ORGANIC SYNTHESES

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METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

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NOTICE

With Volume 62, the Editors of *Organic Syntheses* 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 65–69 have been incorporated into a new five-year version of the collective volumes of *Organic Syntheses* which have appeared as *Collective Volume Eight* 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 9th and 10th 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 Syntheses welcomes and encourages submission of experimental procedures which lead to compounds of wide interest or which illustrate important new developments in methodology. The Editoral 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 Syntheses 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

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HANDLING HAZARDOUS CHEMICALS
A Brief Introduction

General Reference: *Prudent Practices in the Laboratory*, National Academy Press, Washington, D.C. 1996.

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

contact, 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 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. 1996

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 acids, 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 setting,

*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 judgment of an environmentally aware professional.

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

Most organic chemists agree that organic synthesis is not a mature art. We have come a long way, but we have to develop more reliable methods and procedures with improvement in synthetic efficiency. New procedures are needed for safe and economical large scale operation. Despite its great successes, organic synthesis still remains heavily dependent on empirical methods.

While we strive to attain these noble goals, *Organic Syntheses* continues to try to identify important current methods and preparations. Annual Volume 74 contains a series of twenty-eight checked and edited procedures that describe in detail the preparation of generally useful synthetic reagents, intermediates, and heterocycles. It also includes new synthetic methodology which is at the leading edge of organic chemistry.

This collection begins with a series of five procedures illustrating new methods for preparation of important chiral intermediates in enantiomerically pure form. Glyceraldehyde derivatives with one protected and one free hydroxyl function could offer new options. Both enantiomers of **2-O-BENZYL-GLYCERALDEHYDE** can be prepared in three steps from commercially available diethyl D- and L-tartrate. The one-pot conversion of menthol to **1-MENTHOXY-1-BUTYNE** followed by the efficient stereoselective reduction to the corresponding Z- and E-enol ethers is described in the preparation of **(Z)- AND (E)-1-MENTHOXY-1-BUTENE.** Preparation of **(R)-(+)-2-(DIPHENYLHYDROXYMETHYL)PYRROLIDINE,** an important intermediate in the synthesis of chiral ligands, is illustrated. The chemistry reported here is based on the excellent utilization of an asymmetric lithiation/substitution sequence. The putative enantioenriched 2-lithiated pyrrolidine is obtained by the lithiation of Boc-pyrrolidine in the presence of (−)-sparteine. The B-methyloxazaborolidine-catalyzed asymmetric reduction of a cyclopentanone derivative is described in the procedure for **(R)-(−)-2,2-DIPHENYLCYCLOPENTANOL.** An alternative large scale preparation of (S)-1,1-diphenylprolinol via conventional (S)-proline-N-carboxyanhydride and the oxazaborole-borane complex is described in the procedure for the **(S)-TETRAHYDRO-1-METHYL-3,3-DIPHENYL-1H,3H-PYRROLO[1,2c]-[1,3,2]-OXAZABOROLE-BORANE COMPLEX.** This procedure provides a reliable process for oxazaborolidine preparation based on the reaction of

trimethylboroxine with diphenylprolinol derivatives. The oxazaborolidine-borane complex is used for the enantioselective reduction of prochiral 1-indanone in high selectivity (ee = 97.8%).

The next six procedures illustrate the preparation of useful building blocks and intermediates. Large-scale preparation of **1,2,3-TRIPHENYLCYCLOPROPENIUM BROMIDE** by the addition of the phenylchloro carbenoid intermediate to acetylenes is illustrated. A sizeable amount of diphenylacetylene can be converted quantitatively to cyclopropenium bromides in a few hours. The reaction has wide generality and can be applied to other substituted acetylenes. Vinyl triflates are important intermediates in organic syntheses. New triflating reagents, **N-(PYRIDYL)TRIFLIMIDE AND N-(5-CHLORO-2-PYRIDYL)TRIFLIMIDE,** are presented. The preparation of **BIS(TRIMETHYLSILYL)PEROXIDE (BTMSPO)** provides a highly reliable and safe procedure for this widely used reagent. BTMSPO has been used in the preparation of stereochemically pure E- and Z-silyl enol ethers. BTMSPO can also be used as a mild aprotic oxidizing agent for the preparation of sulfoxides, phosphine oxides, and aldehydes. Another useful oxidation agent, **DIMETHYLDIOXIRANE,** and the preparation of **trans-STILBENE OXIDE** are presented. Dimethyldioxirane (DMD) is used widely for epoxidation. The reaction is usually carried out at room temperature in neutral solution and proceeds stereospecifically in essentially quantitative yields. The reaction is applicable to a variety of unsaturated systems. The next procedure describes the convenient preparation of the strong, non-nucleophilic base, **2-tert-BUTYL-1,1,3,3-TETRAMETHYLGUANIDINE.** This strong base provides an inexpensive alternative to the commonly used amidine bases such as DBN or DBU. The synthetic utility of this base is demonstrated in the preparation of **2,2,6-TRIMETHYLCYCLOHEXEN-1-YL IODIDE.** The preparation of **DIETHYL (DICHLOROMETHYL)PHOSPHONATE** is presented. The use of isopropylmagnesium chloride instead of butyllithium reduces the amount of by-products and simplifies the purification steps. The preparation of **(4-METHOXYPHENYL)ETHYNE** via generation and trapping of an unstable phosphorylated carbanion is illustrated. The methodology is well suited for the synthesis of a wide variety of terminal acetylenic compounds.

The next three procedures provide useful building blocks for general syntheses. **2,3-DIBROMO-1-(PHENYLSULFONYL)-1-PROPENE** (DBP) is utilized for the preparation of furans and cyclopentenones. The dibromopropene derivative can be obtained easily by the addition of bromine to a 1,2-propadiene. The resulting dibromide is a stable crystalline solid which may be viewed as a multielectrophilic reagent with a great potential as a nucleophilic acceptor for sequential additions. The reaction of 1,3-dicarbonyl

compounds with DBP affords **2-METHYL-4-[(PHENYLSULFONYL)-METHYL]FURAN.** In contrast, anions derived from 1,3-dicarbonyl compounds substituted at the C-2 position are found to induce a complete reversal in the mode of ring closure to give **2-METHYL-3-[(PHENYLSULFONYL)METHYL]-2-CYCLOPENTEN-1-ONE.** The pendant sulfone group offers a convenient and versatile site for further elaborations. **PHENYL VINYL SULFIDE** shows a number of synthetically useful attributes as an electron-rich alkene in numerous cycloaddition reactions. The product obtained in high yield using common reagents and mild conditions via this procedure is stable at room temperature under a nitrogen atmosphere for months. **NITROACETALDEHYDE DIETHYL ACETAL** has been used to obtain various other acetals by transacetalization. Aliphatic nitro compounds are highly versatile building blocks in organic syntheses. For example, the nitroaldol addition leads to the formation of 1,2-nitro alcohols which are easily transformed into 1,2-aminoalcohols.

The next four procedures describe the regioselective preparation of bicyclic ring systems, specifically, condensed five-membered carbocyclic derivatives. A large number of methods have been developed for the construction of five membered carbocyclic systems. The method for the preparation of **(3aβ,9bβ)-1,2,3a,4,5,9b-HEXAHYDRO-9b-HYDROXY-3a-METHYL-3H-BENZ[e]INDEN-3-ONE** is based on the formal concept of employing cyclopropanone in a mixed aldol condensation with an enolate of another ketone. The aldolate thus obtained exhibits characteristics of a "homoenolate" and undergoes a subsequent annulation reaction. The chemistry of phenylsulfonyl-substituted butadienes is receiving increased attention due to their versatility in organic synthesis. Treatment of 2-butyne-1,4-diol with benzenesulfenyl chloride affords 2,3-bis(phenylsulfinyl)-1,3-butadiene as a result of a series of 2,3-sigmatropic rearrangements. The preparation of **2,3-BIS-(PHENYLSULFONYL)-1,3-BUTADIENE** by oxidation of the disulfoxide is demonstrated, and its [3+2] anionic cyclization to produce **trans-4,7,7-TRICARBOMETHOXY-2-PHENYLSULFONYLBICYCLO[3.3.0]-OCT-1-ENE** is detailed. This strategy can clearly be applied to more complex targets. The generation of an α,β-unsaturated ketene intermediate which undergoes intramolecular [2+2] cyclization to give **1,4-DIMETHYLBICYCLO-[3.2.0]HEPT-3-EN-6-ONE** is illustrated. This synthetic approach demonstrates the simplicity of the procedure and the selectivity by which the thermodynamically more stable isomer can be prepared in high purity and good yield. The last example in this class is the excellent regioselective preparation of **4,6a-DIMETHYL-4,5,6,6a-TETRAHYDRO-3a-HYDROXY-2,3-DIISOPROPOXY-4,6a-1(3aH)-PENTALENONE.** The principal pathway involves trans-1,2-addition of 2-lithiopropene to squarate esters to generate a

cyclobutene dialkoxide which undergoes rapid ring opening to a doubly-charged 1,3,5,7-octatetraene. Following electrocyclization of the octatetraene intermediate to form a cyclooctenyl dienolate, the stage is set for intramolecular aldolization via transannular cyclization.

The next four procedures all involve the preparation of useful olefin derivatives. β,γ-Unsaturated carboxylic acids such as **(E)-4,8-DIMETHYL-3,7-NONADIENOIC ACID** are important intermediates for many natural products syntheses. Allylic barium reagents are prepared via reaction of in situ-generated **ACTIVE BARIUM** with various allylic chlorides, and react with excess carbon dioxide resulting in exclusive α-carboxylation, whereas γ-carboxylation occurs with the magnesium reagent. Allylic barium reagents show high regioselectivity for the α-position, and the double bond geometry of the allyl chloride precursor is completely retained. Geminal dimethylation at a carbon center is a useful method in organic synthesis. Although the Tebbe-like protocol is effective for converting a carbonyl group to a gem-dimethyl group, its application to an allylic carbonyl substrate is limited by poor regioselectivity. The next procedure describes a method based on the nickel-catalyzed cross coupling reactions of dithio acetals with Grignard reagents in the preparation of **(E)-1-PHENYL-3,3-DIMETHYL-1-BUTENE.** The conversion of ethyl propiolate to **(E)- or (Z)-1-IODOHEPT-1-EN-3-OL** and the transformation of a **(Z)-β-IODOACRYLATE** to **(Z)-β-IODOACROLEIN** is illustrated. Regio- and stereoselective conversion of ethyl propiolate with sodium iodide in acetic acid provides the Z-iodoacrylate. The thermal isomerization of the anion formed by Grignard addition provides either (Z)- or (E)-alkylated product. Organometallic derivatives of zirconium (IV) are readily obtained by hydrozirconation of alkenes and alkynes. Transmetalation of alkenylzirconocenes to the corresponding organozinc compounds occurs rapidly at low temperature. Subsequent addition of aldehydes provides an in situ protocol for the conversion of alkynes into allylic alcohols in good yields. Such an example is depicted in the preparation of **1-[(tert-BUTYLDIPHENYLSILYL)OXY]DEC-3-EN-5-OL.** Bromination of 1-alkynes with NBS in the presence of catalytic amounts of silver nitrate is successfully applied for the preparation of **METHYL and tert-BUTYL 3-BROMOPROPIOLATES.** The preparation of **MESITYLENESULFONYLHYDRAZINE** and its application for the preparation of racemic **2,6-DIMETHYLCYCLOHEXANECARBONITRILE** are illustrated. This procedure provides a simple one-pot process for conversion of a moderately hindered ketone to the next higher nitrile analog. Ketones with α,α'-alkyl substituents may be used as diastereomeric mixtures, since they equilibrate to one pair of enantiomers during hydrazone formation, and this stereochemistry is preserved during the cyanide ion reaction.