ORGANIC SYNTHESES

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

VOLUME 51

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ORGANIC SYNTHESES

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ROGER ADAMS

(1889–1971)

We take this occasion to note with regret the death of Dr. Roger Adams, who contributed so much to chemistry and the chemical profession in his lifetime. Dr. Adams was a major influence in the founding of Organic Syntheses, Inc., and his interest in the organization remained intense to the end. His able counsel will be missed by all of us.

THE ACTIVE BOARD
THE ADVISORY BOARD

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 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 commercially 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 refrac-

tion, 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.

PREFACE

Despite the proliferation of the chemical literature, the need continues for well-described and checked procedures for conducting synthetic reactions. Recent volumes of *Organic Syntheses* have stressed model procedures that illustrate important types of reactions having generic character. Thus a number of the procedures included here have major significance in the method, rather than the product, of the synthesis. However, as in previous volumes, procedures for the synthesis of specific reagents of special interest are also included.

The current volume emphasizes the preparation of aldehydes, a reactive class of compounds that serve as intermediates for a variety of derivatives. The methods presented are quite general, and many have only recently been described in full detail. The procedures include methods for obtaining aldehydes from acid chlorides, allyl alcohols, aromatic nitriles, and terminal olefins. Also included are reactions of organometallic reagents with an isonitrile and with two heterocyclic systems that furnish the aldehyde function.

Three of the aldehyde procedures involve the reactions of organometallic reagents. In two of these, heterocyclic nuclei that provide the aldehyde function are alkylated. Thus *n*-PENTADECANAL is prepared by a sequence starting with the alkylation of the anion of *sym*-trithiane with the appropriate alkyl halide, and 1-PHENYLCYCLOPENTANECARBOXALDEHYDE is obtained from the product resulting from alkylation of 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine. The reaction of an alkyllithium reagent with 1,1,3,3-tetramethylbutyl isonitrile, followed by quenching with deuterium oxide, is illustrated by the synthesis of 1-*d*-2-METHYLBUTANAL. Two methods for the conversion of an acid chloride to an aldehyde are given: 3,4,5-TRIMETHOXYBENZALDEHYDE by a modified Rosenmund reduction, which involves hydrogenation at modest pressure, and CYCLOBUTANECARBOXALDEHYDE, in which an

ester-mesylate is reduced by sodium borohydride to yield an acetal that is not subject to further reduction and can be hydrolyzed to an aldehyde. The conversion of aromatic nitriles to aldehydes by reduction with Raney nickel alloy in the presence of formic acid is illustrated by *p*-FORMYLBENZENESULFONAMIDE. The preparation of aldehydes from allylic alcohols by action of phenylpalladium acetate is shown by a method for the synthesis of 2-METHYL-3-PHENYLPROPIONALDEHYDE. Finally, the preparation of aldehydes by the oxidation of terminal olefins with chromyl chloride is exemplified by 2,4,4-TRIMETHYLPENTANAL.

A useful procedure for dehydroxylation of phenols through hydrogenolysis of phenolic ethers is illustrated by the synthesis of BIPHENYL, and iodination of polysubstituted benzenes by the synthesis of IODODURENE. The phenylation of ketones with diphenyliodonium chloride is exemplified by the synthesis of 1-PHENYL-2,4-PENTANEDIONE and the esterification of hindered alcohols by reaction of lithium alkoxides with acid chlorides by *t*-BUTYL *p*-TOLUATE. A more convenient procedure than that conventionally used for the hydrogenation of aromatic nuclei is given in the preparation of 1-DECALOL, and the conversion of phenols to thiophenols through intermediate thermal rearrangement of dialkyl thiocarbamates, followed by hydrolysis, is described in 2-NAPHTHALENETHIOL. A modified Meerwein reaction that is conducted under conditions that avoid dehydrohalogenation of the intermediate is described in the preparation *p*-ACETYL-α-BROMOHYDROCINNAMIC ACID. A general synthesis of amines through intermediate azide formation from mixed carboxylic-carbonic anhydrides is illustrated by the preparation of 1-PHENYLCYCLOPENTYLAMINE, and the synthesis of olefinic systems from tosylhydrazones is illustrated by the synthesis of 2-BORNENE. The preparation of aziridines from olefins via iodine isocyanate is shown sequentially in the conversion of 1,2-dihydronaphthalene to METHYL (*trans*-2-IODO-1-TETRALIN)CARBAMATE and then to 1,2,3,4-TETRAHYDRONAPHTHALENE(1,2)IMINE. An illustration of the preparation of 3-substituted β-diketones by acylation of the intermediate enol acetate is furnished by 3-*n*-BUTYL-2,4-PENTANE-

DIONE. The preparation of ETHYL PYRROLE-2-CARBOXYLATE provides a general method for obtaining esters from pyrrole without the use of organometallic reagents. An intramolecular Wurtz reaction is illustrated by the synthesis of BICYCLO[1.1.0]-BUTANE from 1-BROMO-3-CHLOROCYCLOBUTANE which is obtained from 3-CHLOROCYCLOBUTANECARBOXYLIC ACID by means of a modified Hunsdiecker reaction. Two syntheses of ALKYL IODIDES which lead to improved yields from sterically hindered or heat-sensitive alcohols are given. The synthesis of cyclic ketones by action of dihaloalkanes on lithio-1,3-dithiane is represented by CYCLOBUTANONE. The conversion of a cyclic hydroxymethylene ketone to the diazoketone is illustrated by 2-DIAZOCYCLOHEXANONE.

The synthesis of specific compounds which are of general interest includes *trans*-3-PENTEN-2-ONE, useful for annelation of cyclic ketones; 6-METHOXY-β-TETRALONE, an intermediate to natural products; 4-PHENYL-1,2,4-TRIAZOLINE-3,5-DIONE, an extremely reactive dienophile and dehydrogenation agent under mild conditions; the reactive CARBONYL CYANIDE; and the highly strained QUADRICYCLANE. Improved syntheses of BICYCLO[3.2.1]OCTAN-3-ONE, 1,2,3,4-TETRAHYDRO-β-CARBOLINE, and the reactive alkylating agent TRIMETHYLOXONIUM TETRAFLUOROBORATE are presented.

The Board of Editors takes this opportunity to thank the contributors of preparations. The Editor-in-Chief particularly thanks those who submitted the aldehyde procedures so promptly when invited. The Board of Editors welcomes suggestions of changes that will improve the usefulness of *Organic Syntheses*. The attention of submitters of preparations is particularly drawn to the instructions on pages vii and viii which reflect changes introduced in Volume 49. As begun with Volume 50, *Organic Syntheses* will contain an insert listing 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 preparations accepted by the

Board of Editors will, of course, continue to be checked before final publication.

The Editor-in-Chief wishes to acknowledge the assistance of Miss L. Kathleen Green, who advised on nomenclature and checked the references, and Mrs. Rosalie W. Holland, who typed the manuscript and checked proof.

RICHARD E. BENSON

Wilmington, Delaware
May 1971

CONTENTS

p-ACETYL-α-BROMOHYDROCINNAMIC ACID

(Hydrocinnamic acid, *p*-acetyl-α-bromo-)

$$p\text{-}CH_3COC_6H_4NH_2 \xrightarrow[HBr]{NaNO_2} p\text{-}CH_3COC_6H_4-\overset{\oplus}{N}\equiv N\ Br^-$$

$$p\text{-}CH_3COC_6H_4-\overset{\oplus}{N}\equiv N\ Br^- + CH_2=CHCO_2H \xrightarrow[HBr]{CuBr} p\text{-}CH_3COC_6H_4CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCO_2H$$

Submitted by GEORGE H. CLELAND[1]
Checked by MICHAEL J UMEN and HERBERT O HOUSE

1. Procedure

Caution! Since bromoacetone, a powerful lachrymator, is produced as a by-product in this preparation, the reaction should be performed in a hood.

A tared 500-ml. two-necked round-bottomed flask is equipped with a magnetic stirring bar, a thermometer, and an ice-filled cooling bath. A solution of 13.5 g. (0.10 mole) of *p*-aminoacetophenone (Note 1) in 200 ml. of acetone is placed in the flask and stirred while 32 ml. (about 0.3 mole) of aqueous 48% hydrobromic acid is added After the resulting solution has been cooled to 5–7°, it is stirred continuously while 20 ml. of an aqueous solution containing 6.90 g. (0.10 mole) of sodium nitrite is added rapidly (30 seconds) beneath the surface of the reaction solution by means of a hypodermic syringe or a long-stemmed dropping funnel Stirring and cooling are continued until the exothermic reaction subsides (Note 2) and the reaction solution has cooled to 14–15°. Then 106 g. (100 ml., 1.47 moles) of acrylic acid (Note 3) is added The resulting solution is again cooled to 14–15° with stirring and 0.10–0.11 g. (0.0007 mole) of copper(I) bromide (Note 4) is added. Stirring is continued during which time the solution darkens, and nitrogen evolution

is observed; the temperature of the reaction mixture is kept below 33° by use of the external cooling bath. As soon as the evolution of nitrogen has ceased (usually 20 minutes is sufficient), the reaction solution is concentrated under reduced pressure with a rotary evaporator to give a mixture weighing about 120–130 g. The residual brown suspension is mixed with 5 g. of decolorizing charcoal and 200 ml. of water and the resulting mixture is boiled for 3 minutes and then filtered while hot through a Büchner funnel containing Celite filter aid. The residue on the filter is washed with 100 ml. of boiling water, and the combined filtrates are diluted with 300 ml. of water. The resulting aqueous solution, from which the product begins to crystallize, is cooled in a water bath and then allowed to stand in a refrigerator (0–3°) for 24 hours to complete the crystallization of the crude product. The crystalline solid that separates is collected on a filter, washed with two 100-ml. portions of cold water, and then dried in the air. The crude product, a pale yellow solid amounting to 19.1–22.2 g., is recrystallized from 40 ml. of a 2:3 (v/v) formic acid-water mixture. The resulting crystals are collected on a filter, washed with 20 ml. of a cold mixture of formic acid and water (2:3 v/v), and dried in the air. The product amounts to 16.6–18.2 g. (61–67%) of white needles, m.p. 158–160°, which is sufficiently pure for most purposes. Three additional crystallizations from 20-ml. portions of a 2:3 (v/v) formic acid-water mixture give 15.2–16.0 g. (56–59%) (Note 5) of the pure *p*-acetyl-α-bromohydrocinnamic acid, m.p. 159–161° (Note 6).

2. Notes

1. Commercial grades of acetone and *p*-aminoacetophenone (Matheson Coleman and Bell or Aldrich Chemical Company, Inc.) were used without further purification.

2. The temperature of the reaction mixture rises to about 30° and then falls to 15° as stirring and cooling are continued. If this preparation were performed on a larger scale, it would probably be necessary to add the sodium nitrite solution over a longer period of time in order to control the temperature.

3. A freshly opened bottle of acrylic acid, obtained from Eastman Organic Chemicals, was used without further purification. The checkers encountered difficulty in attempting to use samples of acrylic acid that had been stored in partially filled bottles for long periods of time.

4. A reagent grade of copper(I) bromide, obtained from Fisher Scientific Company, was washed with acetone until the washings were colorless and then dried.

5. The combined filtrates from these recrystallizations can be concentrated to obtain an additional 1–2 g. of product.

6. The product has infrared absorption (KBr pellet) at 1735, 1645, and 1607 cm.$^{-1}$ with an ultraviolet maximum (95% EtOH solution) at 252.5 mμ (ε 17,000). The sample has n.m.r. peaks (CF_3CO_2H solution) at 8.10 (doublet, $J = 9$ Hz., 2H, aryl CH), 7.47 (doublet, $J = 9$ Hz., 2H, aryl CH), 4.60 (triplet, $J = 7.5$ Hz., 1H, CHBr), 3.2–3.9 (multiplet, 2H, benzylic CH_2), and 2.78 p.p.m. (singlet, 3H, CH_3CO). The mass spectrum has weak molecular peaks at *m/e* 270 and 272 with the following relatively abundant fragment peaks: *m/e* (rel. int.), 191 (73), 175 (100), 131 (52), 103 (40), 77 (55), and 51 (43). The product gives a deep red color when treated with sodium nitroprusside and aqueous base; this color changes to dark blue upon acidification with acetic acid.

3. Discussion

This procedure has been used to prepare a variety of substituted α-bromohydrocinnamic acids;[2] *p*-acetyl-α-bromohydrocinnamic acid was prepared for the first time by this method. The method illustrates a typical application of the Meerwein reaction for the arylation of unsaturated substrates.[3] In this reaction a catalytic amount of a copper(I) salt is used to reduce an aryl diazonium salt forming an aryl radical and a copper(II) halide. Addition of the aryl radical to an unsaturated substrate forms an alkyl radical that is reoxidized by the copper(II) halide present forming an alkyl halide and regenerating the copper(I) salt catalyst. In this preparation, the product, an α-bromo acid, is formed in an acidic reaction mixture and dehydrohalogenation does not occur. However, dehydrohalogenation