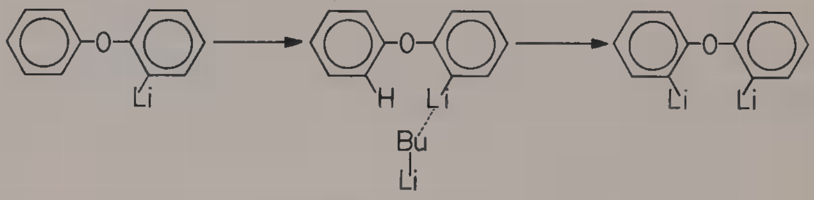
Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

Ether groups exert their *ortho*-directing action in the metallation of aromatic rings mainly *via* their electron-withdrawing inductive effect. Methoxybenzene has been lithiated with BuLi in Et_2O or THF. The metallation in the latter solvent can be carried out in a reasonable time (2–3 h at 20 °C), but part of the butyllithium is consumed by reaction with the solvent, unless a considerable excess of anisole is used. The activating influence of two methoxy groups in 1,3-dimethoxybenzene renders the metallation easier.

The conditions required for the mono-lithiation of diphenyl ether are comparable to those in the case of anisole. One complication, which arises when equivalent quantities of diphenyl ether and BuLi or BuLi · TMEDA are allowed to interact, is the relatively easy subsequent *ortho*-metallation of the other phenyl ring [179].



One can imagine this second lithiation to occur through an intermediary aggregate of BuLi and mono-lithiated diphenyl ether, a situation which is favourable for the removal of the *ortho*-proton of the second ring. This second lithiation can be suppressed by using a large excess of diphenyl ether. For most derivatization reactions, however, this excess probably will give rise to difficulties in the purification of the products.

Procedure

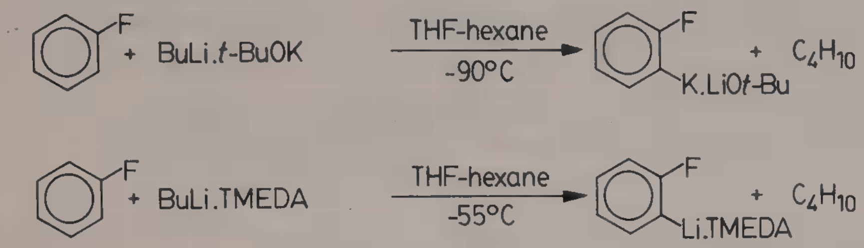
Metallation of 1,3-dimethoxybenzene

1,3-Dimethoxybenzene (6.9 g, 0.05 mol) is added in one portion to a solution of 0.06 mol of BuLi in 42 ml of hexane and 40 ml of THF, cooled at −5 °C. The temperature rises to about 15 °C within 30 min. The mixture is kept for an additional half hour at 25 °C. Addition of dimethyl disulfide (0.07 mol) at −20 °C gives 1,3-dimethoxy-2-(methylthio)benzene as a solid in almost 100 % yield.

Lithiation of diphenyl ether

To a solution of 0.10 mol (17.0 g) of diphenyl ether (excess) in 50 ml of THF is added in 30 min a solution of 0.055 mol of butyllithium in 38 ml of hexane. During this addition the temperature is kept between 25 and 30 °C. After an additional hour the resulting solution is transferred into another flask using a syringe. This flask contains 50 ml of THF through which a vigorous stream of carbon dioxide is passed. During the addition of the solution of the lithiated diphenyl ether, (over 5 min) the temperature of the vigorously stirred mixture is kept below −20 °C. After addition of 100 ml of water, the layers are separated. The aqueous layer is extracted twice with pentane, then 8 g of concentrated hydrochloric acid is added with manual swirling. The carboxylic acid is isolated by extraction with Et_2O (twice), washing of the extracts with water (once), drying of the solution over $MgSO_4$ and evaporation of the solvents *in vacuo*. The acid is obtained in a yield of ca. 90 %. Crystallization from a 1:1-mixture of pentane and ether gives the pure acid, m.p. 112.5 °C.

3.13 Metallation of Fluorobenzene with BuLi · *t*-BuOK and with BuLi · TMEDA



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

In one of his papers [180] Gilman reports on the metallation of fluorobenzene. Interaction at −50 °C between this compound and BuLi in THF for 7 hours, followed by carboxylation gave a reasonable yield of fluorobenzoic acid. Fluorine activates vicinal protons exclusively by its (strong) -I effect, and it should be possible to shorten the reaction time by using more strongly basic systems. Indeed, if the reaction in THF is carried out with BuLi · TMEDA, the formation of *o*-lithiofluorobenzene appears to be complete after about 1 hour (at −55 °C) [9]. A practically instantaneous metallation can be realized with the 1:1 mixture of butyllithium and *t*-BuOK in THF at very low temperatures; we assume that in this case the *potassium* compound is formed [9]. The solutions of potassio- and lithiofluorobenzene can be used for the preparation of a number of derivatives, e.g. 1-fluoro-2-(trimethylsilyl)benzene and 1-fluoro-2-(methylthio)benzene. It is even possible to alkylate or hydroxyalkylate metallated fluorobenzene with alkyl halides and oxirane, respectively. In these reactions HMPT has to be used as a co-solvent in order to attain a satisfactory rate of conversion at low temperatures: above −45 °C metallated fluorobenzene eliminates alkali fluoride with initial formation of benzyne (which gives rise to a number of subsequent products).

Procedure

Metallation with BuLi · t-BuOK

A solution of 0.11 mol (12.3 g) of *t*-BuOK in 77 ml of THF is added to a solution of 0.11 mol of butyllithium in 77 ml of hexane with cooling to between −95 and −105 °C (care should be taken that no solid crust is formed on the bottom of the flask during cooling with liquid nitrogen). Subsequently a mixture of 0.15 mol (14.4 g) of fluorobenzene and 35 ml of THF is added dropwise with efficient stirring and cooling to between −90 and −100 °C. Five minutes after the addition further reactions can be carried out with the light-brown to colourless solution. Alternatively, the hexane solution of BuLi is added dropwise at −90 °C to a solution of fluorobenzene and *t*-BuOK in THF.

Metallation with BuLi · TMEDA

A solution of 0.105 mol of butyllithium in 74 ml of hexane is added to a mixture of 0.105 mol (12.2 g) of TMEDA, 0.20 mol (19.2 g) of fluorobenzene and 80 ml of THF with cooling to between −55 and −60 °C. After this addition, which takes 30 min, the solution is stirred for an additional hour at −55 °C. Care should be taken that the temperature does not rise above −50 °C. The upper part of the flask is covered with cotton wool and stirring is carried out at a moderate rate to prevent decomposition by splashing of the solution into the upper reaches.

Reaction of potassiofluorobenzene and lithiofluorobenzene with dimethyl disulfide and trimethylchlorosilane

The solutions of metallated fluorobenzene are cooled to −100 °C and a mixture of 0.13 mol (12.2 g) of dimethyl disulfide or trimethylchlorosilane (14.1 g) and 50 ml of Et_2O is added over 1 min with vigorous stirring. The cooling bath is removed, and when the temperature of the reaction mixture has reached −40 °C, 100 ml of water is added to the white suspension. After separation of the layers, three extractions with Et_2O are carried out. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Careful distillation of the remaining liquid through a 30-cm Vigreux column gives the expected products in yields of 90 % or higher. o-F—C_6H_4—$SiMe_3$ has b.p. 60 °C/15 mm, n_D^{26} 1.4760, o-F—C_6H_4—SCH_3 has b.p. 80 °C/15 mm and n_D^{20} 1.5527.

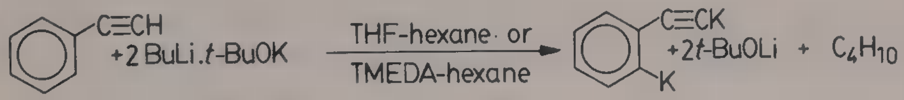
Reaction of potassiofluorobenzene with bromohexane

Bromohexane (0.10 mol, 16.5 g) is added over a few min to a solution of 0.10 mol of o-KC_6H_4F cooled at −100 °C. Subsequently a mixture of 25 ml of purified HMPT (see Chap. I-2) and 10 ml of THF is added over 10 min, while keeping the temperature between −85 and −90 °C. The mixture is stirred for about 1 h at ca. −85 °C, then the temperature is allowed to rise gradually over 30 min to −40 °C. Water (150 ml) is added with vigorous stirring and after separation of the layers the aqueous layer is extracted three times with pentane. The combined organic solutions are washed four times with brine and are subsequently dried over $MgSO_4$. Concentration *in vacuo*, followed by careful distillation through a 40-cm Vigreux column, gives o-F—C_6H_4—n-C_6H_{13}, b.p. 98 °C/12 mm, n_D^{20} 1.4731, in 88 % yield.

The reaction with oxirane, affording o-F—C_6H_4—CH_2CH_2OH, can be carried out in a similar way and gives the alcohol in a reasonable (about 70 %) yield. Oxirane is added in an excess of 30 %. In the absence of HMPT the reaction is very slow. Couplings with aldehydes and ketones or thiolation with elemental sulfur have to be carried out with the *lithium* compound, which can be prepared as indicated, or by addition of a solution of anhydrous LiBr in THF to the solution of the potassium compound. t-BuOLi present in the solution may give rise to aldol condensation of enolizable aldehydes and ketones, particularly at temperatures in the region of 0 °C. Therefore, the use of an excess of the aldehyde or ketone should be avoided.

Methoxybenzene (10 to 20 % excess) can be potassiated in an essentially similar way: subsequent reaction with dimethyl disulfide gives 1-methoxy-2-methylthiobenzene in more than 90 % yield.

3.14 Dimetallation of Phenylacetylene with BuLi · *t*-BuOK in THF-Hexane and with BuLi · *t*-BuOK · TMEDA in Hexane

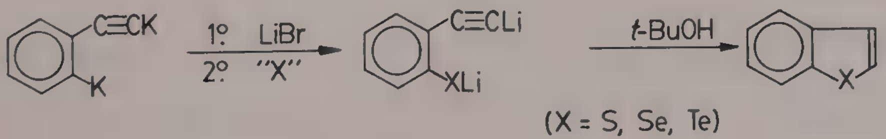


Scale: 0.05 molar (phenylacetylene).

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction
Treatment of phenylacetylene with a strongly basic reagent results in an instantaneous formation of the alkali acetylide. If an excess of base is present, one could imagine deprotonation of the ring under suitable conditions. Interaction at about −70 °C between phenylacetylene and at least two equivalents of the strongly basic couple BuLi · *t*-BuOK in THF results in a remarkably smooth and very efficient di-metallation [46]: quenching with an excess of trimethylchlorosilane affords the disilylated product *o*-$Me_3Si—C_6H_4—C≡C—SiMe_3$ in greater than 90% yield. Competition experiments show that the ring-metallation is much faster than deprotonation of benzene. The almost exclusive metallation in the *ortho*-position of the acetylide function might seem a little surprising. It is possible, however, that the function of the acetylide moiety is that of a group complexing with the second equivalent of basic reagent (analogous to the situation in the metallation of $PhCH_2NMe_2$ with BuLi, (see Exp. 11) thus triggering the metallation toward the *ortho*-position. The activating effect of the acetylide function is weak when compared with that of a OCH_3 group: methoxybenzene is *ortho*-metallated much more easily than alkali phenylacetylides. The di-metallation can also be brought about in the apolar solvent hexane, using two equivalents of the ternary system BuLi · *t*-BuOK · TMEDA; the advantage is that there is no possibility of competitive attack of the solvent, so that the excess of base can be limited. The results are the same or even better than those with BuLi · *t*-BuOK in THF. Heating of lithium phenylacetylide with BuLi · TMEDA under reflux for a few hours results also in an almost quantitative ring-metallation, but in this case metallation at the *meta*- and *para*-position occurs to about 10 to 15%.

The di-potassio derivative of phenylacetylene can be used to synthesize a number of derivatives [46]. Prior to adding the requisite reagent, a sufficient amount of THF has to be added as co-solvent. In some cases potassium has to be replaced by lithium or magnesium halide (MgX) (addition of LiBr or MgX_2) in order to achieve a satisfactory functionalization. Alkyl- or allyl halides, dialkyl disulfides, bromine, iodine, dimethylformamide, sulfur, selenium and tellurium react specifically with the ring, if added in equivalent amounts. Subsequent addition of *t*-butylalcohol (as proton donor) to the reaction mixture obtained with S, Se and Te gives benzothiophene and its Se- and Te-analogues in good yields [46]:



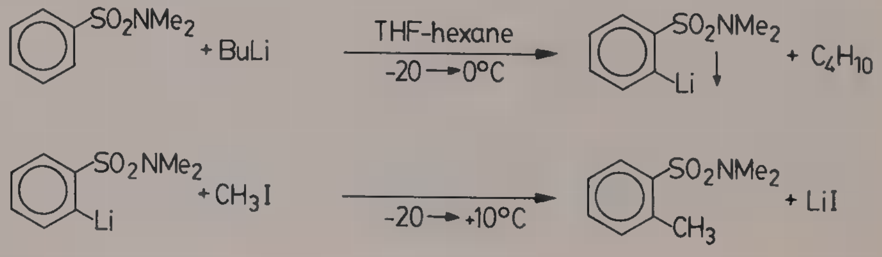
Procedure

THF (50 ml) is added to a solution of 0.12 mol (excess) of butyllithium in hexane cooled to below −10 °C. Phenylacetylene (0.05 mol, 5.1 g) is subsequently introduced dropwise over 5 min with cooling to below −40 °C. The resulting solution or thin suspension is cooled to −75° and a solution of 0.12 mol (13.4 g) of *t*-BuOK in 40 ml of THF is then added over 45 min, while maintaining the temperature between −70 and −75 °C. After stirring for an additional half hour at −75 °C, the cooling bath is removed and the temperature allowed to rise to +15 °C. Under these conditions the metallated THF (formed from the excess of base) decomposes to ethene and potassium ethenolate. The dilithium- and di-Grignard compounds are obtained by subsequently adding (with vigorous stirring) a solution of 0.12 mol (10.4 g) of anhydrous lithium bromide in 40 ml of THF, or the oily, lower layer, obtained from the reaction of 0.15 mol (28.2 g) of 1,2-dibromoethane and 50 % excess of magnesium turnings in Et_2O, respectively. This addition is carried out at about 10 °C. (The anhydrous lithium bromide is obtained by heating a relatively small amount of the commercial anhydrous salt, about 50 g, for 1 h at 150 °C in a 1-l round-bottomed flask, evacuated at 1 mmHg or lower pressure.) Quenching at −30 °C with excess of Me_3SiCl gives the di-silyl derivative in more than 90 % yields. For the preparation of other derivatives see Ref. [46].

Metallation with BuLi · t-BuOK · TMEDA [21]

A solution of 0.12 mol of butyllithium in 84 ml of hexane is added over a few min to a mixture of 0.12 mol of *t*-BuOK (13.4 g), 40 ml of hexane and 0.12 mol (13.9 g) of TMEDA. During this addition the temperature is kept between −40 and −60 °C. After an additional 10 min a mixture of 0.05 mol (5.1 g) of phenylacetylene [6] and 20 ml of hexane is added dropwise over 5 min with cooling to between −30 and −50 °C. The mixture is then stirred for 2 h at −20 to −25 °C. The initial precipitate becomes thin towards the end of this period. THF (70 ml) is then added to the red to pink solution, and the mixture is stirred for 15 min at +10 °C (see above).

3.15 Lithiation of *N*,*N*-Dimethyl Benzenesulfonamide and Subsequent Methylation



Apparatus: Chap. I, Fig. 1, 500 ml.

Scale: 0.05 molar.

Introduction

The SO_2NMe_2 function is one of the most powerful *ortho*-directing groups in aromatic and hetero-aromatic metallations [1, 181, 182]. It has not only strong electron-withdrawing properties, but is also able to coordinate with the organometallic reagent. *N*,*N*-dimethyl benzenesulfonamide is lithiated by butyllithium with the same ease as thiophene [183].

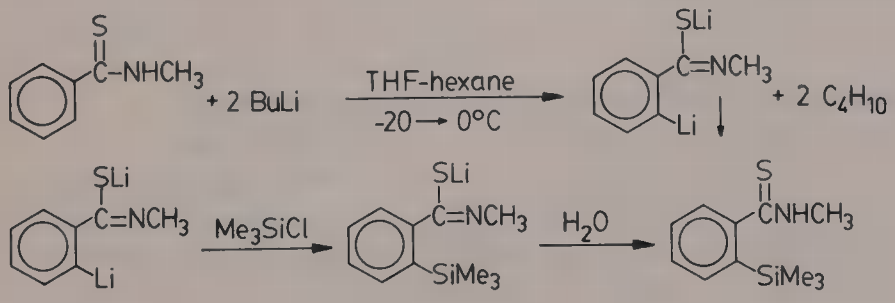
Procedure

THF (40 ml) is added to a solution of 0.06 mol of butyllithium in 42 ml of hexane cooled to below −10 °C. Subsequently a solution of 0.05 mol (9.25 g) of the sulfonamide in 10 ml of THF is added in one portion at −30 °C. The reaction is markedly exothermic causing the temperature to rise by some 15 °C. A white suspension is formed. The suspension is stirred for an additional 15 min at 0 °C, after which 10 g (0.07 mol) of methyl iodide is added in one portion at −25 °C. The temperature rises to about +10 °C within one minute and after 15 min water (100 ml) is added. The aqueous layer is extracted four times with Et_2O. The unwashed extracts are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. The weight of the viscous residue (practically pure methylation product) corresponds to a yield of ca. 90 %. Addition of DMF at −30 °C resulted in a fast reaction during which most of the solid disappeared. Subsequent addition of water afforded the expected aldehyde in an excellent yield. Butyl bromide reacted very slowly at 15–20 °C, so that HMPT has to be used as a co-solvent.

Preparation of N,N-dimethyl benzenesulfonamide

Benzenesulfonyl chloride (0.1 mol, 17.7 g) is added to a vigorously stirred mixture of 200 ml of dichloromethane and 0.3 mol (13.5 g) of Me_2NH cooled at −50 °C. After the addition the temperature is allowed to rise to 0 °C. Water (50 ml) is added and, after separation of the layers, the aqueous layer is extracted 6 times with small portions of dichloromethane. The unwashed organic solutions are dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gives practically pure *N*,*N*-dimethylbenzenesulfonamide (white crystals) in ca. 90 % yield.

3.16 Metallation of *N*-Methyl Benzenecarbothioamide and Subsequent Trimethylsilylation

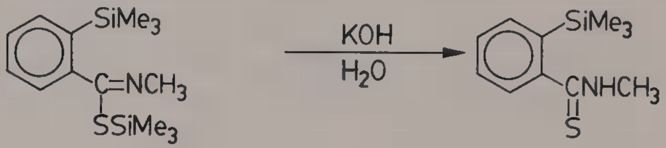


Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

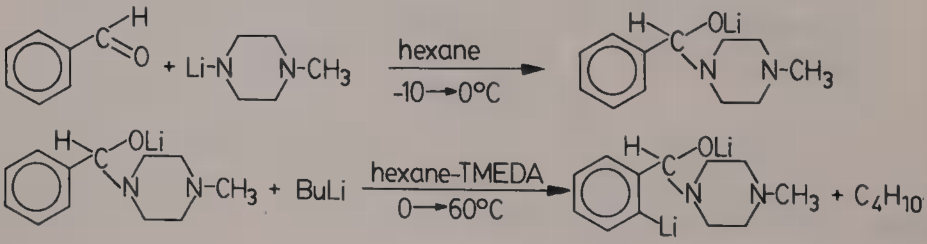
Reaction of *N*-substituted thioamides [184] with butyllithium primarily leads to the abstraction of the amide proton with formation of a thiolate. The C=N bond in the thiolate still has electron-withdrawing, and probably also coordinating properties, so that further interaction with butyllithium gives rise to removal of an *ortho*-proton. A somewhat unfavourable condition for this ring metallation is the slight solubility of the lithium "salt" of the thioamide primarily formed. It therefore takes at least four hours (at 0 °C) to bring the metallation to completion, while an excess of butyllithium is required to compensate for the loss owing to the reaction with the solvent THF. Reactions of the di-lithiated thioamide with one equivalent of reactive "electrophiles" have been shown to give the expected thioamides with an *ortho* substituent. In this manner Me_3Si- and PhS groups have been introduced into the ring. For *alkylation* the perspectives for a specific lithiation seem less good, since reaction with the thiolate moiety may occur with comparable ease. The reaction with trimethylchlorosilane, as described in the procedure below, is carried out with an excess of this reagent and will undoubtedly lead to partial S-silylation. However, treatment with aqueous alkali will result in a smooth cleavage of the S-Si bond while the *C*-Si bond remains unattacked.

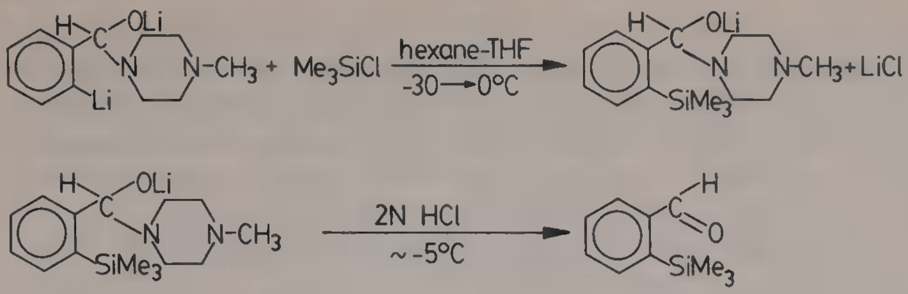


Procedure

A solution of 0.12 mol of butyllithium in 84 ml of hexane is added to the thioamide (0.05 mol (7.6 g, see Exp. 2) dissolved in 80 ml of THF with cooling to between 0 and −20 °C. The suspension is then stirred for 4 h at 0 °C. During this period the colour becomes very dark, while most of the suspended material dissolves. After cooling to −60 °C, 0.15 mol (16.3 g) (excess) of trimethylchlorosilane is added in one portion and the mixture is then stirred for 1 h at −20 °C. A solution of 20 g of potassium hydroxide in 100 ml of water is then added with vigorous stirring, while allowing the temperature to rise to 20 °C. Stirring is continued for 15 min, after which the product is extracted with Et_2O. The dark-yellow solution is washed with water, dried over $MgSO_4$ and then concentrated *in vacuo*. A residue of 10.5–11.0 g of yellow-brown crystalline material is obtained, consisting of almost pure trimethylsilylated thioamide.

3.17 Protection of the Formyl Group of Benzaldehyde and Subsequent *Ortho*-Lithiation and Trimethylsilylation





Scale: 0.05 molar.

Apparatus: Chap. I, Fig. 1, 500 ml.

Introduction

A well-established method for the preparation of aldehydes consists of converting an organolithium (or sometimes Grignard) compound RM with dimethylformamide and subsequently hydrolyzing the adduct $RCH(OLi)NMe_2$. This method has led to the idea of *protecting* an aldehyde function by reaction with a lithium dialkylamide [13–15]. Stimulated by successful results in the thiophene series [12] this concept has been applied in some recent papers to introduce or replace substituents in aromatic aldehydes. Although in a few cases good results have been obtained, more research seems to be necessary to develop this method to a generally successful one. Unsatisfactory aspects in the *ortho*-metallation of protected aldehydes are the use of a 200 mol % excess of butyllithium (presumably as a compensation for the loss owing to reaction with THF) and the long reaction times. The amides, most frequently applied for the protection, are lithium morpholide and lithium *N*-methylpiperazide; it is not clear why other amides (e.g. lithium dimethylamide and LDA) are not used. The grouping (—CH(OLi)N<), formed in the addition of the lithium amide, in general directs the lithiation towards the *ortho*-position. Since it is hardly likely that this grouping has electron-withdrawing properties, it must exert its action by forming a coordination complex with butyllithium. In this respect the situation is analogous to that in the lithiation of benzyl dimethylamine (Exp. 11). The difference with this amine, however, is that the assistance of TMEDA is often required to attain an acceptable rate of conversion. We have carried out a few *ortho*-functionalizations with protected aldehydes on a larger scale, using a modest excess of butyllithium. We are not completely satisfied with our results. The procedure below describes the *ortho*-trimethylsilylation of protected benzaldehyde.

Procedure

TMEDA (0.06 mol, 7.0 g) is added to a solution of 0.06 mol of BuLi in 42 ml of hexane without external cooling. *N*-methylpiperazine (0.06 mol, 6.0 g) and 20 ml of benzene are added to the resulting solution with cooling to between 0 and 10 °C. A thick white suspension is formed. After an additional 10 min a mixture of 0.05 mol (5.3 g) of benzaldehyde and 25 ml of hexane is added dropwise with cooling to between −10 and −20 °C. A much thinner suspension is formed. After this addition, the mixture is allowed to warm up to 20 °C, then 0.06 mol of butyllithium in 42 ml of hexane is added in one portion. The temperature rises to ca. 35 °C in 1 to 2 min. The suspension is heated for an additional 30 min at 55 °C, then it is cooled to 20° and 50 ml of THF are added. The resulting light-brown solution is cooled to −20 °C and 0.07 mol (7.6 g) of trimethylchlorosilane is added in one portion. The temperature rises within 1 min to about 10 °C. After an additional 15 min the mixture is poured into 200 ml of 2 N hydrochloric acid, cooled to ca. −5 °C. After vigorous shaking for some minutes, the layers are separated and the aqueous layer is extracted three times with Et_2O. The combined organic solutions are washed with water, dried over $MgSO_4$ and subsequently concentrated *in vacuo*. Careful distillation of the remaining light-brown liquid gives (after a forerun of benzaldehyde) *o*-(trimethylsilyl)benzaldehyde, b.p. 98 °C/12 min, n_D^{19} 1.5262, in 43–52 % yields.

3.18 Reaction of Phenylmagnesium Bromide with 1,2-Dibromodiethyl Ether. Preparation of 1-Ethoxy-1-Phenylethene

$$\mathrm{PhBr + Mg \xrightarrow{Et_2O} PhMgBr}$$

$$\mathrm{H_2C{=}CH{-}OC_2H_5 + Br_2 \xrightarrow{Et_2O} BrCH_2CHBrOC_2H_5}$$

$$\mathrm{PhMgBr + BrCH_2CHBrOC_2H_5 \xrightarrow[-20\ \to\ 0\,^{\circ}C]{Et_2O} BrCH_2CH(Ph){-}OC_2H_5 + MgBr_2}$$

$$\mathrm{BrCH_2{-}CH(Ph){-}OC_2H_5 + 2\ \mathit{t}\text{-}BuOK \xrightarrow[20\ \to\ 65\,^{\circ}C]{THF}}$$

$$\mathrm{H_2C{=}C(Ph){-}OC_2H_5 + KBr + \mathit{t}\text{-}BuOK \cdot \mathit{t}\text{-}BuOH}$$

Scale: 0.20 molar (in bromine).

Introduction

The procedure for 1-ethoxy-1-phenylethene is an illustration of a general synthetic method for 1-substituted vinyl ethers, which are not accessible *via* 1-metallation [9] (compare Chap. IV, Exp. 1). The synthesis starts with the reaction of a Grignard compound with a 1,2-dibromoalkyl ether [231]. A halogen atom in the 1-position of an ether group is very readily replacable, even under non-polar conditions. This reaction is a special case of nucleophilic displacement in which the carbenium-like transition state is stabilized by the adjacent oxygen lone pair $(\overset{-}{\mathrm{Hal}}\ldots\overset{+}{\mathrm{C}}{-}\mathrm{OR} \leftrightarrow \overset{-}{\mathrm{Hal}}\ldots\mathrm{C}{=}\overset{+}{\mathrm{O}}\mathrm{R})$. Although in the case of 1-haloethers (e.g. $ClCH_2OCH_3$, compare Chap. V, Exp. 33) both lithium- and Grignard compounds give good results, the results with *1,2-dibromoethers* are much better when the substitution reaction is carried out with the *Grignard*-derivatives. 1,2-Dibromotetrahydrofuran and 1,2-dibromotetrahydropyran seem to be less reactive than the open-chain ethers, but also in these cases specific displacement of the bromine atom in the 1-position can be realized [9] if the reaction is carried out in THF. We found acetylenic Grignard compounds to be less reactive than alkyl- and arylmagnesium halides. The coupling products of RMgX and 1,2-dihaloethers have been used in the Boord-synthesis of alkenes [185], e.g.:

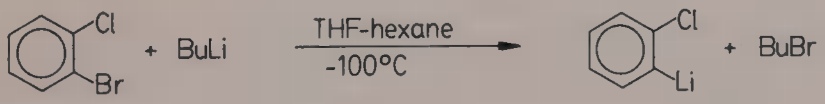
$$\mathrm{Br{-}CH_2{-}CH(R)OC_2H_5 \xrightarrow{Mg} H_2C{=}CH{-}R}$$

The present procedure describes another useful application of the intermediates: treatment with an excess of *t*-BuOK in THF results in a smooth dehydrohalogenation to 1-substituted enol ethers. This reaction (which is probably fairly general) requires the use of two equivalents of the base, since *t*-BuOH formed during the elimination complexes with *t*-BuOK. This 1:1-complex is considerably less reactive.

Procedure

A solution of phenylmagnesium bromide in 200 ml of Et_2O is prepared in the usual way (compare also Ref. [7]) from 0.23 mol (36.1 g) of bromobenzene and a 100 % excess of magnesium turnings. The supernatant solution is transferred into a 1-l round-bottomed, three-necked flask (see Chap. I, Fig. 1). In another flask 1,2-dibromodiethyl ether is prepared by adding 0.20 mol (32.0 g) of bromine to a mixture of 0.25 mol (18.0 g) of ethyl vinyl ether and 100 ml of Et_2O with cooling to between −40 and −80 °C. The resulting solution is added dropwise to the Grignard solution with cooling to between −20 and 0 °C. The resulting clear solution (or thin suspension) is cautiously poured into 200 ml of an aqueous solution of 40 g of ammonium chloride. After some manual swirling the mixture is shaken vigorously for a few seconds, after which the layers are separated. The aqueous layer is extracted twice with Et_2O. The combined organic solutions are dried over $MgSO_4$ and subsequently concentrated *in vacuo*. The remaining liquid is added in a number of portions to a vigorously stirred solution of 0.40 mol (44.8 g) of *t*-BuOK in 200 ml of THF. The reaction is strongly exothermic and occasional cooling is necessary to keep the temperature between 50 and 60 °C. After the addition, heating at 50 to 60 °C is continued for 15 min, then 200 ml of ice water is added with vigorous stirring. After separation of the layers, extraction of the aqueous layer with Et_2O, drying the organic solutions over $MgSO_4$ and concentration *in vacuo* the product is obtained by distillation through a 30-cm Vigreux column: b.p. 90 °C/10 mm, n_D^{20} 1.5310, overall yield 82 %.

3.19 Generation of *o*-Lithiochlorobenzene from 2-Bromochlorobenzene



Scale: 0.10 molar.

Apparatus: Chap. I, Fig. 1, 1 l.

Introduction

The thermal stability of "arynoids" *o*-C_6H_4—X decreases rapidly in the order X = F > Cl > Br. *Ortho*-lithiofluorobenzene is stable at temperatures up to about −45 °C, and can be conveniently prepared as described in the experiments 1 and 13 of this chapter. The analogous chlorointermediate has a very limited life time at temperatures above −80 °C, and therefore has to be generated at temperatures in the region of −100 °C. The bromo-"arynoid" is even more unstable and can be generated only at temperatures below −120 °C [175]. We have tried to *ortho*-metallate chlorobenzene with the very active basic reagent BuLi · *t*-BuOK in THF, but the results were disappointing. However, the halogen-metal exchange reaction with *o*-Cl—C_6H_4—Br in THF can be completed in a relatively short time, and the desired intermediate can be trapped with very reactive reagents, such as dimethyl disulfide.

Procedure

THF (100 ml) is added to a solution of 0.11 mol of butyllithium in 77 ml of hexane with cooling to below 0 °C. The mixture is cooled (occasionally cooling in a bath with liquid nitrogen) to ca. −105 °C. A mixture of 0.10 mol (19.2 g) of 1-bromo-chlorobenzene and 30 ml of Et_2O is added dropwise over 10 min, while keeping the temperature between −100 and −105 °C. A white suspension is formed. After an additional 10 min 0.12 mol (11.3 g) of dimethyl disulfide is added over 10 min with vigorous stirring while keeping the temperature below −80 °C. During the addition the suspension disappears. The temperature is allowed to rise to −20 °C and a somewhat gelatinous suspension re-appears. Water (100 ml) is added, after which the product is isolated in the usual way. *Ortho*-Cl—C_6H_4—SCH_3, b.p. 109 °C/15 mm, n_D^{20} 1.6054, is obtained in 94 % yield.

Appendix

1. Generation of Polar Organometallic Intermediates by Deprotonation with Strongly Basic Reagents[8]

$(i\text{–}C_3H_7)_2N\mathbf{H}$

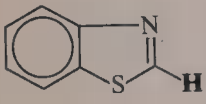
3

$RC{\equiv}C\mathbf{H}$

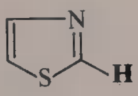
1–3

$\mathbf{H}\text{–}C(=S)NMe_2$

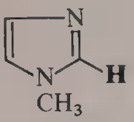
2



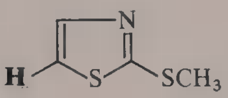
1, 2, 3b–d



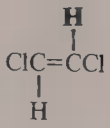
2?, 3b–d



3b–d



1b, c, 2, 3b–d



$Cl\underset{H}{C}=\overset{\mathbf{H}}{C}Cl$

3d, h

1b?, c, 2, 3d?, e?

$\mathbf{H}\text{–}C(=O)NMe_2$

2

$H_2C=C=C\mathbf{H}\text{–}SCH_3$

1, 2, 3

$H_2C=C=C=C\mathbf{H}\text{–}OR$

3b–e

$H_2C=C\mathbf{H}\text{–}C{\equiv}C\text{–}SR$

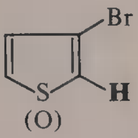
2

$H_2C=C=C\mathbf{H}\text{–}OR$

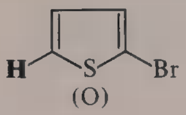
3b–h

$H_2C=C=C\mathbf{H}_2$

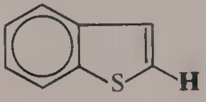
3d



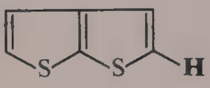
1b?, c, 2



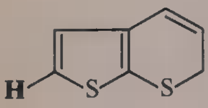
2



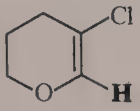
1c?, 2, 3b–f



1c?, 2?, 3b–i



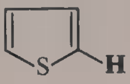
3b–e



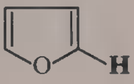
2?, 3b?, c–f

$\mathbf{CH}_3C{\equiv}CSCH_3$

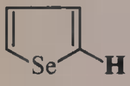
3d, e



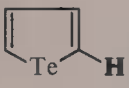
2, 3a–i



3a–i



2?, 3b–d



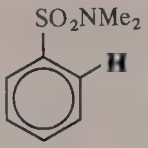
3b–d, 2?

$H_2C=C=C(CH_3)_2$

3d

$CH_3C{\equiv}C\mathbf{CH}_3$

3c–i



3d

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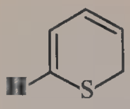
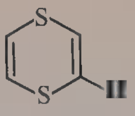
[8] The most acidic protons (in a kinetic sense) are indicated in bold. This table gives a very rough impression of relative acidities. Compounds in one row, and also the compounds $H_2C{=}C{=}CH_2$ to 3-chloropyridine have comparable acidities (in synthetic experiments). Code numbers of reagents: 1a = $LiNH_2/NH_3$; 1b = $NaNH_2/NH_3$; 1c = KNH_2/NH_3; 2 = LDA/THF; 3a = BuLi/THF/hexane; 3b = BuLi · LiBr/Et_2O; 3c = BuLi/Et_2O/hexane; 3d = BuLi/THF/hexane; 3e = BuLi · TMEDA/THF; 3f = BuLi · TMEDA/hexane; 3g = BuLi · *t*-BuOK/Et_2O; 3h = BuLi · *t*-BuOK/THF; 3i = BuLi · *t*-BuOK · TMEDA/hexane.



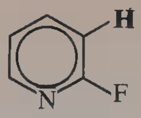
3e



3d, e

$H_2C{=}C\mathbf{H}{-}SPh$

2? , 3d, e



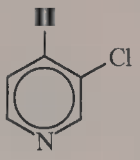
2

$H_2C{=}CH{-}CH{=}C\mathbf{H}{-}SCH_3$

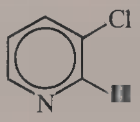
3h

$H_2C{=}CH{-}CH{=}C\mathbf{H}{-}OCH_3$

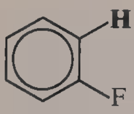
3h, i



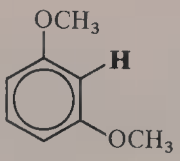
2



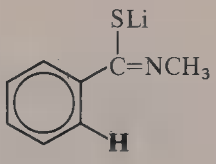
3c



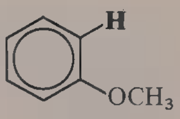
3d–i



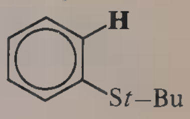
3b–i



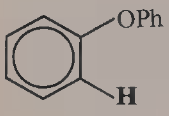
3d, e



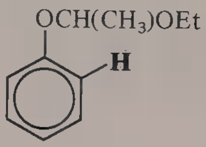
3b–i



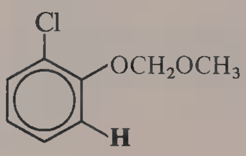
3f, 3h–i?



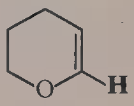
3d



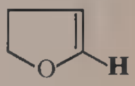
3b–i



3f



3e–i



3e–i

$H_2C{=}C\mathbf{H}{-}OCH_3$

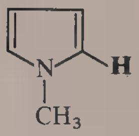
3f–i

$H_2C{=}C\mathbf{H}{-}SCH_3$

3f–i

$CH_3S{-}CH{=}C\mathbf{H}{-}SCH_3$ (*Z*)

3e, 3h?



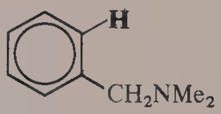
3d–i

$H_2C{=}C\mathbf{H}{-}C{\equiv}C{-}NMe_2$

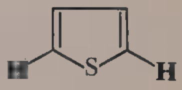
3h, 3i?

$\mathbf{H}{-}C{\equiv}C{-}C\mathbf{H}{=}CH_2$

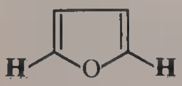
3h, 3i?



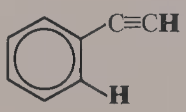
3a, c



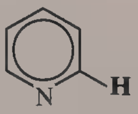
3f–i



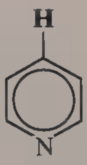
3i



3f, h, i

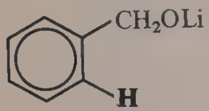


3g



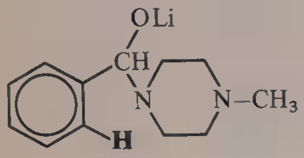
3h, then HMPT

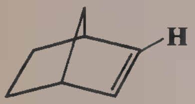

3h, i

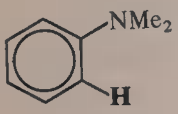

3f

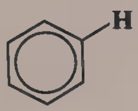
$\mathbf{H}_2$

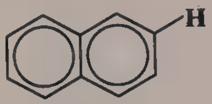
3d, i

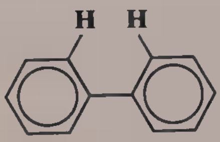

3f


3h, i


3f


3f, i


3i


3f


3i

$H_2C{=}\mathbf{CH_2}$

3i

$t\text{-Bu}{-}CH{=}\mathbf{CH_2}$

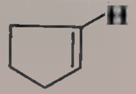
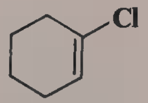
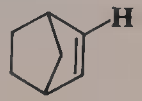
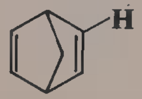
3i

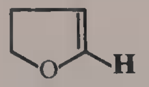
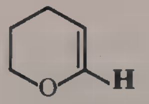
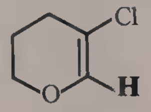
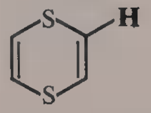
$(\mathbf{CH_3})_4Si$

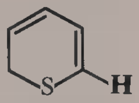
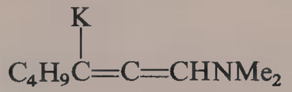
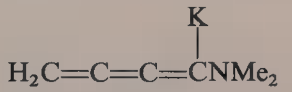
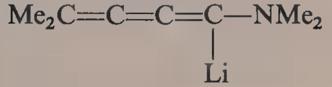
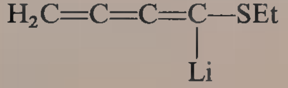
3f, i

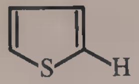
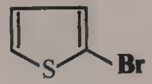
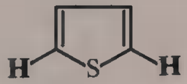
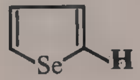

3i? ?

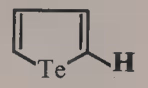
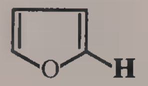
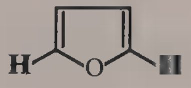
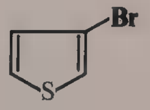
2. Metallation-Functionalization Index[9]

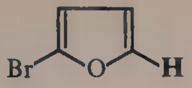
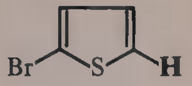
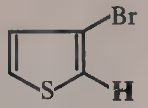
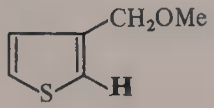
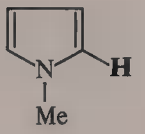
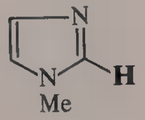
Starting compound[9]	Metallic derivative	Metallation conditions	Functionalization reagents and conditions	Page or [Ref.]
Chapter III				
$H_2C{=}CH_2$	RK	BuLi · *t*-BuOK · TMEDA, hexane	THF, then LiBr, $PhCH{=}O$ PhSSPh	69 [21] [21]
$H_2C{=}CH\mathbf{Br}$	RMgBr	Mg, THF	Me_3SiCl $SnCl_4$ $PhCH{=}O$	48 49 49
$Me_2C{=}CH\mathbf{Br}$	RMgBr	Mg, THF	$PhCH{=}O$	49
$PhC(\mathbf{Br}){=}CH_2$	RLi	EtLi · LiBr, Et_2O	CH_3SSCH_3	72
Z-**Br**$CH{=}CHOEt$	*Z*-RLi	EtLi · LiBr, Et_2O	CH_3SSCH_3	70
	RK	BuLi · *t*-BuOK · TMEDA, hexane	CH_3SSCH_3	54
	RLi	Li, Et_2O	DMF, then H_2O, H^+	51
Chlorocycloheptene	RLi	Li, Et_2O	DMF, then H_2O, H^+	51
	RK RK	BuLi · *t*-BuOK, THF BuLi · *t*-BuOK · TMEDA	LiBr, then $ClCOOCH_3$ THF, then CH_3SSCH_3	54 70
	RK RK	BuLi · *t*-BuOK, THF BuLi · *t*-BuOK · TMEDA, hexane	LiBr, DMF, then H^+, H_2O THF, then CH_3SSCH_3	53 70
	RLi RK	LDA, THF KNH_2, NH_3	$PhCH{=}O$ *n*-$C_6H_{13}Br$	57 55

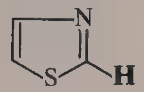
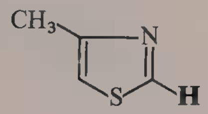
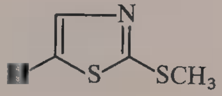
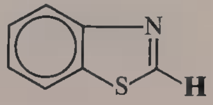
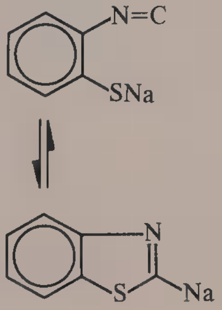
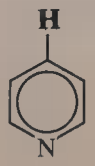
$\mathbf{H}C\equiv C{-}C\mathbf{H}{=}CH_2$	RK_2	BuLi · *t*-BuOK, THF	*n*-$C_7H_{15}Br$	58
$H_2C{=}C{=}C\mathbf{H}_2$	RLi	BuLi, THF	CO_2	[7], 62
$HC\equiv C{-}CH_2\mathbf{Br}$	Allenyl-MgBr	Mg, Et_2O	Bu_3SnCl	[7]
			Me_3SiCl	[6b]
			$RCH{=}O$	[6]
$H_2C{=}C{=}C\mathbf{H}_2$	RLi	BuLi, THF	*n*-$C_7H_{15}Br$	61, [7]
$Me_2C{=}C{=}C\mathbf{H}_2$	RLi	BuLi, THF	CS_2, then CH_3I	[197]
$R'{-}C\equiv C{-}C\mathbf{H}_3$	$H_2C{=}C{=}C(R')Li$	BuLi, THF	Me_3SiCl	65
Chapter IV				
$H_2C{=}CH{-}OEt$	RK	BuLi · *t*-BuOK, THF	$C_9H_{19}Br + HMPT$	84
			$PhCH{=}O$	34
			LiBr, then acetone	84
			LiBr, then cyclopentanone	84
$H_2C{=}CHSCH_3$	RK	BuLi · *t*-BuOK, THF	oxirane	89
			$CH_3N{=}C{=}S$	89
			LiBr, then acetone	89
	RK	BuLi · *t*-BuOK · TMEDA, hexane	THF, then EtSSEt	86
	RK	BuLi · *t*-BuOK · TMEDA, hexane	THF, then CH_3SSCH_3	86
	RLi	BuLi, THF	CH_3SSCH_3	87
	RLi	BuLi · TMEDA, THF	CH_3SSCH_3	91
			Me_3SiCl	91
			CH_3I	91

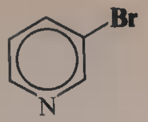
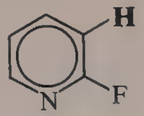
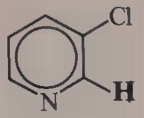
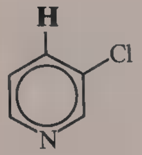
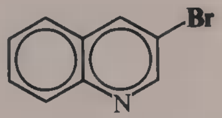
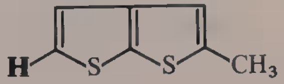
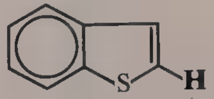
Starting compound	Metallic derivative	Metallation conditions	Functionalization reagents and conditions	Page or [Ref.]
	RLi	BuLi · TMEDA, THF	EtI	93
Z—CH_3S—CH=**CH**—SCH_3	RLi	BuLi · TMEDA, THF	CH_3I	90
H_2C=CH—CH=**CH**—OCH_3	RK	BuLi · t-BuOK, THF	various reagents	[91]
H_2C=CH—CH=**CH**—SCH_3	RK	BuLi · t-BuOK, THF	various reagents	92
E—ClCH=**CH**Cl	RK	BuLi · t-BuOK, THF	n-$C_6H_{13}Br$ + HMPT	94
Cl**CH**=$C(NMe_2)_2$	(RK) ↓ Me_2N—C≡C—NMe_2	KNH_2, NH_3	–	95
H_2C=C=**CH**—OCH_3	RLi	BuLi, THF	various reagents	[7], 96
R**CH₂**C≡C—SR′	RCH=C=C(Li)SR′	BuLi · TMEDA, THF	various reagents	[7], 96
	RCH=C=C(K)SR′	BuLi · t-BuOK, THF	various reagents	[7], 96
H_2C=C=**CH**—NMe_2	RLi	BuLi, THF	–	97
R**CH₂**C≡C—NEt_2	RCH=C=C(K)NEt_2	BuLi · t-BuOK, THF	LiBr, then Me_3SiCl	98
C_4H_9C≡C—**CH₂**OMe	C_4H_9CH=C=C(K)OMe	BuLi · t-BuOK, THF, then HMPT	n-C_3H_7Br	99
C_4H_9C≡C—**CH₂**NMe_2	 $C_4H_9\overset{K}{C}=C=CHNMe_2$	BuLi, THF, then t-BuOK	t-BuOH	100
H_2C=**CH**—C≡C—NMe_2	 $H_2C=C=C=\overset{K}{C}NMe_2$	BuLi · t-BuOK, THF	t-BuOH	102
MeO—$C(Me)_2C$≡C**CH₂**NMe_2	 $Me_2C=C=C=\underset{Li}{C}-NMe_2$	BuLi, THF	Me_3SiCl	104
H_2C=**CH**—C≡C—SEt	 $H_2C=C=C=\underset{Li}{C}-SEt$	LDA, THF	H_2O	105

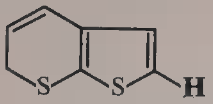
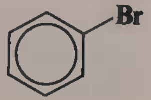
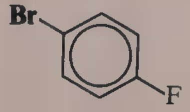
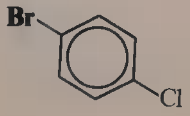
H—C(=O)NMe$_2$	RLi	LDA, THF	t-BuCH=O	112
H—C(=S)NMe$_2$	RLi	LDA, THF	PhCH=O	112
				[108–111]
Chapter V				
	RLi	EtLi · LiBr, Et$_2$O	CH$_3$I	121
		BuLi, THF	n-C$_4$H$_9$Br	124
			oxirane	125
			BrCH$_2$CH(OEt)$_2$	126
			PhCH$_2$Br	128
	RK	BuLi, THF, then t-BuOK	(CH$_2$O)$_n$	34
	RLi	BuLi, THF	CS$_2$	149
			CH$_3$N=C=S	152
			PhN=S=O	152
			PhN=C=S	152
			PhN=C=O	152
			"Se", then CH$_3$I	151
			"Te", then CH$_3$I	151
			ClCOOCH$_3$	145
			ClC(=O)NMe$_2$	146
			CuBr (catal.), then CS$_2$, then CH$_3$I	149
			SCl$_2$	162
			CuCl$_2$	163
	RMgBr	Mg, THF	CuBr(catal.), then CS$_2$, then CS$_2$, CH$_3$I	148
	RK$_2$	BuLi · t-BuOK, THF	Me$_3$SiCl	164
	RLi	BuLi, THF	DMF, then H$_2$O, H$^+$	144

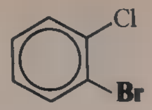
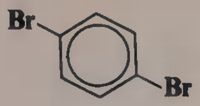
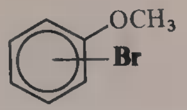
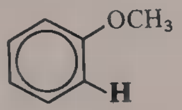
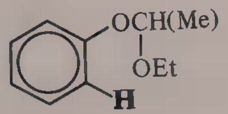
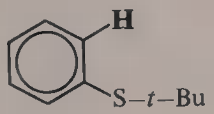
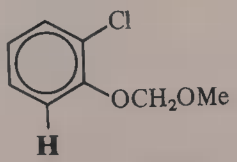
Starting compound	Metallic derivative	Metallation conditions	Functionalization reagents and conditions	Page or [Ref.]
	RLi	EtLi · LiBr, Et_2O	DMF, then H_2O, H^+	143
	RLi	EtLi · LiBr, Et_2O	Br_2	134
	RLi	BuLi, Et_2O	HMPT, $C_8H_{17}Br$	127
	RLi	BuLi, THF	I_2	135
			$PhCH_2Br$	128
			$BrCH_2CH(OEt)_2$	126
			PhN=S=O, PhN=C=O	152
			SCl_2	162
			$CuCl_2$	163
			ClC(=O)NMe_2	146
	RK_2	BuLi · *t*-BuOK · TMEDA	THF, then CH_3SSCH_3	165
	RLi	BuLi, THF	H_2C=CH—CH_2Br	123
			SCl_2	162
			$CuCl_2$	163
			$\left\{\begin{matrix} MgBr_2 \cdot Et_2O\text{, then} \\ PhCOOO\text{—}t\text{-Bu} \end{matrix}\right\}$	158
			$MgBr_2 \cdot Et_2O$, then I_2	157
			PhC(=O)NMe_2, then H_2O, H^+	160
			CH_3SSCH_3	160
			$ClCH_2OCH_3$	160
			"S", then H_2O, then H^+	150
	RLi	BuLi, Et_2O	DMF, then H_2O, H^+	160

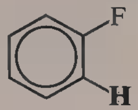
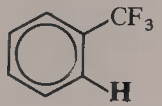
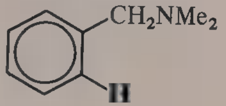
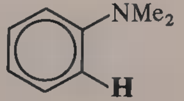
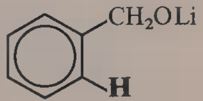
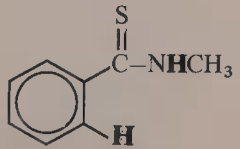
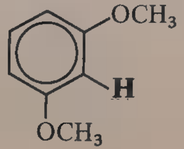
	RLi	LDA, THF	CH_3SSCH_3	156
	RLi	LDA, THF	CH_3SSCH_3	156
	RLi	LDA, THF	CO_2 oxirane DMF, then H_2O, H^+ Me_3SiCl CH_3SSCH_3 $(CH_2O)_n$	154 154 154 154 154 154
	RK	KNH_2, NH_3	C_2H_5Br oxirane	130 130
	RLi	BuLi, THF	DMF, then H_2O, H^+	161
	RLi	BuLi, THF BuLi · TMEDA, hexane	n-C_4H_9Br THF, then CO_2, then H_2O, H^+ THF, then I_2 $ClCOOCH_3$	129 136 167 146
	RK	BuLi · *t*-BuOK, THF	CH_3SSCH_3	166
	RLi	BuLi, THF	CH_3SSCH_3	138

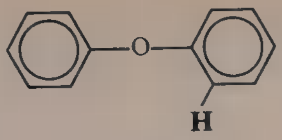
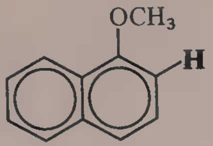
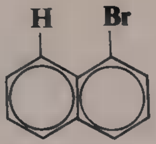
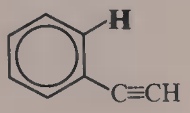
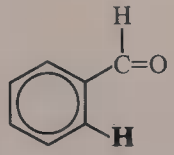
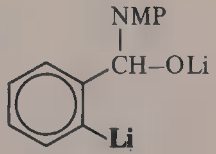
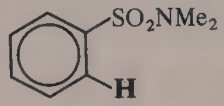
Starting compound	Metallic derivative	Metallation conditions	Functionalization reagents and conditions	Page or [Ref.]
	RLi	BuLi, THF	Me_3SiCl t-BuCH=O	138 139
	RLi	BuLi, THF	DMF, then H_2O, H^+ $CH_3N{=}C{=}S$, $PhN{=}C{=}S$, then H_2O, H^+	142 153
	RNa	$NaNH_2$, NH_3	C_2H_5Br	132
	RLi	BuLi, THF	DMF, then H_2O, H^+	143
		$NaNH_2$, NH_3	C_2H_5Br	141
			$CH_3SC{\equiv}N$	141
	RLi	BuLi, THF	Me_3SiCl	140
	RK	BuLi · t-BuOK, THF then HMPT + pyridine	LiBr, then I_2	175

	RLi	BuLi, THF	CH_3SSCH_3 $D—OCH_3$	172 172
	RLi	LDA, THF	$CH_3SC{\equiv}N$	169
	RLi	BuLi, THF	CH_3SSCH_3	171
	RLi	LDA, THF	Me_3SiCl	170
	RLi	BuLi, THF	Me_3SiCl	174
	RLi	BuLi, THF	CH_3I	134
	RLi	BuLi, THF	Cl_3CCCl_3	168

Starting compound	Metallic derivative	Metallation conditions	Functionalization reagents and conditions	Page or [Ref.]
	RLi	BuLi, THF	CH_3I	133
Chapter VI				
	RLi	BuLi · TMEDA, hexane	–	192
	RK	BuLi · *t*-BuOK · TMEDA, hexane	THF, then CH_3SSCH_3	193
			THF, then DMF, then H_2O, H^+ THF + LiBr, then "Se" then CH_3I	197
			THF, then LiBr, then "Te", then CH_3I	197
	RMgBr	Mg, THF	$BrCH_2CH(Br)OEt$	212
	RLi	BuLi, THF	$CH_3N{=}C{=}S$	190
	RLi	BuLi, Et_2O	oxirane $(CH_2O)_n$	192 192
	RLi	BuLi, THF	CuBr(catal.), then CS_2, then CH_3I $ClC(=O)NMe_2$	191 190
	RLi	BuLi, THF	$CH_3N{=}C{=}S$	190

	RLi	BuLi, THF	CH_3SSCH_3	213
	RLi	BuLi, THF	CH_3SSCH_3	190
	RLi_2	2 BuLi, THF	CH_3SSCH_3	190
	RLi	BuLi, THF	CH_3SSCH_3 CuBr(catal.), then CS_2, then CH_3I	190 191
	RLi	BuLi · TMEDA, hexane	THF, then CH_3SSCH_3	199
	RK	BuLi · *t*-BuOK, THF	CH_3SSCH_3	206
	RLi	BuLi · TMEDA, hexane	THF, then CH_3SSCH_3	199
	RLi	BuLi · TMEDA, hexane	THF, then C_2H_5Br	30
	RLi	BuLi · TMEDA, hexane	THF, then DMF, then H_2O, H^+	199

Starting compound	Metallic derivative	Metallation conditions	Functionalization reagents and conditions	Page or [Ref.]
	RLi	BuLi · TMEDA, THF	CH_3SSCH_3	206
	RK	BuLi · *t*-BuOK, THF	CH_3SSCH_3	206
			n-$C_6H_{13}Br$ + HMPT	206
			oxirane + HMPT	206
	RLi	BuLi · TMEDA, hexane	CH_3SSCH_3	199
	RLi	BuLi, Et_2O	DMF, then H_2O, H^+	202
			I_2	203
	RLi	BuLi · TMEDA, hexane	THF, then CH_3SSCH_3	203
	RLi	BuLi · TMEDA, hexane	THF, then CH_3SSCH_3	203
			THF, then n-C_4H_9Br	201
	RLi_2	BuLi, THF	Me_3SiCl, then H_2O, OH^-	209
	RLi	BuLi, THF	CH_3SSCH_3	203

	RLi	BuLi, THF	CO_2, then H_2O, H^+	204
	RLi	BuLi · TMEDA, hexane	THF, then CO_2, then H_2O, H^+	198
	RLi_2	BuLi, Et_2O, then BuLi · TMEDA, hexane	CH_3SSCH_3	195
	RK_2	BuLi · *t*-BuOK, THF	various reagents	207 [46]
		BuLi · *t*-BuOK · TMEDA hexane	–	207
		LiNMP, hexane, then TMEDA and BuLi	Me_3SiCl, then H^+, H_2O	210
	RLi	BuLi, THF	CH_3I	208
Naphthalene (**2—H**)	RK	BuLi · *t*-BuOK · TMEDA, hexane	THF, then CH_3SSCH_3	194

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[9] The hydrogen or halogen atoms in the starting compounds that are replaced by metal (Li, Na, K or MgBr), are indicated in bold in the first column

3. Index of Reaction Types

Alkylation with alkyl halides	Page or [Ref.]
In liq. NH_3:	
1-methylcyclopropene + KNH_2 + $C_6H_{13}Br$	55
$RC{\equiv}CH + MNH_2 + RBr$	[6, 7]
$RCH{=}C{=}C(Na)SR' + RBr$	[6, 7]
3-bromothiophene + KNH_2 + C_2H_5Br	130
2-(CH_3S)-thiazole + $NaNH_2$ + C_2H_5Br	132
benzothiazole + $NaNH_2$ + C_2H_5Br	141
In Et_2O:	
thiophene + $EtLi \cdot LiBr$ + CH_3I	121
furan + BuLi + $C_8H_{17}Br$, (co-solvent: HMPT)	127
In THF:	
$KC{\equiv}C{-}C(K){=}CH_2 + C_7H_{15}Br$	58
allene + BuLi + $C_7H_{15}Br$	61, [7]
$H_2C{=}C(K)OEt + C_9H_{19}Br$, (co-solvent: HMPT)	84
$CH_3SCH{=}CH{-}SCH_3$ + BuLi · TMEDA + CH_3I	90
1,4-dithiin + BuLi · TMEDA + CH_3I	91
$H_2C{=}CH{-}CH{=}C(K){-}XCH_3 + CH_3I$ ($X{=}O$ or S)	[91], 92
E-ClCH=CHCl + BuLi · *t*-BuOK-THF + $C_6H_{13}Br$, (co-solvent: HMPT)	94
$H_2C{=}C{=}C(Li)OCH_3 + RBr$, (co-solvent: HMPT)	[7], 96
$C_4H_9CH{=}C{=}C(K)OCH_3 + C_3H_7Br$, (co-solvent: HMPT)	99
thiophene + BuLi + C_4H_9Br	124
thiophene + BuLi + $PhCH_2Br$	126
furan + BuLi + $PhCH_2Br$	128
3-thienyl-Li + allyl bromide	123
1-methylpyrrole + BuLi + BuBr	129
2-methylthienothiophene + BuLi + CH_3I	134
thienothiopyran + BuLi + CH_3I	133
2 H-thiopyran + BuLi · TMEDA + C_2H_5I	93
$PhSO_2NMe_2$ + BuLi + CH_3I	208
fluorobenzene + BuLi · *t*-BuOK + $C_6H_{13}Br$, (co-solvent: HMPT)	206
$PhCH_2OH$ + 2 BuLi · TMEDA + C_4H_9Br	201
PhS—*t*-C_4H_9 + BuLi · TMEDA + C_2H_5Br	30

Other types of alkylating reagents	Page or [Ref.]
In liq. NH_3:	
3-Br-thiophene + KNH_2 + oxirane	130
$RCH{=}C{=}C(Na)SR'$ + oxirane	[6]
In Et_2O:	
$PhMgBr + BrCH_2CH(Br)OEt$	212
p-Li—C_6H_4—F + oxirane	192

Other types of alkylating reagents, continued	Page or [Ref.]
In THF:	
$H_2C{=}C(K)SCH_3$ + oxirane	89
2-thienyl-Li + oxirane	125
2-thienyl-Li + $BrCH_2CH(OEt)_2$	126
2-furyl-Li + $BrCH_2CH(OEt)_2$	126
3-Br-2-lithiothiophene + oxirane	154
3-thienyl-Li + $ClCH_2OCH_3$	160
o-K—C_6H_4—F + oxirane, (co-solvent: HMPT)	206

Carboxylation with CO_2 (THF)	Page or [Ref.]
$H_2C{=}C{=}CHLi$, (reversed order addition)	[7], 62
2-lithio-1-methylpyrrole, (reversed order addition)	136
3-Br-2-lithiothiophene, (normal order addition)	154
o-lithiodiphenyl ether, (reversed order addition)	204
2-thienyl-Li, (normal order addition)	33

Carboxyalkylations with $ClCOOCH_3$ (THF) (all reversed order addition)	Page or [Ref.]
norbornenyl-Li	54
2-thienyl-Li	145
2-Li-1-methylpyrrole	146

Carbamoylations with $ClCONMe_2$ (THF)	Page or [Ref.]
2-thienyl-Li	146
2-furyl-Li	146
p-F—C_6H_4—Li	190

Chalcogenations with S, Se, Te (THF)	Page or [Ref.]
2-thienyl-Li + Se + CH_3I	151
2-thienyl-Li + Te + CH_3I	151
Ph—Li + Se + CH_3I	197
Ph—Li + Te + CH_3I	197
3-thienyl-Li + S + H^+, H_2O	150
o-Li—$C_6H_4C{\equiv}C$—Li + S, Se or Te + *t*-BuOH	[46]

Protonation and deuteration	Page or [Ref.]
$H_2C{=}C{=}C{=}C(K)NMe_2$ + *t*-BuOH	102
3-lithiopyridine + CH_3OD	173
$Me_2C{=}C{=}C{=}C(Li)NMe_2$	[118], 104
$H_2C{=}C{=}C{=}C(Li)SEt$	105

Halogenations	Page or [Ref.]
norbornadienyl-Li + I_2 (THF)	[77]
2-furyl-Li + I_2 (THF)	135
2-furyl-Li + Br_2 (Et_2O)	134
2-Li-benzothiophene + $Cl_3C—CCl_3$ (THF)	168
o-Li—$C_6H_4CH_2NMe_2$ + I_2 (THF)	203
2-Li-1-methylpyrrole + I_2 (THF)	167
4-lithiopyridine + I_2 (THF)	175
o-Li—C_6H_4—C≡C—Li + $Cl_3C—CCl_3$ (THF)	[46]
3-thienyl-MgBr + I_2 (THF)	157
o-MgBr—C_6H_4—C≡C—MgBr + I_2 (THF)	[46]
o-Li—C_6H_4—C≡C—Li + Br_2 (THF)	[46]

Hydroxyalkylations in THF or Et_2O	Page or [Ref.]
$H_2C=CH—MgBr$ + PhCH=O (THF)	49
$Me_2C=CH—MgBr$ + PhCH=O (THF)	49
$H_2C=C(Li)OEt$ + acetone (THF)	84
$H_2C=C(Li)SCH_3$ + acetone (THF)	89
$H_2C=CH—CH=C(K)—XCH_3$ + $CH_3CH=O$ (THF) (X = O or S)	[91]
$H_2C=C=C(Li)OEt$ + various ketones and aldehydes (Et_2O or THF)	[7]
$LiC(=O)NMe_2$ + t-BuCH=O (THF)	[108–111]
$LiC(=S)NMe_2$ + PhCH=O (THF)	112
2-thienyl-K + $(CH_2O)_n$ (THF)	34
3-Br-2-lithiothiophene + $(CH_2O)_n$ (THF)	154
2-lithiothiazole + t-$C_4H_9CH=O$ (THF)	139
p-Li—C_6H_4F + $(CH_2O)_n$ (Et_2O)	152
$H_2C=C=CH—MgBr$ + various aldehydes (Et_2O)	[6]
$H_2C=C(Li)OEt$ + cyclopentanone	84

Introduction of an —O—t-C_4H_9 group	Page or [Ref.]
3-thienyl-MgBr + PhCOOO—t-C_4H_9	158

Thiocarboxylations with CS_2 in THF	Page or [Ref.]
$(CH_3)_2C=C=CHLi$ + CS_2 then CH_3I	[197]
2-furyl-Li + CuBr(catal.), then CS_2, then CH_3I	149
2-thienyl-MgBr + CS_2 + CuBr(catal.), then CH_3I + HMPT	148
p-Li—C_6H_4F + CuBr(catal.), then CS_2, then CH_3I	191
o-Li—$C_6H_4OCH_3$ + CuBr(catal.), then CS_2, then CH_3I	191

Additions to RN=C=S, RN=C=O and PhN=S=O in THF	Page or [Ref.]
$H_2C{=}C(K)SCH_3 + CH_3N{=}C{=}S$	89
2-thienyl-Li + $CH_3N{=}C{=}S$	152
2-furyl-Li + $CH_3N{=}C{=}S$	152
2-furyl-Li + PhN=S=O	152
2-thienyl-Li + PhN=C=S	152
2-thienyl-Li + PhN=S=O	152
2-thienyl-Li + PhN=C=O	152
PhLi + $CH_3N{=}C{=}S$	190
p-Cl—C_6H_4Li + $CH_3N{=}C{=}S$	190

Formylations with DMF and reactions with dimethylbenzamide	Page or [Ref.]
2-cyclohexenyl-Li (Et_2O)	51
2-cycloheptenyl-Li (Et_2O)	51
norbornadienyl-Li (THF)	53
3-thienyl-Li (THF)	160
2-lithioselenophene (THF)	143
2-lithiotellurophene (Et_2O)	144
3-Br-2-lithiothiophene (THF)	154
2-Li-3-(CH_3OCH_2)-thiophene (THF)	161
o-Li—C_6H_4—SO_2NMe_2 (THF)	208
2-Li-4-methylthiazole (THF)	142
5-Li-2-CH_3S-thiazole (THF)	143
Ph—K (THF)	31
3-Cl-1-Li-2-(OCH_2OCH_3)-benzene (THF)	199
o-Li—$C_6H_4CH_2NMe_2$ (THF)	202
3-Li-thiophene + $PhCONMe_2$ (THF)	160

Reactions with SCl_2 and $SnCl_4$ (THF)	Page or [Ref.]
$H_2C{=}CH$—MgBr + $SnCl_4$	49
2-furyl-Li + SCl_2	162
2-thienyl-Li + SCl_2	162
3-thienyl-Li + SCl_2	162
p-Li—C_6H_4—F + SCl_2	190

Reactions with CH_3SSCH_3, $C_2H_5SSC_2H_5$, $CH_3SC{\equiv}N$ and Me_3SiCl (THF or Et_2O)	Page or [Ref.]
Several examples (see Index 2)	

Couplings with $CuCl_2$ (THF)	Page or [Ref.]
2-furyl-Li	163
2-thienyl-Li	163
3-thienyl-Li	163

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