Reagents for Organic Synthesis

VOLUME 4

Mary Fieser

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PREFACE

This volume covers literature on reagents published for the most part in 1970–1972, with some references to literature published in the early months of 1973. It includes references to 297 reagents reviewed by us for the first time as well as new references to 350 reagents previously discussed. We are surprised that so many new reagents have been introduced for organic synthesis. It is also interesting that new procedures have been developed for old reagents, for example, aluminum chloride and potassium permanganate.

We are indebted to our colleagues who have sent us additional information or suggested suitable topics for inclusion. We are pleased to acknowledge the help of Professor P. L. Fuchs, Professor J. Secrist, Dr. M. Wuonola, Dr. R. Wingard, R. L. Danheiser, and R. H. Wollenberg who have agreed to read proof.

Miss Theodora S. Lytle and Miss Lenor Kirkeby typed the manuscript and drew the formulas.

Dr. S. Brachwitz and Dr. A. Vasella have also been most helpful in proofreading. The photograph on the dust cover was taken by E. M. Bellott.

We thank Research Corporation for continued financial support.

This is the first of our books, except for unauthorized translations, that does not include a picture of a cat. It is dedicated, however, to the many cats that we have had the pleasure of knowing.

Cambridge, Massachusetts
June 3, 1973

MARY FIESER
LOUIS F. FIESER

We sincerely regret the delay in publication of this book. It has been caused by several factors, one of which has been beyond the control of the publisher. The manuscript was set in type in England during the energy crisis there.

CONTENTS

Introduction 1

Reagents (A–Z) 4

Errata for Volume 3 580

Additional Suppliers 580

Index of Reagents according to types 581

Author index 593

Subject index 623

Introduction

Arrangement. For enhanced usefulness the book is provided not only with a subject and an author index but also with an index of types, that is, types of reactions or types of compounds, for example: acetylation, bromination, cycloaddition, decarboxylation, or: acetonides, benzyne precursors, carbene precursors. Listed alphabetically under each such entry are all the reagents which figure in the operation or group cited, whether as prime reactant, catalyst, solvent, scavenger, etc. A given reagent may fit appropriately in two or more categories. When a reagent does not fit easily into a reasonable category, we leave it unclassified rather than make a forced assignment. With so many reagents available as oxidants and for use as reducing reagents, it seems out of the question to attempt to indicate in the index of types further details about these general reactions.

Names and spelling. One guideline we have followed is the rule recently adopted by *Organic Syntheses* that when an ester, ether, or peroxide contains two or more alkyl, aryl, or acyl groups the name must indicate the number of such groups:

Formula	*Correct*	*Incorrect*
$(CH_3)_2O$	Dimethyl ether	Methyl ether
$(C_2H_5O)_2SO_2$	Diethyl sulfate	Ethyl sulfate
$(C_6H_5)_2O$	Diphenyl ether	Phenyl ether
$(CO_2CH_3)_2$	Dimethyl oxalate	Methyl oxalate
$CH_2(CO_2C_2H_5)_2$	Diethyl malonate	Ethyl malonate
$(C_6H_5COO)_2$	Dibenzoyl peroxide	Benzoyl peroxide
$HC(OC_2H_5)_3$	Triethyl orthoformate	Ethyl orthoformate
$(C_2H_5O)_4C$	Tetraethyl orthocarbonate	Ethyl orthocarbonate

That the situation previously was highly confused is evident from the following entries in the index of *Org. Syn., Coll. Vol.*, **4**: "Diethyl oxalate" and "Diethyl malonate" (both correct), but "Ethyl orthoformate" and "Ethyl orthocarbonate" (both incorrect). The following entry is describable as a double error: "Triethyl orthoformate, *see* Ethyl orthoformate." To locate all references to a given ester, it is thus necessary to search under two names. We urge suppliers to revise their catalogs in accordance with the rule cited. In this book we do not even list, with cross references, names which we consider to be incorrect.

Similar reform in the nomenclature of polyhalogen compounds may come some day, but for the present we consider it imprudent to do more than make a start. Thus the correct names for BF_3 and for $ClCH_2CH_2Cl$ surely are boron trifluoride and ethylene dichloride, and we feel no restraint from using them. However, although the names

methylene chloride for CH_2Cl_2 and aluminum chloride for $AlCl_3$ seem incorrect, we cannot bring ourselves to break with tradition and employ other names.

Abbreviations. Short forms of abbreviations of journal titles are as follows:
Accounts of **Chemical Research**
Journal of the **American** Chemical **Society**
Analytical Letters
Angewandte Chemie
Angewandte Chemie, international Edition in English
Annalen der Chemie
Annales de chimie (Paris)
Australian Journal of **Chemistry**
Chemische **Berichte** (formerly **Berichte** der deutschen chemischen Gesellschaft)
Bulletin de la **société** chimique de France
Canadian Journal of **Chemistry**
Carbohydrate Research
Chemical Communications
Chemical and **Pharmaceutical Bulletin Japan**
Acta **Chemica Scandinavica**
Chemistry and **Industry**
Chemical Reviews
Collection of **Czechoslovak** Chemical Communications
Comptes rendus hebdomadaires des séances de l'académie des sciences
Gazzetta Chimica Italiana
Helvetica Chimica Acta
Inorganic Synthesis
Journal of **Chemical Education**
Journal of the **Chemical Society** (London)
J.C.S. Chemical Communications
Journal of **Heterocyclic Chemistry**
Journal of **Medicinal Chemistry**
Journal of **Organic** Chemistry
Journal of **Organometallic Chemistry**
Journal für **praktische Chemie**
Monatschefte für Chemie
Organic Syntheses
Organic Syntheses, Collective Volume
Proceedings of the **Chemical Society**
Records of **Chemical Progress**
Receuil des **travaux** chimique des Pays-Bas (The Netherlands)

The book by one of us, **Organic Experiments**, 2nd Ed., D. C. Heath and Co., Boston (1968), is referred to as **Org. Expts.**

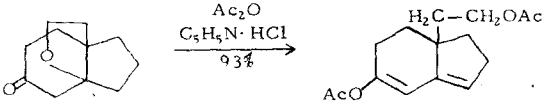
Abbreviations

Ac	Acetyl
AcOH	Acetic acid
BuOH	Butanol
Bz	Benzoyl
CAN	Ceric ammonium nitrate
Cathyl	Carboethoxy
Cb	Carbobenzoxy
DABCO	1,4-Diazabicyclo[2,2,2]octane
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Diglyme	Diethylene glycol dimethyl ether
Dimsyl sodium	Sodium methylsulfinylmethide
DMA	Dimethylacetamide
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNF	2,4-Dinitrofluorobenzene
DNP	2,4-Dinitrophenylhydrazine
EtOH	Ethanol
Glyme	1,2-Dimethoxyethane
HMPT	Hexamethylphosphoric triamide
MeOH	Methanol
DME	Dimethoxyethane
MMC	Magnesium methyl carbonate
Ms	Mesyl, CH_3SO_2
NBA	N-Bromoacetamide
NBS	N-Bromosuccinimide
Ph	Phenyl
Phth	Phthaloyl
PPA	Polyphosphoric acid
PPE	Polyphosphate ester
Py	Pyridine
THF	Tetrahydrofurane
TMEDA	N,N,N,N-Tetramethylethylenediamine
Triglyme	Triethylene glycol dimethyl ether
Trityl	$(C_6H_5)_3C-$
Ts	Tosyl, p-$CH_3C_6H_4SO_2-$
TsCl	Tosyl chloride
TsOH	Tosic acid, p-$CH_3C_6H_4SO_3H$
TTFA	Thallium(III) trifluoroacetate

A

Acetic anhydride–Pyridine hydrochloride.

Ether cleavage.[1] Treatment of the keto ether (1, 9-oxatricyclo[4.3.3.0]dodecane-3-one) with acetic anhydride and pyridine hydrochloride (reflux 5.5 hr.) yields the diacetate (2, 4-acetoxy-1-(2-acetoxyethyl)bicyclo[4.3.0]nonadiene-4,6) in 93 % yield.

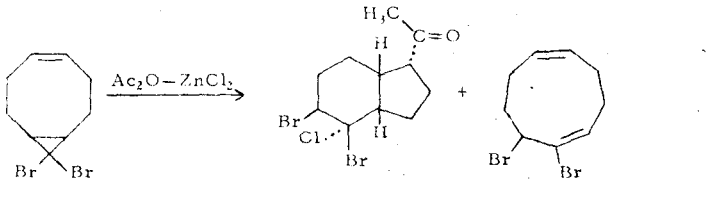


(1) (2)

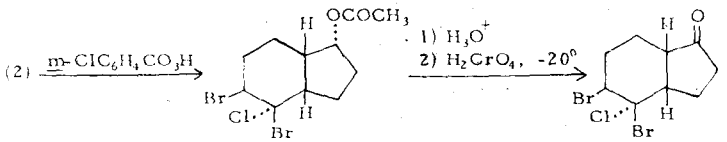
[1]N. P. Peet and R. L. Cargill, *J. Org.*, **38**, 1215 (1973).

Acetic anhydride–Zinc chloride.

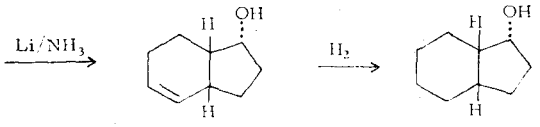
cis-Hydrindane-1-ol.[1] Reaction of the dibromide (1)[2] with acetic anhydride–zinc chloride in methylene chloride gives the ketone (2) in 30 % yield together with the dibromide (3), 21 % yield. Acetic anhydride is essential for the transannular cyclization reaction; treatment of (1) with zinc chloride alone in methylene chloride merely isomerizes (1) to the *trans*-isomer of (3). Baeyer–Villiger oxidation of (2) affords (4),



(1) (2, 30%) (3, 21% yield)



(4) (5)



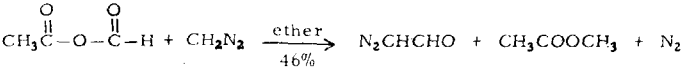
(6) (7)

which is hydrolyzed to the alcohol and oxidized with Jones reagent. Reduction of (5) with lithium in ammonia yields a single alcohol (6), which is hydrogenated to *cis*-hydrindane-1-ol (7).

[1]L. W. Boyle and J. K. Sutherland, *Tetrahedron Letters*, 839 (1973).
[2]L. Skattebøl, *Chem. Scand.*, **17**, 1683 (1963).

Acetic-formic anhydride, **1**, 4; **2**, 10–12; **3**, 4.

Diazoacetaldehyde.[1] Diazoacetaldehyde is prepared conveniently in 46% yield by the reaction of acetic-formic anhydride with diazomethane. The coproduct, methyl

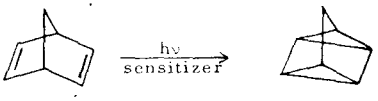


acetate, is readily removed by rotary evaporation. Diazoacetaldehyde is a precursor of formylcarbene (**2**, 101–102) and has been used for ethanalation of olefins (**3**, 73).

[1]J. Hooz and G. F. Morrison, *Org. Prep. Proc. Int.*, **3**, 227 (1971).

Acetophenone, $C_6H_5COCH_3$, B.p. 202°/749 mm.

Photoisomerization of bicyclo[2.2.1]hepta-2,5-diene (1) in the presence of acetophenone as sensitizer provides a method for the preparation of quadricyclane (2). The



(1) (2)

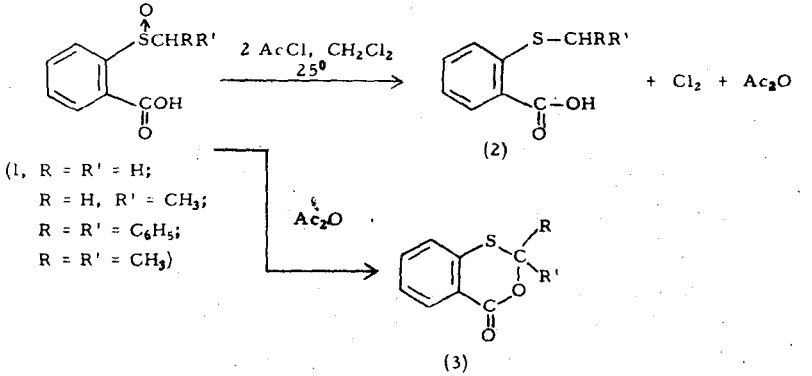
reaction is carried out with 180 g. of (1) in 1 l. of ether in a commercial 550-W immersion photochemical reactor equipped with a stirrer and a condenser under nitrogen with 8 g. of acetophenone as photosensitizer for 36–48 hr.; yield 70–80%.[1]

[1]C. D. Smith, *Org. Syn.*, **51**, 133 (1971).

Acetyl chloride, **1**, 11; **2**, 383; **3**, 8.

Acetylation of γ-(naphthyl-2)-butyric acid ethyl ester with aluminum chloride in nitrobenzene.[1]

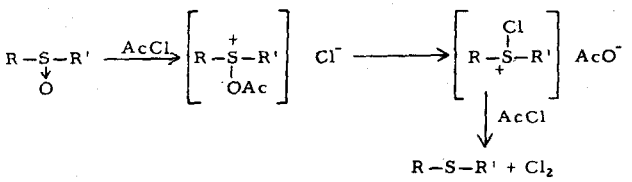
Reduction of sulfoxides.[2] When an alkyl *o*-carboxyphenyl sulfoxide (1) is treated with acetyl chloride in methylene chloride at room temperature an exothermic reaction takes place with evolution of chlorine to give the sulfide (2) in nearly quantitative yield.



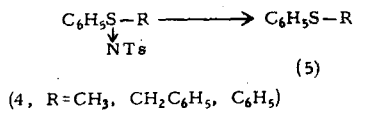
Note that treatment of (1) with acetic anhydride gives a 3,1-benzoxathiane-4-one (3) via a Pummerer rearrangement in good yield.[3]

The reduction of sulfoxides by acetyl chloride is a general reaction and yields are generally high. However, the reduction of di-*n*-butyl sulfoxide with acetyl chloride gives di-*n*-butyl sulfide in only 70% yield.

The mechanism formulated is suggested for the reduction.



Sulfilimines (4) are also reduced to sulfides (5) by acetyl chloride in nearly quantitative yield.

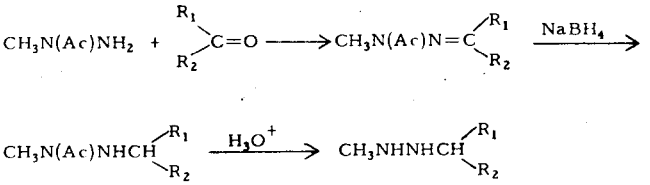


[1]A. U. Rahman and C. Perl, *Ann.*, **718**, 127 (1968).
[2]T. Numata and S. Oae, *Chem. Ind.*, 277 (1973).
[3]*Idem*, *ibid.*, 726 (1972).

1-Acetyl-1-methylhydrazine, $CH_3N(Ac)NH_2$. Mol. wt. 88.11, b.p. 103°/8 torr, m.p. 16°.

The reagent is best prepared by acetylation of methylhydrazine (Matheson, Coleman and Bell) with acetic anhydride in pyridine (76% yield).[1]

1-Alkyl-2-methylhydrazines.[2] 1-Acetyl-1-methylhydrazine reacts with aldehydes or ketones, usually in quantitative yield, to give acetylmethylhydrazones, which are



converted into 1-alkyl-2-methylhydrazines by reduction ($NaBH_4$) and hydrolysis (yields 40–80%).

[1]F. E. Condon, *J. Org.*, **37**, 3608 (1972).
[2]*Idem*, *ibid.*, **37**, 3615 (1972).

Acetyl sulfuric acid.

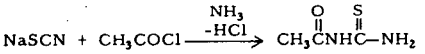
The statement in Vol. **2**, 389 that the correct formula for sulfoacetic acid is $HOOCCH_2SO_2OH$ needs to be elaborated by the further statement that the compound mentioned in **1**, 1117 is acetyl sulfuric acid.

Sulfoacetic acid is best prepared by the action of sodium sulfite on sodium chloroacetate.[1]

[1]E. E. Gilbert, *Sulfonation and Related Reactions*, Interscience, New York, 277 (1965).

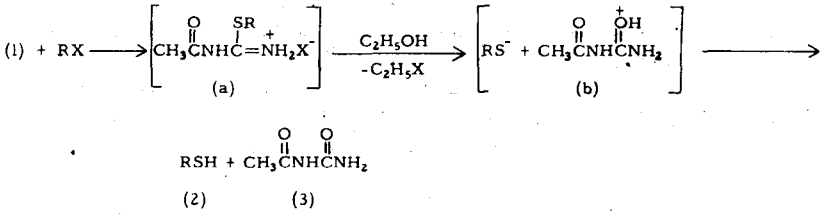
1-Acetyl-2-thiourea, $CH_3\overset{O}{\overset{\|}{C}}NH\overset{S}{\overset{\|}{C}}-NH_2$. Mol. wt. 118.16, m.p. 165–169°. Supplier: Aldrich.

The reagent (1) is prepared by the reaction of sodium thiocyanate (**1**, 1105–1106) with acetyl chloride followed by treatment with aqueous ammonia[1]:



(1)

Synthesis of mercaptans.[1] Mercaptans can be obtained in 30–75% yield by heating (1) with an alkyl halide in ethanol for 24 hr. Acetylurea (3) is the other product. An intermediate 1-acetyl-2-alkyl-2-thiopseudourea hydrohalide (a) is involved. These thiopseudoureas can be isolated if prepared in acetonitrile solution. Yields of mercaptans are high when primary halides are used but rather low in the case of secondary



halides. The reaction of (1) with *t*-butyl bromide did not give a mercaptan. Benzoylthiourea can be used in place of (1), but yields of mercaptans are lower.

[1]D. L. Klayman, R. J. Shine, and J. D. Bower, *J. Org.*, **37**, 1532 (1972).

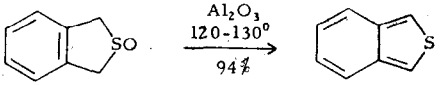
Acetyl *p*-toluenesulfonate, **2**, 14–15. Supplier: Aldrich.

Definitive papers on the preparation and reactions have now been published.[1]

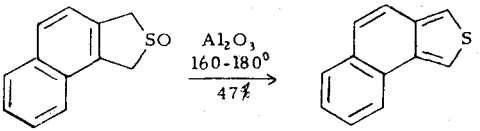
[1]M. H. Karger and Y. Mazur, *J. Org.*, **36**, 528, 532, 540 (1971).

Alumina, **1**, 19–20; **2**, 17; **3**, 6.

Sulfoxide dehydration. When a mixture of the sulfoxide 1,3-dihydrobenzo[*c*]thiophene 2-oxide and grade I neutral alumina (Woelm) is heated under 25-mm. pressure at 120–130° in a sublimer, almost pure benzo[*c*]thiophene (2) condenses on the



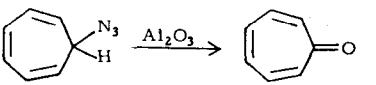
(1) (2)



(3) (4)

cold-finger in 94% yield. Naphtho[1,2-*c*]thiophene (4) was obtained from 1,3-dihydronaphtho[1,2-*c*]thiophene 2-oxide (3) in 47% yield.[1]

Tropone.[2] Tropone (2) can be prepared from tropylium fluoroborate (**1**, 1261) in



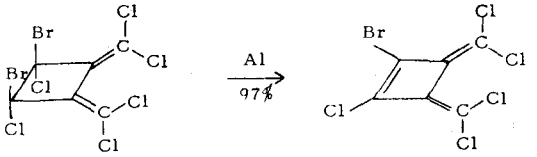
(1) (2)

52% yield by treatment with sodium azide in water to give tropylium azide (1). Treatment of the azide with alumina (Fisher A-540) with vigorous stirring overnight yields tropone (2).

[1]M. P. Cava, N. M. Pollack, O. A. Mamer, and M. J. Mitchell, *J. Org.*, **36**, 3932 (1971).
[2]L. N. McCullagh and D. W. Wulfman, *Synthesis*, 422 (1972).

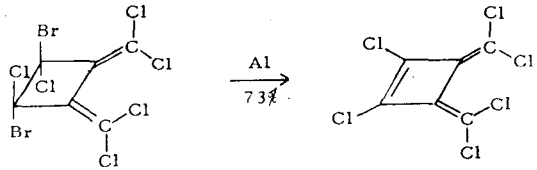
Aluminum, 2, 19.

Dehalogenation.[1] A solution of 1 g. of *cis*-3,4-dibromohexachloro-1,2-dimethylenecyclobutane (1) in 50 ml. of absolute ether is refluxed with 2 g. of aluminum foil with exclusion of moisture for 3 hr. The solution is filtered, washed with water, dried, and evaporated to give colorless needles of (2) from acetone, m.p. 145–146°.



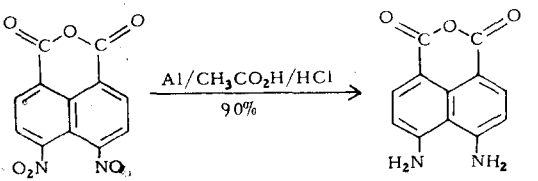
(1) (2)

Similarly:



(3) (4)

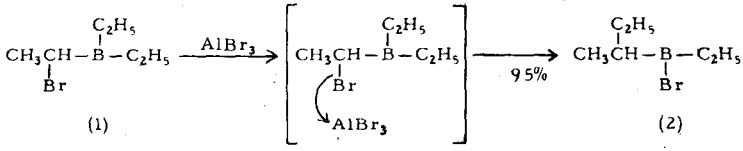
Reduction of nitro groups[2]***:***



[1]A. Roedig, N. Detzer, and G. Bonse, *Ann.*, **752**, 60 (1971).
[2]O. Christmann, *ibid.*, **716**, 147 (1968).

Aluminum bromide, **1**, 22–23; **2**, 19–21; **3**, 7.

Rearrangement of α-bromoethyldiethylborane.[1] α-Bromoethyldiethylborane (1) is isomerized almost instantaneously at 25° to *s*-butylethylboron bromide (2) by treatment



(1) (a) (2)

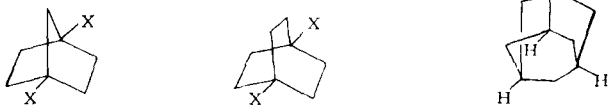
with aluminum bromide in carbon disulfide. Some other Lewis acids are about as effective ($AlCl_3$, $ZnCl_2$, $AgBF_4$): $HgCl_2$, $SnCl_4$, $SbCl_3$, and $TiCl_4$ are less effective.

[1]H. C. Brown and Y. Yamamoto, *J.C.S. Chem. Comm.*, 71 (1972).

Aluminum bromide prepared *in situ*.

Aluminum bromide can be prepared *in situ* from aluminum foil and bromine (or iodine for aluminum iodide).

Bridgehead halogen exchange.[1] Exchange of bridgehead halogen is usually difficult. It can be performed easily and rapidly using aluminum bromide prepared *in situ* and the solvents CH_3I or CH_2I_2 for iodine exchange, CH_2Br_2 or $CHBr_3$ for bromine transfer, and $CHCl_3$ or CCl_4 for chlorine transfer. Yields are in the range 50–90%. The method has been used for exchange at the bridgeheads of (1), (2), and (3).

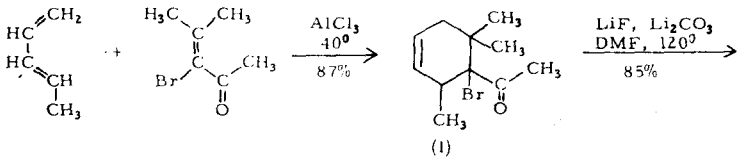


(1) (2) (3)

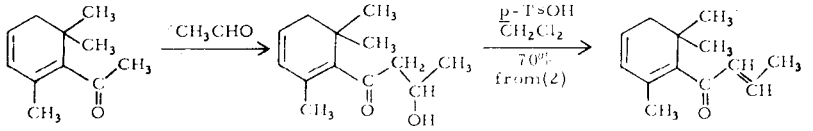
[1]J. W. McKinley, R. E. Pincock, and W. B. Scott, *Am. Soc.*, **95**, 2030 (1973).

Aluminum chloride, **1**, 24–34; **2**, 21–23; **3**, 7–9.

Diels–Alder catalyst (**1**, 31–32; **2**, 21–22; **3**, 8–9).[1] The Diels–Alder adduct (1) of 1,3-pentadiene with 3-bromo-4-methylpentene-3-one-2 (bromomesityl oxide) can be



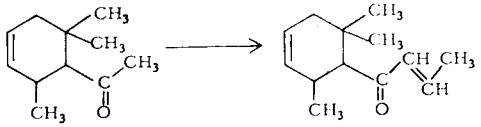
(1)



(2) (3) (4)

obtained in 87% yield (glc) by use of aluminum chloride as catalyst. The adduct (1) was converted into β-damascenone (4) by dehydrobromination (2), condensation with acetaldehyde catalyzed by N-methylanilinomagnesium bromide[2] (3), and dehydration.

δ-Damascone (6) was synthesized by a similar sequence starting with the condensation of 1,3-pentadiene with mesityl oxide to give the adduct (5).

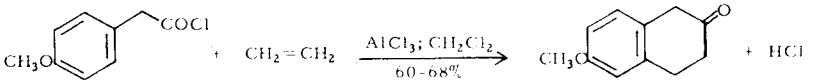


(5) (6)

Addition reactions (**1**, 29). 1,5-Dichloropentane-3-one can be prepared by reaction of 3-chloropropionyl chloride with ethylene in methylene chloride in the presence of anhydrous aluminum chloride.[3] The yield of product as a dark brown oil is 93–96%.

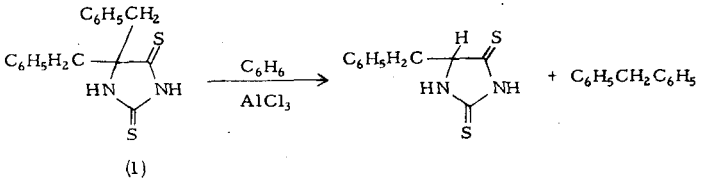
$$ClCH_2CH_2COCl + C_2H_4 \xrightarrow{AlCl_3} (ClCH_2CH_2)_2CO$$

Acid chloride—olefin addition and Friedel-Crafts cyclization.[4] A previous procedure was improved by use of methylene chloride as solvent rather than carbon disulfide. To check the progress of the reaction, one can quench a 2–3-ml. aliquot with water in a test tube, separate and dry the organic phase, and evaporate. The infrared spectrum will show disappearance of the acid chloride carbonyl band at 5.60 μ and appearance of the

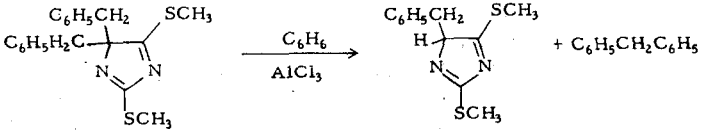


6-methoxy-β-tetralone carbonyl at 5.88 μ; in addition, peaks at 5.78 and 6.02 μ finally disappear. Workup and distillation gives 21–24 g. (60–68%) of 6-methoxy-2-tetralone, b.p. 114–116° (0.2 mm.). On standing in a refrigerator the product solidifies to a white solid, m.p. 33.5–35°.

Cleavage of benzyl groups.[5] On refluxing 5,5-dibenzyldithiohydantoin (1) and 4,4-dibenzyl-2,5-bis(methylthio)-4H-imidazole (2) with an aromatic hydrocarbon and



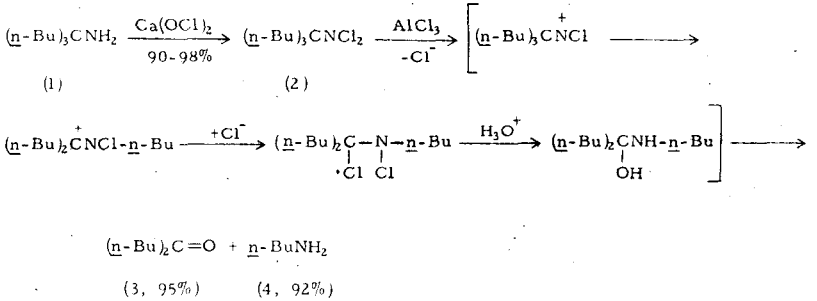
(1)



(2)

aluminum chloride, one of the C-benzyl groups is cleaved off the heterocycle and transferred to the solvent.

Rearrangement of N,N-dihaloamines.[6] N,N-Dichloro-tri-*n*-butylcarbinamine (2), prepared by treatment of tri-*n*-butylcarbinamine (1) with calcium hypochlorite,[7] when treated with aluminum chloride in methylene chloride at $-30°$, followed by acid hydrolysis, gives di-*n*-butyl ketone (3) and *n*-butylamine (4) in high yield. The reaction is considered to involve alkyl migration to electron-deficient nitrogen.



Application of the reaction to 1-N,N-dichloroaminoapocamphane (5) gives, in addition to the expected product (6), (7), (8), and (9), arising from β-scission.[8]