ORGANIC SYNTHESES

ORGANIC SYNTHESES

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

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HANS THACHER CLARKE
(1887–1972)

LEE IRVIN SMITH
(1891–1973)

We regretfully note the deaths of Hans Thacher Clarke and Lee Irvin Smith. These chemists, pioneers in their specialties, contributed greatly to the development of *Organic Syntheses*. Hans Clarke edited Volumes 3 and 10 and Lee Smith edited Volumes 22 and 23. They were esteemed colleagues—we shall miss both of them.

The Active Board
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NOMENCLATURE

Preparations appear in the alphabetical order of common names of the compounds or names of the synthetic procedures. For convenience in surveying the literature concerning any preparation through *Chemical Abstracts* subject indexes, the *Chemical Abstracts* indexing name for each compound is given as a subtitle if it differs from the common name used as the title.

SUBMISSION OF PREPARATIONS

Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds that are of general interest, as well as procedures that illustrate synthetic methods of general utility. It is fundamental to the usefulness of *Organic Syntheses* that submitted procedures represent optimum conditions, and the procedures should have been checked carefully by the submitters, not only for yield and physical properties of the products, but also for any hazards that may be involved. Full details of all manipulations should be described, and the range of yield should be reported rather than the maximum yield obtainable by an operator who has had considerable experience with the preparation. For each solid product the melting-point range should be reported, and for each liquid product the range of boiling point and refractive index should be included. In most instances, it is desirable to include additional physical properties of the product, such as ultraviolet, infrared, mass, or nuclear magnetic resonance spectra, and criteria of purity such as gas chromatographic data. In the event that any of the reactants are not readily commerically available at reasonable cost, their preparation should be described in as complete detail and in the same manner as the preparation of the product of major interest. The sources of the reactants should be described in notes, and

the physical properties (such as boiling point, index of refraction, melting point) of the reactants should be included except where standard commercial grades are specified.

Beginning with Volume 49, Sec. 3., Method of Preparation, and Sec. 4., Merits of the Preparation, have been combined into a single new Sec. 3., Discussion. In this section should be described other practical methods for accomplishing the purpose of the procedure that have appeared in the literature. It is unnecessary to mention methods that have been published but are of no practical synthetic value. Those features of the procedure that recommend it for publication in *Organic Syntheses* should be cited (synthetic method of considerable scope, specific compound of interest not likely to be made available commercially, method that gives better yield or is less laborious than other methods, etc.). If possible, a brief discussion of the scope and limitations of the procedure as applied to other examples as well as a comparison of the method with the other methods cited should be included. If necessary to the understanding or use of the method for related syntheses, a brief discussion of the mechanism may be placed in this section. The present emphasis of *Organic Syntheses* is on model procedures rather than on specific compounds (although the latter are still welcomed), and the Discussion section should be written to help the reader decide whether and how to use the procedure in his own research. Three copies of each procedure should be submitted to the Secretary of the Editorial Board. It is sometimes helpful to the Board if there is an accompanying letter setting forth the features of the preparations that are of interest.

Additions, corrections, and improvements to the preparations previously published are welcomed and should be directed to the Secretary.

PREFACE

This volume continues the policy of its predecessors by emphasizing the preparation of new and versatile chemicals as well as model procedures that are of general interest. Positive identification of intermediates and end products is made by giving pertinent spectroscopic information. At the same time hazardous reactions and exposure to dangerous chemicals are mentioned prominently.

Three procedures, which involve organometallic reactions, broaden the utility of this increasingly important type of reaction. Thus the homogeneous catalytic hydrogenation of DIHYDROCARVONE, the oxymercuration-reduction to give 1-METHYLCYCLOHEXANOL, and a variation of the well-known Clemmensen reduction, providing conditions that allow selective deoxygenation of ketones in polyfunctional molecules, are mentioned. Syntheses using organoboranes are illustrated by the preparation of ketones and alcohols via borane intermediates, by the introduction of sodium cyanoborohydride in hexamethylphosphoramide as a potent and convenient reagent for the reduction of halides and tosylates to the corresponding hydrocarbons, and by the use of diborane for reducing dinitriles. The use of lithium aluminum tri-*tert*-butoxyhydride for the reduction of acid chlorides to aldehydes is illustrated with the preparation of 3,5-DINITROBENZALDEHYDE.

Other new reagents of preparative value are involved in the selective bromination of an aralkyl ketone with phenyltrimethylammonium tribromide, the partial ether cleavage of aromatic *O*-methyl ethers with sodium ethyl mercaptide in dimethylformamide, and the preparation of DIDEUTERIODIAZOMETHANE which could be an important reagent for labeling studies. The preparation of furans using acetylenic sulfonium salts, the direct lithiation of aromatic compounds, and the preparation of 4,4-disubstituted cyclohexen-2-ones by addition

of methyl vinyl ketones to enamines—an interesting variation of the Robinson annelation reaction—are properly described with appropriate model examples. This group of new methods of general interest is completed by discussions of the isoxazole ring annelation, illustrated by the preparation of 1-METHYL-4,4a,5,6,7,8-HEXAHYDRONAPHTHALEN-2(3*H*)-ONE; a useful method for preparing β-hydroxyesters from esters and ketones with the help of lithium bis(trimethylsilyl)amide; the preparation of α,β-unsaturated aldehydes using diethyl 2-(cyclohexylamino)vinylphosphate via a Wittig reaction; the stereoselective synthesis of trisubstituted olefins; and the base-induced rearrangement of epoxides illustrated by the preparation of *trans*-PINOCARVEOL.

Finally, the syntheses of specific compounds include those of ISOCROTONIC ACID, 1-PHENYL-4-PHOSPHORINANONE, ADAMANTANONE, AZETIDINE, DIAMANTANE and *tert*-BUTYLOXYCARBONYL-L-PROLINE.

The Board of Editors thanks the contributors of the preparations and welcomes suggestions of changes that will improve the usefulness of *Organic Syntheses*. The Editor-in-Chief urges that the application of enzyme-catalyzed reactions, the continued use of new types of organometallic intermediates, and the use of fermentation procedures for the preparation of organic compounds be given serious consideration by his successors. The attention of submitters of preparations is drawn to the instructions on page vii. As initiated in Volume 50, *Organic Syntheses* contains an insert listing unchecked preparations that have been received during the preceding year. These are available from the Secretary's office for a nominal fee prior to checking. The Editorial Board of *Organic Syntheses*, with the help of the Secretary, has issued a style guide for preparing submissions to *Organic Syntheses* and the submitters are urged to follow its suggestions in preparing their manuscripts. An innovation that has been introduced in this volume is the inclusion of an Author Index at the end of the volume as a replacement for the list of contributors that has traditionally appeared at the beginning.

The Editor-in-Chief wishes to acknowledge the great assistance of Dr. Albert I. Rachlin who, with his professional advice and

editing was instrumental in the successful completion of this volume. Additional thanks go to Miss Helen Rennie who typed much of the manuscript and checked proof; also to Dr. S. Kasparek who prepared the Contents and the Author and Subject Indexes.

Nutley, New Jersey
May 1973

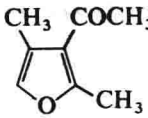
ARNOLD BROSSI

CONTENTS

3-ACETYL-2,4-DIMETHYLFURAN

(2,4-Dimethyl-3-furyl methyl ketone)

A. $(CH_3)_2S + BrCH_2C{\equiv}CH \longrightarrow (CH_3)_2\overset{+}{S}CH_2C{\equiv}CH\ Br^-$

B. $(CH_3)_2\overset{+}{S}CH_2C{\equiv}CH\ Br^-$ + $CH_3COCH_2COCH_3$ $\xrightarrow[\text{ethanol, }\Delta]{C_2H_5ONa}$  $+ (CH_3)_2S$

Submitted by P. D. Howes and C. J. M. Stirling[1]
Checked by C. Reese, M. Uskoković, and A. Brossi

1. Procedure

Caution! These reactions should be performed in a hood because of the noxious odors.

A. *Dimethylprop-2-ynylsulfonium Bromide.* A mixture of 6.2 g. (0.1 mole) of dimethyl sulfide (Note 1), 11.9 g. (0.1 mole) of 3-bromopropyne (Note 2), and 10 ml. of acetonitrile (Note 3) is stirred magnetically for 20 hours (Note 4) in a darkened 100-ml. round-bottomed flask (Note 5) fitted with a calcium chloride drying tube. The resulting white, crystalline mass is filtered with suction and washed with three 50-ml. portions of dry ether (Note 6) to give 16.4 g. (90%) of the sulfonium salt, m.p. 105–106°. This material may be used in the next step without purification but, if desired, it may be recrystallized from ethanol-ether (Note 7) with minimal loss to give a product melting at 109–110°.

B. *3-Acetyl-2,4-dimethylfuran.* To a solution of 8.7 g. (0.087 mole) of acetylacetone (Note 8) in 175 ml. of 0.5*M* ethanolic sodium ethoxide (0.087 mole), contained in a 500-ml. round-bottomed flask fitted with a condenser topped with a calcium chloride drying tube, is added a solution of 15.75 g. (0.087 mole) of dimethylprop-2-ynylsulfonium bromide in

150 ml. of ethanol (Note 9). The mixture is refluxed until the odor of dimethyl sulfide is no longer appreciable (Note 10). The reaction flask is then fitted with a 30-cm. helix-packed column, and by heating the flask with a water bath, ethanol is distilled through the column (Note 11). The residue is treated with 200 ml. of ether, and the suspension is filtered. Ether is distilled from the filtrate at atmospheric pressure, and the residue is distilled to give 9.7 g. (81%) of 3-acetyl-2,4-dimethylfuran (Notes 12 and 13), b.p. 90–95° (12 mm.), n^{24} D 1.4965.

2. Notes

1. Dimethyl sulfide was used as supplied by British Drug Houses.

2. 3-Bromopropyne, supplied by British Drug Houses, was distilled before use (b.p. 84–86°).

3. Acetonitrile (Matheson Coleman and Bell, spectral grade) was used without further treatment.

4. The maximum yield was obtained after 20 hours. Shorter reaction times give slightly lower yields.

5. If a brown glass flask is unavailable, an ordinary flask wrapped with aluminum foil may be used.

6. The ether was dried over sodium.

7. The salt was dissolved in 10 ml. of ethanol, 75 ml. of ether was added portionwise, and the mixture was allowed to stand overnight at room temperature.

8. Acetylacetone, supplied by British Drug Houses, was distilled before use (b.p. 137°).

9. The ethanol was dried with magnesium ethylate.[2]

10. About 6 hours is required on this scale.

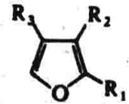
11. Distillation through the packed column is essential to prevent loss of furan by codistillation with ethanol.

12. The product has i.r. absorption (neat) at 1690 cm.$^{-1}$ (ketone C=O) and n.m.r. peaks (CCl_4) at δ 2.20 (s, 3, $COCH_3$), 2.40 (s, 3, CH_3), 3.60 (s, 3, CH_3), and 7.40 (s, 1, furyl).

13. In a convenient modification of this procedure which gives the furan in 70–75% yield, the sulfonium salt is preformed in acetonitrile and, without isolation, the other reagents are added.

TABLE I

FURANS PREPARED VIA ACETYLENIC SULFONIUM SALTS



Sulfonium Salt	Addend	R_1	R_2	R_3	Yield, %[a]
$(CH_3)_2\overset{+}{S}CH_2C\equiv CH\ Br^-$	$CH_3COCH_2CO_2C_2H_5$	CH_3	$CO_2C_2H_5$	CH_3	86
$(CH_3)_2\overset{+}{S}CH_2C\equiv CH\ Br^-$	$CH_3COCH_2SO_2C_6H_4$-*p*-CH_3	CH_3	$SO_2C_6H_4$-*p*-CH_3	CH_3	78
$(CH_3)_2\overset{+}{S}CH_2C\equiv CH\ Br^-$	$C_6H_5COCH_2COC_6H_5$	C_6H_5	COC_6H_5	CH_3	72
$(CH_3)_2\overset{+}{S}CH_2C\equiv CC_6H_5\ Br^-$	$CH_3COCH_2CO_2C_2H_5$	CH_3	$CO_2C_2H_5$	$CH_2C_6H_5$	63
$(CH_3)_2\overset{+}{S}CH(CH_3)C\equiv CH\ Br^-$	$CH_3COCH_2CO_2C_2H_5$	CH_3	$CO_2C_2H_5$	C_2H_5	50

3. Discussion

This procedure illustrates a recently published,[3] simple, general method for the synthesis of substituted furans. The scope of the reaction is shown in Table I. Many variations of this procedure are clearly possible.

The method described has some features in common with the well-known, but apparently little-used, Feist-Benary furan synthesis,[4] which uses an α-haloketone in place of the sulfonium salt. Acetylenic bromides suitable for preparing the sulfonium salts are readily available by well-documented procedures involving acetylenic organometallic compounds.

The mechanism of furan formation by this route is determined by the structure of the sulfonium salt; the course, hence the end product, is governed by whether an α-substituent is present. This must be considered when syntheses based on this procedure are being planned. Plausible mechanisms for the reaction have been suggested.[3]

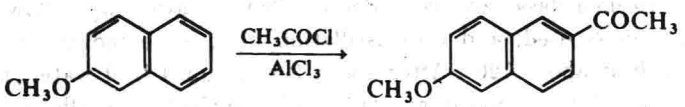
Direct treatment of propargyl halides with β-dicarbonyl compounds and subsequent treatment of the products with zinc carbonate yields 2,3,5-trisubstituted furans.[5]

1. School of Physical and Molecular Sciences, University College of North Wales, Bangor, Caernarvonshire, U.K.

2. D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, "Purification of Laboratory Chemicals," 1st ed., Pergamon Press, New York, 1966, p. 157.
3. J. W. Batty, P. D. Howes, and C. J. M. Stirling, *J. Chem. Soc.*, Perkin I, 65 (1973).
4. A. T. Blomquist and H. B. Stevenson, *J. Amer. Chem. Soc.*, **56**, 146 (1934).
5. K. E. Schulte, J. Reisch, and A. Mock, *Arch. Pharm*, **295**, 627 (1962).

2-ACETYL-6-METHOXYNAPHTHALENE

(6′-Methoxy-2′-acetonaphthone)



Submitted by L. ARSENIJEVIC,[1] V. ARSENIJEVIC,[1] A. HOREAU,[2] and J. JACQUES[2]
Checked by DAVID WALBA and ROBERT E. IRELAND

1. Procedure

A 1-l. three-necked round-bottomed flask fitted with a mechanical stirrer is charged with 200 ml. of dry nitrobenzene (Note 1) followed by 43 g. (0.32 mole) of anhydrous aluminum chloride. The stirrer is started and after the aluminum chloride has dissolved, 39.5 g. (0.25 mole) of finely ground 2-methoxynaphthalene (nerolin) (Note 2) is added. One neck of the flask is fitted with a thermometer with the bulb in the solution, and the third neck of the flask is fitted with a 50-ml. pressure-equalizing addition funnel, carrying a drying tube that is attached to a gas trap. The flask is immersed in a slush of ice and water, and after the stirred solution has cooled to about 5°, 25 g. (22.6 ml., 0.32 mole) of redistilled acetyl chloride (Note 3) is added dropwise from the funnel in 15–20 minutes. The stirring and the addition rate are adjusted so that the temperature holds between 10.5 and 13° (Note 4). After addition of the acetyl chloride is complete, the flask is kept immersed in the ice water while stirring is continued for 2 hours. The mixture is then allowed to stand at room temperature for at least 12 hours.

The reaction mixture is cooled in an ice bath and poured, with manual stirring, into a 600-ml. beaker containing 200 g. of crushed ice, and then treated with 100 ml. of concentrated

hydrochloric acid. The resulting two-phase mixture is transferred to a 1-l. separatory funnel, to which about 50 ml. of chloroform is also added (Note 5). The chloroform-nitrobenzene layer is separated and washed with three 100-ml. portions of water. The organic layer is then transferred to a 2-l. round-bottomed flask, and is steam-distilled. A fairly rapid flow of steam is used, and the distillation flask is heated in an oil bath at about 120°. After about 3 hours (3–4 l. of water) the distillation is stopped, and the residue in the flask is allowed to cool. Residual water in the flask is decanted from the solid organic material and extracted with chloroform. The solid residue in the flask is dissolved in 100 ml. of chloroform, separated from any water left in the flask, and the chloroform layers are combined and dried over anhydrous $MgSO_4$. The chloroform is stripped on a rotary evaporator and the solid residue, weighing 50–65 g. (still slightly wet with chloroform), is distilled under vacuum (Note 6). The receiving flask should be immersed in ice water, and the fraction boiling about 150–165° (0.02 mm.) is collected (Note 7).

The yellow distillate (*ca.* 40 g., m.p. 85–95°) is recrystallized from 75 ml. of methanol, cooled in an ice bath (Note 8) and filtered. The yield of white crystalline 2-acetyl-6-methoxynaphthalene (Note 9) is 22.5–24 g. (45–48%), m.p. 106.5–108° (lit. 104–105°).[3]

2. Notes

1. The nitrobenzene may be dried by distilling the first 10% and using the residue directly, or by standing over anhydrous calcium chloride overnight and filtering.

2. 2-Methoxynaphthalene (Matheson Coleman and Bell), m.p. 71.5–73°, was used without further purification.

3. Acetic anhydride can be used instead of acetyl chloride. However, it is then necessary to take two molecular equivalents of aluminum chloride per mole of anhydride and the amount of nitrobenzene must be increased by about 30%. About the same yield of ketone is obtained.

4. Temperature control is very important (see discussion).

5. The addition of chloroform is not always indispensable, but it is very useful to prevent emulsification and to facilitate