ORGANIC SYNTHESES

AN ANNUAL PUBLICATION OF SATISFACTORY METHODS FOR THE PREPARATION OF ORGANIC CHEMICALS

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NOTICE

With Volume 62, the Editors of *Organic Synthesis* began a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure. The soft cover edition of this volume is produced by a rapid and inexpensive process, and is sent at no charge to members of the Organic Divisions of the American and French Chemical Society. The Perkin Division of the Royal Society of Chemistry, and The Society of Synthetic Organic Chemistry, Japan. The soft cover edition is intended as the personal copy of the owner and is not for library use. A hard cover edition is published by John Wiley & Sons, Inc. in the traditional format, and differs in content primarily in the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Annual Volumes 70–74 have been incorporated into a new five-year version of the collective volumes of *Organic Syntheses* which has appeared as *Collective Volume Nine* in the traditional hard cover format. It is available for purchase from the publishers. The Editors hope that the new *Collective Volume* series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning the new editions.

NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the recent Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendixes. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is preferred.

SUBMISSION OF PREPARATIONS

Organic Synthesis welcomes and encourages submission of experimental procedures which lead to compounds of wide interest or which illustrate important new developments in methodology. The Editorial Board will consider proposals in outline format as shown below, and will request full experimental details for those proposals which are of sufficient interest. Submissions which are longer than three steps from commercial sources or from existing *Organic Syntheses* procedures will be accepted only in unusual circumstances.

Organic Synthesis Proposal Format

1) Authors
2) Title
3) Literature reference or enclose preprint if available
4) Proposed sequence
5) Best current alternative(s)
6) a. Proposed scale, final product:
   b. Overall yield:
   c. Method of isolation and purification:
   d. Purity of product (%):
   e. How determined?

7) Any unusual apparatus or experimental technique?
8) Any hazards?
9) Source of starting material?
10) Utility of method or usefulness of product

Submit to: Dr. Jeremiah P. Freeman, Secretary
Department of Chemistry
University of Notre Dame
Notre Dame, IN 46556

Proposals will be evaluated in outline form, again after submission of full experimental details and discussion, and, finally by checking experimental procedures. A form that details the preparation of a complete procedure (Notice to Submitters) may be obtained from the Secretary.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary. However, checking of such improvements will only be undertaken when new methodology is involved. Substantially improved procedures have been included in the Collective Volumes in place of a previously published procedure.

ACKNOWLEDGMENT

Organic Synthesis wishes to acknowledge the contributions of ArQule, Hoffmann-La Roche, Inc. and Merck & Co. to the success of this enterprise through their support, in the form of time and expenses, of members of the Boards of Directors and Editors.

HANDLING HAZARDOUS CHEMICALS
A Brief Introduction

General Reference: *Prudent Practices in the Laboratory*; National Academy Press; Washington, DC, 1995.

Physical Hazards

Fire. Avoid open flames by use of electric heaters. Limit the quantity of flammable liquids stored in the laboratory. Motors should be of the nonsparking induction type.

Explosion. Use shielding when working with explosive classes such as acetylides, azides, ozonides, and peroxides. Peroxidizable substances such as ethers and alkenes, when stored for a long time, should be tested for peroxides before use. Only sparkless "flammable storage" refrigerators should be used in laboratories.

Electric Shock. Use 3-prong grounded electrical equipment if possible.

Chemical Hazards

Because all chemicals are toxic under some conditions, and relatively few have been thoroughly tested, it is good strategy to minimize exposure to all chemicals. In practice this means having a good, properly installed hood; checking its performance periodically; using it properly; carrying out most operations in the hood; protecting the eyes; and, since many chemicals can penetrate the skin, avoiding skin contact by use of gloves and other protective clothing.

a. Acute Effects. These effects occur soon after exposure. The effects include burn, inflammation, allergic responses, damage to the eyes, lungs, or nervous system (e.g., dizziness), and unconsciousness or death (as from overexposure to HCN). The effect and its cause are usually obvious and so are the methods to prevent it. They generally arise from inhalation or skin con-

tact, so should not be a problem if one follows the admonition "work in a hood and keep chemicals off your hands". Ingestion is a rare route, being generally the result of eating in the laboratory or not washing hands before eating.

b. Chronic Effects. These effects occur after a long period of exposure or after a long latency period and may show up in any of numerous organs. Of the chronic effects of chemicals, cancer has received the most attention lately. Several dozen chemicals have been demonstrated to be carcinogenic in man and hundreds to be carcinogenic to animals. Although there is no simple correlation between carcinogenicity in animals and in man, there is little doubt that a significant proportion of the chemicals used in laboratories have some potential for carcinogenicity in man. For this and other reasons, chemists should employ good practices.

The key to safe handling of chemicals is a good, properly installed hood, and the referenced book devotes many pages to hoods and ventilation. It recommends that in a laboratory where people spend much of their time working with chemicals there should be a hood for each two people, and each should have at least 2.5 linear feet (0.75 meter) of working space at it. Hoods are more than just devices to keep undesirable vapors from the laboratory atmosphere. When closed they provide a protective barrier between chemists and chemical operations, and they are a good containment device for spills. Portable shields can be a useful supplement to hoods, or can be an alternative for hazards of limited severity, e.g., for small-scale operations with oxidizing or explosive chemicals.

Specialized equipment can minimize exposure to the hazards of laboratory operations. Impact resistant safety glasses are basic equipment and should be worn at all times. They may be supplemented by face shields or goggles for particular operations, such as pouring corrosive liquids. Because skin contact with chemicals can lead to skin irritation or sensitization or, through absorption, to effects on internal organs, protective gloves are often needed.

Laboratories should have fire extinguishers and safety showers. Respirators should be available for emergencies. Emergency equipment should be kept in a central location and must be inspected periodically.

DISPOSAL OF CHEMICAL WASTE

General Reference: *Prudent Practices in the Laboratory*, National Academy Press, Washington, D.C. 1995

Effluents from synthetic organic chemistry fall into the following categories:

1. **Gases**

   1a. Gaseous materials either used or generated in an organic reaction.
   1b. Solvent vapors generated in reactions swept with an inert gas and during solvent stripping operations.
   1c. Vapors from volatile reagents, intermediates and products.

2. **Liquids**

   2a. Waste solvents and solvent solutions of organic solids (see item 3b).
   2b. Aqueous layers from reaction work-up containing volatile organic solvents.
   2c. Aqueous waste containing non-volatile organic materials.
   2d. Aqueous waste containing inorganic materials.

3. **Solids**

   3a. Metal salts and other inorganic materials.
   3b. Organic residues (tars) and other unwanted organic materials.
   3c. Used silica gel, charcoal, filter aids, spent catalysts and the like.

The operation of industrial scale synthetic organic chemistry in an environmentally acceptable manner* requires that all these effluent categories be dealt with properly. In small scale operations in a research or academic set-

*An environmentally acceptable manner may be defined as being both in compliance with all relevant state and federal environmental regulations *and* in accord with the common sense and good judgement of an environmentally aware professional.

ting, provision should be made for dealing with the more environmentally offensive categories.

1a. Gaseous materials that are toxic or noxious, e.g., halogens, hydrogen halides, hydrogen sulfide, ammonia, hydrogen cyanide, phosphine, nitrogen oxides, metal carbonyls, and the like.

1c. Vapors from noxious volatile organic compounds, e.g., mercaptans, sulfides, volatile amines, acrolein, acrylates, and the like.

2a. All waste solvents and solvent solutions of organic waste.

2c. Aqueous waste containing dissolved organic material known to be toxic.

2d. Aqueous waste containing dissolved inorganic material known to be toxic, particularly compounds of metals such as arsenic, beryllium, chromium, lead, manganese, mercury, nickel, and selenium.

3. All types of solid chemical waste.

Statutory procedures for waste and effluent management take precedence over any other methods. However, for operations in which compliance with statutory regulations is exempt or inapplicable because of scale or other circumstances, the following suggestions may be helpful.

Gases

Noxious gases and vapors from volatile compounds are best dealt with at the point of generation by "scrubbing" the effluent gas. The gas being swept from a reaction set-up is led through tubing to a (large!) trap to prevent suckback and on into a sintered glass gas dispersion tube immersed in the scrubbing fluid. A bleach container can be conveniently used as a vessel for the scrubbing fluid. The nature of the effluent determines which of four common fluids should be used: dilute sulfuric acid, dilute alkali or sodium carbonate solution, laundry bleach when an oxidizing scrubber is needed, and sodium thiosulfate solution or diluted alkaline sodium borohydride when a reducing scrubber is needed. Ice should be added if an exotherm is anticipated.

Larger scale operations may require the use of a pH meter or starch/iodide test paper to ensure that the scrubbing capacity is not being exceeded.

When the operation is complete, the contents of the scrubber can be poured down the laboratory sink with a large excess (10–100 volumes) of water. If the solution is a large volume of dilute acid or base, it should be neutralized before being poured down the sink.

Liquids

Every laboratory should be equipped with a waste solvent container in which *all* waste organic solvents and solutions are collected. The contents of these containers should be periodically transferred to properly labeled waste solvent drums and arrangements made for contracted disposal in a regulated and licensed incineration facility.**

Aqueous waste containing dissolved toxic organic material should be decomposed *in situ*, when feasible, by adding acid, base, oxidant, or reductant. Otherwise, the material should be concentrated to a minimum volume and added to the contents of a waste solvent drum.

Aqueous waste containing dissolved toxic inorganic material should be evaporated to dryness and the residue handled as a solid chemical waste.

Solids

Soluble organic solid waste can usually be transferred into a waste solvent drum, provided near-term incineration of the contents is assured.

Inorganic solid wastes, particularly those containing toxic metals and toxic metal compounds, used Raney nickel, manganese dioxide, etc. should be placed in glass bottles or lined fiber drums, sealed, properly labeled, and arrangements made for disposal in a secure landfill.** Used mercury is particularly pernicious and small amounts should first be amalgamated with zinc or combined with excess sulfur to solidify the material.

Other types of solid laboratory waste including used silica gel and charcoal should also be packed, labeled, and sent for disposal in a secure landfill.

Special Note

Since local ordinances may vary widely from one locale to another, one should always check with appropriate authorities. Also, professional disposal services differ in their requirements for segregating and packaging waste.

**If arrangements for incineration of waste solvent and disposal of solid chemical waste by licensed contract disposal services are not in place, a list of providers of such services should be available from a state or local office of environmental protection.

PREFACE

The series of annual volumes published by *Organic Syntheses* has provided organic chemists with carefully checked and edited experimental procedures that describe useful synthetic methods, transformations, reagents, and building blocks or intermediates. This, the 76th volume in the series, continues this rich tradition and provides 30 such procedures. Given the diversity of synthetic organic chemistry, there is no underlying theme, but the procedures fall generally into four broad areas: (1) reagents and methods for asymmetric synthesis; (2) useful synthetic transformations; (3) organometallic chemistry and transformations of organometallic reagents; (4) synthetically useful reagents and compounds.

This collection begins with four procedures for the preparation of chiral ligands that have found broad use in organic synthesis. The **RESOLUTION OF 1,1′-BI-2-NAPHTHOL** provides facile access to both enantiomers of this important chiral reagent and ligand. The following procedure for the synthesis of **(R)-(+)- AND (S)-(–)-2,2′-BIS(DIPHENYLPHOSPHINO)-1,1′-BINAPHTHYL (BINAP)** then provides details for the preparation of a chiral bisphosphine ligand that has been widely used in catalytic asymmetric transformations. The TADDOLS constitute an important class of chiral auxiliaries, and the preparation of **(4R,5R)-2,2-DIMETHYL-α,α,α′,α′-TETRA(NAPHTH-2-YL)-1,3-DIOXOLANE-4,5-DIMETHANOL** from dimethyl tartrate and 2-naphthylmagnesium bromide is representative of the general method for their preparation. TADDOL derivatives have been used in asymmetric synthesis in a variety of highly enantioselective processes including lithium aluminum hydride reductions, Michael additions, and hydrosilylations. They have also been used to prepare chiral Lewis acids that serve as catalysts in nucleophilic additions to carbonyl compounds and Diels-Alder reactions. Chiral diamines such as **(R,R)- AND (S,S)-N,N′-DIMETHYL-1,2-DIPHENYLETHYLENE-1,2-DIAMINE** are not only efficacious chiral auxiliaries for asymmetric synthesis, but they may be also used in analytical applications. These compounds are prepared by reductive dimerization of imines followed by resolution.

The series then continues with two procedures for preparing chiral reagents that are used in enantioselective synthesis. Chiral sulfoxides such as

1S-(–)-1,3-DITHIANE 1-OXIDE, which is prepared via an asymmetric oxidation, are useful sources of chirality in asymmetric carbon-carbon bond constructions. A (salen) Mn-catalyzed epoxidation reaction is featured in the enantioselective synthesis of **(1S,2R)-1-AMINOINDAN-2-OL,** a versatile chiral ligand and auxiliary that may be used in a range of asymmetric transformations including Diels-Alder reactions, carbonyl reductions, diethyl zinc additions to aldehydes, and enolate additions.

The series on asymmetric synthesis then concludes with procedures for the preparation of enantiomerically pure products. The asymmetric syntheses of unnatural α-amino acids by the alkylation of pseudoephedrine glycinamide is nicely exemplified by the preparation of **L-ALLYLGLYCINE** and **N-BOC-L-ALLYLGLYCINE.** One of the advantages of this method is the ready availability of the chiral auxiliary and the mildness of the conditions required for the hydrolysis of the pseudophedrine amide to provide the α-amino acid. Biocatalytic transformations are also gaining importance in asymmetric synthesis as illustrated by the preparation of **1-CHLORO-(2S,3S)-DIHYDROXYCYCLOHEXA-4,6-DIENE** by the microbial oxidation of chlorobenzene. Such cyclohexadiene diols are becoming widely used as starting materials in asymmetric synthesis. The synthesis of **(2S,3S)-(+)-(3-PHENYLCYCLOPROPYL)METHANOL** illustrates a powerful method for the enantioselective cyclopropanation of allylic alcohols using an easily-prepared, chiral dioxaborolane ligand in a modification of the Simmons-Smith reaction. A general method for the preparation of chiral non-racemic diols by the opening of **(S,S)-1,2,3,4-DIEPOXYBUTANE** is illustrated by the preparation of **(2S,3S)-DIHYDROXY-1,4-DIPHENYLBUTANE.** Enantiomerically pure α-N,N-dibenzylamino aldehydes undergo a variety of stereoselective nucleophilic additions, and the preparation of **S-2-(N,N-DIBENZYLAMINO)-3-PHENYLPROPANAL** outlines a convenient method for the synthesis of these important intermediates. The use of amino acids as starting materials for the synthesis of other chiral building blocks is exemplified by the synthesis of **METHYL (S)-2-PHTHALIMIDO-4-OXOBUTANOATE.**

The next eight procedures highlight important synthetic transformations. A method for the synthesis of tertiary amines from nitriles is illustrated by the preparation of **N,N-DIMETHYLHOMOVERATRYLAMINE**; this technique may also be applied to the synthesis of secondary amines. The synthesis of **ETHYL 5-CHLORO-3-PHENYLINDOLE-2-CARBOXYLATE** is representative of a general procedure for the reductive cyclization of amino carbonyl derivatives using low-valent titanium reducing agents. Because of their biological significance, the synthesis of fluorine-containing compounds

has become increasingly important. The procedure for the synthesis of **4-HYDROXY-1,1,1,3,3-PENTAFLUORO-2-HEXANONE HYDRATE** features a convenient procedure for generating lithium pentafluoropropen-2-olate and its subsequent use in an aldol reaction. The electrophilic bromofluorination of alkenes, which is illustrated by the synthesis of **1-BROMO-2-FLUORO-2-PHENYLPROPANE,** represents another route to a number of monofluorinated compounds. The mono-C-methylation of arylacetonitriles and methyl arylacetates by dimethyl carbonate as a route to 2-arylpropionic acids is exemplified by the synthesis of **2-PHENYLPROPIONIC ACID,** the simplest member of an important class of anti-inflammatory agents.

The next three procedures feature a rearrangement as a key transformation. The first involves the preparation of **(tert-BUTYLDIMETHYLSILYL)ALLENE.** This method, which is performed in a single operation, involves conversion of a propargylic alcohol into a propargylic diazene that then undergoes a sigmatropic elimination of dinitrogen. Because of the mildness of the reaction conditions, the procedure may be applied to preparing allenes bearing sensitive functional groups. Vinylcyclobutenediones are pivotal intermediates for the synthesis of cyclobutenediones and quinones. This chemistry is nicely illustrated by a procedure for preparing **2-BUTYL-6-ETHENYL-5-METHOXY-1,4-BENZOQUINONE** by a sequence that involves the ring expansion of a 1,2-adduct of **3-ETHENYL-4-METHOXYCYCLOBUTENE-1,2-DIONE.** This procedure also provides a convenient method for the preparation of **DIMETHYL SQUARATE**, an important intermediate. The synthesis of **(1R*,6S*,7S*)-4-(tert-BUTYLDIMETHYLSILOXY)-6-(TRIMETHYLSILYL)BICYCLO-[5.4.0]UNDEC-4-EN-2-ONE** is representative of a general protocol for the construction of cycloheptenones by a [3 + 4] annulation. The method features the addition of a lithium enolate to an acryloyl silane to give a 1,2-adduct that undergoes a novel sequence of a concerted Brook rearrangement/cyclopropanation and an anionic oxy-Cope rearrangement.

The next six procedures involve various aspects of organometallic chemistry. The synthesis of **6-PHENYLHEX-2-YN-5-EN-4-OL** features an inexpensive and convenient method for the generation of 1-propynyllithium from (Z/E)-1-bromo-1-propene. The reaction of α,ω-bromochloroalkenes with allylmagnesium bromide provides a convenient route to **6-CHLORO-1-HEXENE** and **8-CHLORO-1-OCTENE.** These halo alkenes are useful intermediates for the synthesis of long-chain alkenols and alkenolic acids. The reactions of carbonyl compounds with organolithium or Grignard reagents to give alcohols is sometimes accompanied by undesired side reactions such as enolization, reduction, condensation, conjugate addition, and

pinacol coupling. The suppression of these aberrant transformations using cerium(III) chloride is a generally useful tactic and is illustrated in the synthesis of **1-BUTYL-1,2,3,4-TETRAHYDRO-1-NAPHTHOL.** Two problems that are commonly associated with the classical alkylation of lithium enolates are a loss of regioselectivity and the formation of polyalkylated products. By contrast, the regioselective monoalkylation of the manganese enolates of ketones is normally observed as is illustrated by the efficient synthesis of **2-BENZYL-6-METHYLCYCLOHEXANONE** from 2-methylcyclohexanone. The copper-catalyzed conjugate addition of functionalized organozinc reagents to α,β-unsaturated ketones is exemplified by the preparation of **ETHYL 5-(3-OXOCYCLOHEXYL)PENTANOATE.** This general procedure may be readily applied to a variety of enones and alkyl zinc reagents containing diverse functionality such as chloro, cyano, keto, and ester groups. β-Alkynyl allylic alcohols, which are prepared by the palladium-catalyzed coupling of allylic bromides with acetylenes, may be isomerized using catalytic amounts of silver nitrate on silica gel to give substituted furans as illustrated by an efficient synthesis of **2-PENTYL-3-METHYL-5-HEPTYLFURAN.**

The volume concludes with the preparation of four useful reagents and compounds. Oligonucleoside phosphorothioates may be prepared using **2-CHLOROPHENYL PHOSPHORODICHLORIDOTHIOATE** as a coupling agent. A convenient synthesis of multigram quantities of **VITAMIN D_2 FROM ERGOSTEROL** is detailed, and the syntheses of **5,15-DIPHENYLPORPHYRIN**, and **9,10-DIPHENYLPHENANTHRENE** constitute the final two procedures in this volume.

The continued process of the series *Organic Syntheses* derives from the concerted commitment and dedication of numerous individuals. I am particularly grateful to my colleagues on the Editorial Board for their combined assistance and insight in selecting interesting procedures for checking. I am also grateful to them and the members of their respective research groups for carefully checking and sometimes modifying and even improving the procedures presented herein. Of course, were it not for the synthetic community at large and the submitters in particular who are continuously developing innovative synthetic organic chemistry, there would be no procedures to check. I am especially grateful to Professor Jeremiah P. Freeman, Secretary to the Board of Editors. Through his tireless efforts, all the multifarious aspects of selecting, checking, and publishing procedures proceed smoothly and in an organized manner. I am also grateful to Dr. Theodora W. Greene, the Assistant Editor, who ensured that all of the procedures were complete and properly formatted and who also assembled the index, a truly tedious task.

Finally, I thank the many members of the Martin Research Group at the University of Texas who have checked procedures contained in this and other volumes of *Organic Syntheses* and who also carefully read the procedures of this volume making useful suggestions for revisions.

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