ORGANIC SYNTHESES

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

VOLUME 50

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NOMENCLATURE

Preparations appear in the alphabetical order of common names of the compounds. 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 yields 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. The methods of preparation or 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., Methods 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.

FIFTY YEARS OF ORGANIC SYNTHESES

The genesis of *Organic Syntheses* coincided with the initiation of a rapid development of the organic chemical industry in the United States. Prior to the advent of World War I the investigator in the field of organic chemistry depended for his supply of chemicals and reagents primarily on the German chemical concern of Kahlbaum. This company distributed throughout the world, either directly or through supply houses, a large variety of chemicals and reagents in various sized containers.

The British blockade of German shipping in 1914 resulted in the stoppage of importation of German chemicals. The supply of chemicals still in storage in the United States was soon exhausted. The investigator was thus faced with the necessity of devoting valuable research time to the preparation of his previously purchased raw materials.

No satisfactory directions were available for the preparation of such compounds. This situation induced Hans T. Clarke, James B. Conant, and me, while together at a Chemical Society Meeting, to discuss the possibility of publishing a series of annual volumes of preparations of organic compounds. The preparations would be described in such detail that they could, if carefully followed, be readily duplicated by a student. The novel feature was adopted that each preparation before publication must be checked in the laboratory of an editor and always in a laboratory other than that of the contributor. When the decision was made to proceed, Oliver Kamm of Parke Davis and Company was invited to join in the formation of the original editorial board.

A description of the plan and those of several preparations in finished form were submitted in succession to three different publishers, each of which declined acceptance. This was discouraging. It seemed incredible to the editors that the publishing concerns should show so little interest, since the

probably low profits of such a publication would be offset by the fringe benefit of closer acquaintance with the current and future editors who might be potential authors of more profitable books. It then came to light that each publisher had sent the manuscript to the same referee who had decidedly unfavorable comments.

Mr. E. P. Hamilton of John Wiley and Sons happened into my office about this time. The manuscript was submitted to him with the proviso that the referee to be selected should not be the one who had already expressed his opinion three times. Soon after, John Wiley and Sons agreed to be the publisher and the first volume of *Organic Syntheses* appeared in 1921.

Following the appearance of the first two or three volumes more editors were added gradually until the total reached nine or ten, a number that has been maintained ever since. When ten volumes had appeared, the policy was established that each member of the editorial board from then on would serve seven years, one of which would be as editor-in-chief of a volume. He would then become a member of the Advisory Board and an Active Editor would be elected in his place. This policy is still in effect. A Secretary to the Board was appointed whose term of office was unspecified; each has served ten years or more.

The nature of the preparations in *Organic Syntheses* has changed with the years. In the 1920s and 1930s as the organic chemical industry in the United States expanded, the preparations selected were of more complex compounds. Emphasis was placed on preparations involving new techniques and procedures that might have wider application.

At the close of World War I, the Eastman Kodak Company established a division for production of research chemicals. One or two other concerns of lesser significance entered the same field some time later. Several years after World War II, however, additional concerns began marketing such chemicals. This situation induced the Active Board of Organic Syntheses to devote more effort to uncovering preparations involving new and improved procedures.

With more and more chemicals available from industry, the future program of *Organic Syntheses* required consideration. The Active Board came to the wise conclusion that a change must be made in the general character of the preparations, if the publication was to be of continuing value to the research chemist. It was decided that preparations exemplifying new and general types of compounds, involving novel reagents and reactions, would be most acceptable. This plan was initiated first in Volume 41, edited by John D. Roberts; this and succeeding volumes have demonstrated the utility of such preparations to the needs and current developments of organic chemistry.

The standard presentation of each preparation from the start was under the following headings: (1) Procedure, (2) Notes, and (3) Methods of Preparation. To these was added in the volumes published during the past ten years a desirable fourth heading, Merits of the Method, which explains why the method was deemed worthy of publication. Spectroscopic data, such as UV, IR, and NMR, have been added where pertinent.

The Collective Volumes containing in revised form and in logical order the preparations appearing in the previous ten annual volumes have been published every ten years. Several indices have been incorporated in the decennial publications so that the investigator may locate with a minimum of search a particular compound, a type of reaction, or a reagent. The fifth decennial volume is now being assembled.

It would be futile to attempt to forecast what the research chemist will require most in the future. It is reasonable to assume that the content of *Organic Syntheses* can be adjusted from time to time to be of continuing value to the current demands of the investigator in the field of organic chemistry.

May 7, 1970 ROGER ADAMS

EDITOR'S PREFACE

The appearance of this Golden Anniversary Volume of *Organic Syntheses* testifies to the continued importance of synthesis in our science, and to the continued need for well-described and checked procedures for carrying out synthetic reactions. Whereas in the early years *Organic Syntheses* served the critical function of providing directions for the preparation of useful specific compounds, in modern times the emphasis has changed. Recent volumes stress model procedures which illustrate important types of reactions, and attention is paid to the generality of the procedure as well as to the interest of the particular example which is described. The current volume continues this trend, and in many of these "preparations" the general reaction which is illustrated is of more importance than the specific compound which results.

Thus β-PHENYLCINNAMALDEHYDE illustrates the use of the Schiff base of an aldehyde to direct a mixed aldol condensation, while 2,2-DIMETHYL-4-PHENYLBUTYRIC ACID involves alkylation of the lithium enolate of a carboxylate ion. The use of cyclooctatetraene as a source of four carbons in sequences terminating in a reverse Diels-Alder reaction is illustrated in *cis*-3,4-DICHLOROCYCLOBUTENE and in *trans,trans*-1,4-DIACETOXYBUTADIENE, while in DIETHYL *trans*-Δ^4-TETRAHYDROPHTHALATE sulfolene is used, in a Diels-Alder reaction, as a more convenient equivalent of 1,3-butadiene.

Several of the examples involve the use of metals. Thus copper(I) is used in DIETHYL *tert*-BUTYLMALONATE to induce 1,4 addition of a Grignard reagent to an unsaturated ester, in 1-PHENYL-1,4-PENTADIYNE to promote coupling of a Grignard reagent with a halide, and in 2,2′-DITHIENYL SULFIDE to catalyze displacement of an aryl halogen. N,N-DIMETHYLDODECYLAMINE OXIDE produces an anhydrous amine oxide by

oxidation using a vanadium catalyst, while in *cis*-4-*tert*-BUTYLCYCLOHEXANOL an iridium catalyst is used to hydrogenate a cyclohexanone to the axial alcohol. An aromatic ring is partially reduced with sodium amalgam in *trans*-1,2-DIHYDROPHTHALIC ACID, and with lithium and ethylamine in $\Delta^{9,10}$-OCTALIN.

A useful modification of the Arndt-Eistert reaction is used in ETHYL 1-NAPHTHYLACETATE, while a general procedure for the preparation of hydrazones free of azines is described in ACETOPHENONE HYDRAZONE. Two ways to use chlorosulfonyl isocyanate in the preparation of nitriles are illustrated in CINNAMONITRILE and 2,4-DIMETHOXYBENZONITRILE, while 1-NITROCYCLOOCTENE involves the use of N_2O_4 to convert an olefin to the nitro-olefin. α,α'-DIBROMODIBENZOSULFONE illustrates two general procedures for preparing α-halosulfones, 2-THIOPHENE THIOL involves direct metallation of thiophene, and *cis*-2-PHENYLCYCLOPROPANECARBOXYLIC ACID utilizes selective ester hydrolysis to separate the *cis*, *trans* mixture.

Convenient syntheses are also described for compounds of utility or importance, such as the useful oxidizing agent *m*-CHLOROPERBENZOIC ACID and the versatile formylating agent ACETIC FORMIC ANHYDRIDE. 1,3-DITHIANE is an intermediate in some novel aldehyde and ketone syntheses, *t*-BUTYL AZIDOFORMATE is useful for the protection of amino groups, and TRIMETHYLSILYL AZIDE is a convenient, and stable, substitute for hydrazoic acid in some reactions. The preparation of highly reactive 2-DIAZOPROPANE and its perfluoro derivative, BIS(TRIFLUOROMETHYL)DIAZOMETHANE, are described, as are the theoretically important CYCLOBUTADIENE-IRON TRICARBONYL and 2,3-DIPHENYLVINYLENE SULFONE. 2,3-DIPHENYL-1,3-BUTADIENE is prepared by an unusual new reaction.

The members of the Editorial Board take this opportunity to thank the contributors of preparations. They welcome suggestions of changes that would improve the usefulness of *Organic Syntheses*. The attention of submitters of preparations is particularly drawn to the instructions on pages v and vi, which reflect changes introduced in the preceding volume. In

addition, this and future volumes of *Organic Syntheses* will contain an insert listing all preparations which have been received during the preceding year. These are available from the Secretary's office, prior to checking, for a nominal fee. In this way, we hope to make preparations more quickly available, and to gain further information concerning the types of preparations found valuable by users of *Organic Syntheses*. All procedures will, of course, continue to be checked before final publication.

RONALD BRESLOW

ORGANIC SYNTHESES

CONTENTS

ACETIC FORMIC ANHYDRIDE

(Acetic acid, anhydride with formic acid)

$$CH_3COCl + HCOONa \rightarrow CH_3COOCHO + NaCl$$

Submitted by LEWIS I. KRIMEN[1]
Checked by JAMES SAVAGE and PETER YATES

1. Procedure

A dry 2-l. three-necked round-bottomed flask equipped with a stirrer, a thermometer, a reflux condenser with calcium chloride tube, and a dropping funnel is charged with 300 g. (4.41 moles) of sodium formate (Note 1) and 250 ml. of anhydrous ether (Note 2). To this stirred mixture is added 294 g. (266 ml., 3.75 moles) of acetyl chloride (Note 3) as rapidly as possible, while the temperature is maintained at 23–27° (Note 4). After the addition is complete, the mixture is stirred for 5.5 hours at 23–27° to ensure complete reaction. The mixture is then filtered with suction, the solid residue is rinsed with 100 ml. of ether, and the washings are added to the original filtrate (Note 5). The ether is removed by distillation at reduced pressure, and the residue is distilled to yield 212 g. (64%) of colorless acetic formic anhydride, b.p. 27–28° (10 mm.), 38–38.5° (39 mm.); $n^{20}D$ 1.388 (Note 6).

2. Notes

1. Reagent grade sodium formate from J. T. Baker Chemical Co. was used; it was finely ground to ensure better contact. It is imperative that extreme care be taken to ensure anhydrous conditions throughout the procedure, since hydrolysis produces formic and acetic acids, which are very difficult to remove from the product. A slight excess of sodium formate ensures a product free of acetyl chloride.

2. Mallinckrodt AR grade ether was used without further drying by the submitter. The checkers, working at half scale, found it essential to dry the ether over sodium.

3. Acetyl chloride from Matheson, Coleman and Bell was used without further purification.

4. The addition of acetyl chloride is mildly exothermic; the exotherm can be controlled by slower addition or by the use of a cooling bath (20–24°). The addition is completed in *ca.* 5 minutes.

5. The filtration and subsequent ether rinse should be carried out quickly in order to keep the filtrate dry.

6. The acetic formic anhydride may be stored at 4° in a standard-taper round-bottomed flask fitted with a polyethylene stopper. Moisture catalyzes the decomposition of the product to acetic acid with the evolution of carbon monoxide. *The material must not be stored in sealed containers!*

7. The infrared spectrum of neat acetic formic anhydride shows two bands in the carbonyl region at 1765 and 1791 cm.$^{-1}$ and carbon-oxygen-carbon stretching absorption at 1050 cm.$^{-1}$ (a band at 1180 cm.$^{-1}$ could also be due to C—O—C). The n.m.r. spectrum (neat, tetramethylsilane as an internal standard) shows a singlet at δ 2.25 (acetyl protons) and a singlet at δ 9.05 (formyl proton). If the product is not pure, the following peaks may also be observed: δ 2.05 (CH_3CO_2H), 2.20 [$(CH_3CO)_2O$], 2.68 (CH_3COCl), 8.05 (HCOOH), 8.85 [$(HCO)_2O$]. The spectrum of the product obtained by the checkers showed slight contamination with acetic anhydride and formic anhydride.

3. Discussion

Acetic formic anhydride has been prepared by the reaction of formic acid with acetic anhydride[2,3] and ketene,[4,5] and of acetyl chloride with sodium formate.[6] The present procedure is essentially that of Muramatsu.[6] It is simpler than others previously described and gives better yields. It is easily adapted to the preparation of large quantities, usually with an increase in yield. Acetic formic anhydride is a useful intermediate for the formylation of amines,[3,7] amino acids,[8,9] and alcohols,[2,10] for the synthesis of aldehydes from Grignard reagents,[11] and for the preparation of formyl fluoride.[12]

1. Chemical Development Department, Abbott Laboratories, North Chicago, Illinois.
2. A. Behal, *Compt. Rend.*, **128**, 1460 (1899).