

# ORGANIC SYNTHESSES

*Collective Volume 5*

A REVISED EDITION OF  
ANNUAL VOLUMES 40-49

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## *Collective Volume 5*

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A REVISED EDITION OF  
ANNUAL VOLUMES 40-49

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THIS BOOK IS DEDICATED TO THE MEMORY OF  
PROFESSOR ROGER ADAMS (1889-1971),  
ONE OF THE FOUNDERS OF ORGANIC SYNTHESSES, INC.,  
AND ITS LEADER DURING THE PERIOD, 1920-1971.

## PREFACE

Collective Volume 5 of *Organic Syntheses* consists of the procedures previously published in annual Volumes 40–49, revised and updated where necessary. Errors found in the original printings have been corrected, calculations and references have been checked, and modifications and improvements brought to the attention of the Editorial Board have been incorporated in the procedures. This general plan is similar to that followed for the preceding four collective volumes; however, because of the change in emphasis on the types of procedures chosen for recent annual volumes, the specific plan followed in the revision of procedures in this volume was somewhat different than that for previous volumes.

Beginning in Volume 41 the Editorial Board made a deliberate change of emphasis away from procedures describing the preparation of specific organic compounds and toward model procedures that illustrate important types of reactions. This change was the result of the reduced need for directions for the preparation of many specific organic chemicals because of the increasingly effective efforts of the manufacturers of fine organic chemicals in the U.S.A. and abroad to provide chemists with the chemicals needed for their research at reasonable prices. Thus, this volume contains both procedures directed toward the preparation of a specific chemical or reagent and those intended to illustrate a reaction or method of synthesis. Revision of the procedures based largely on information gathered by the Editor-in-Chief from *Chemical Abstracts* (as was done in previous collective volumes) appeared inadequate for the expanded scope of the procedures in this collective volume. Therefore, the Editor-in-Chief attempted to obtain from the original submitters any new information on their procedures of value to the users of *Organic Syntheses*. Although not all submitters could be contacted, replies were received from about 80% of the submitters. Suggestions received from the submitters ranged from no change to complete replacement of the original procedure. The Editor-in-Chief is indebted to the submitters for their generous assistance in bringing these procedures up to date. Additional changes in the Methods of Preparation, Merits of the Preparation, and Discussion Sections have been made by the Editor-

in-Chief based largely on information taken from *Chemical Abstracts*, *Organic Reactions*, and the Fieser's invaluable work, *Reagents for Organic Synthesis* (Volumes 1-3). Apart from numerous minor revisions and a number of suggestions for possibly superior alternative methods, new, checked procedures are given to replace the preparations published in the annual volumes for 2,5-dihydro-2,5-dimethoxyfuran, methanesulfinyl chloride, and *p*-toluenesulfonylhydrazide. Checked procedures for the preparation of 2,4,6-trimethylpyrilium tetrafluoroborate and 2,4,6-trimethylpyrilium trifluoromethanesulfonate, which may be used as substitutes for the more hazardous 2,4,6-trimethylpyrilium perchlorate, are given here for the first time. The procedure for the preparation of  $\alpha$ -chloroanisole which appeared in Volume 47 is not included in this volume because the procedure has been found to give largely *p*-chloroanisole rather than the title compound.

The practice has been continued of noting which of the compounds, whose preparations have been described, have become commercially available. This information was obtained from *Chemical Sources* (1972 edition) and the catalogs issued through November 1972 by the principal suppliers of fine organic chemicals in the U.S.A. Available compounds are indicated by asterisks after the title of the preparations.

A considerable number of warning notices have been added to the procedures in this volume on the basis of information supplied by users of the annual volumes. During the period covered by this volume *Organic Syntheses* began the practice of publishing in the annual volumes warning and correction notices pertaining to procedures published in any previous volume, annual or collective. Previously the notices had been distributed as separates for incorporation in the volume referred to. This practice has been continued along with the publication in the current annual volumes. Those notices published within the time span of this volume, 1959-1972, and referring to any procedure published through annual Volume 49 are republished in this volume. The continuing appearance of hazard notices suggests that many of the procedures and chemicals described in this series may be hazardous and should be treated with due caution, as dictated by one's experience and knowledge and by good organic chemical practice.

All of the services provided to users in previous collective volumes are continued in this volume. Thus, the first reference number in

each procedure is used to indicate the laboratory in which the directions were developed. Indices included in this volume are Type of Reaction Index, Type of Compound Index, Formula Index, Preparation or Purification of Solvents and Reagents Index, Apparatus Index, Author Index, and General Index. A collective index covering collective Volumes 1-5 is in the process of preparation and is expected to be published in the near future.

Readers interested in the history and evolution of *Organic Syntheses* may find a brief description written by one of the founders, Roger Adams, in annual Volume 50 (p. vii). Further information may be obtained from the prefaces in the 52 annual volumes published to date.

The editors of *Organic Syntheses* are indebted to the contributors and users of these volumes and appreciate the assistance that they have provided during the half century that the series has been published. Additional suggestions, comments, and corrections will be welcomed and should be sent to the Secretary to the Editorial Board.

To reduce the probability of introducing new errors and to keep the cost to the user down, this volume was planned to use as much of the previously published copy as was feasible. For this reason the procedures appear in several formats and the journal abbreviations (which have been made internally consistent) in the references are those in vogue toward the end of the period 1959-1969. Potential contributors to this series should refer to the most recent annual volume and to the *Organic Syntheses* style sheet (available from the Secretary) for the current style and format. Submissions of directions for the annual volumes should also be sent to the Secretary. Details about submissions may also be obtained from the preface to the most recent annual volume.

The Editor-in-Chief takes this opportunity to acknowledge the invaluable service provided to the publication of this series during the past thirteen years by Mrs. June A. Splichal, who handled all of the typing and reproduction of submitted procedures as well as all correspondence with submitters and users.

February, 1973

HENRY E. BAUMGARTEN

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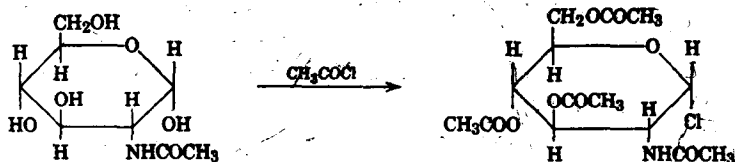
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PERBENZOIC ACID ( <i>Warning</i> ) .....	900	THIOBENZOYLTHIOGLYCOLIC ACID .....	1046
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PEROXYBENZOIC ACID .....	904	2 $\alpha$ -THIOHOMOPHTHALIMIDE .....	1051
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PHENOLS: 6-METHOXY-2-NAPHTHOL .....	918	<i>p</i> -TOLUENESULFONYLHYDRAZIDE .....	1055
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**2-ACETAMIDO-3,4,6-TRI-*O*-ACETYL-2-DEOXY- $\alpha$ -D-  
GLUCOPYRANOSYL CHLORIDE**

(Glucopyranosyl chloride, 2-acetamido-2-deoxy-,  
triacetate,  $\alpha$ -D-)



Submitted by DEREK HORTON<sup>1</sup>

Checked by A. L. JOHNSON and B. C. MCKUSICK

### 1. Procedure

In a 500-ml. round-bottomed flask equipped with a magnetic stirrer bar and a reflux condenser protected by a tube of calcium chloride is placed 100 ml. of acetyl chloride; this operation and the subsequent reaction are conducted in a hood. The condenser is temporarily removed, and 50 g. (0.226 mole) of dried 2-acetamido-2-deoxy-D-glucose (*N*-acetylglucosamine) (Note 1) is added in the course of 2 or 3 minutes with good stirring. The mixture is stirred for 16 hours without external heating at a room temperature of approximately 25°. The mixture boils spontaneously during the first hour of reaction. It is a clear, viscous, amber liquid at the end of the reaction (Note 2).

Through the condenser there is added 400 ml. of chloroform (U.S.P. grade), and the solution is poured with vigorous stirring onto 400 g. of ice and 100 ml. of water in a 3-l. beaker. The mixture is transferred to a 1-l. separatory funnel and shaken. The organic solution is drawn off without delay into a 3-l. beaker containing ice and 400 ml. of saturated sodium bicarbonate solution. The mixture in the beaker is stirred, and the neutralization is completed by shaking the mixture in the separatory funnel. The organic layer is run directly into a flask containing

about 25 g. of anhydrous magnesium sulfate. The entire washing procedure should be completed within 15 minutes (Note 3). The solution is shaken or stirred with the drying agent for 10 minutes (Note 4). The drying agent is separated on a 7.5-cm. Büchner funnel and is well washed with dry, alcohol-free chloroform or methylene chloride (Note 5). The filtrate passes through an adaptor directly into a 1-l. round-bottomed flask. The filtrate is concentrated to 75 ml. on a rotary evaporator at 50°, and dry ether (500 ml.) is rapidly added with swirling to the warm solution (Note 6). Crystallization usually begins after about 30 seconds. The flask is stoppered and set aside for 12 hours at room temperature.

The product is scraped from the walls of the flask and broken up by means of a curved spatula. The solid is collected on a 12.5-cm. Büchner funnel, washed with two 150-ml. portions of dry ether, dried by suction on the filter for 5 minutes, and stored in a desiccator over sodium hydroxide and phosphorus pentoxide. Analytically pure 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\alpha$ -D-glucopyranosyl chloride is obtained; weight 55–65 g. (67–79%); m.p. 127–128° (Fisher-Johns apparatus) (Note 7); typical  $\text{—NHCOCH}_3$  absorptions at 6.09  $\mu$  and 6.49  $\mu$  in the infrared; nmr ( $\text{CDCl}_3$ )  $\delta$  6.25 and  $J_{1,2}$  3.5 Hz for the H-1 doublet. Evaporation of the mother liquors and addition of ether to the concentrated solution gives an additional 4–6 g. (5–7%) of crystalline product, m.p. 125–127°, that is sufficiently pure for most purposes. The pure product may be stored in an open dish in a desiccator at room temperature for at least 3 years without decomposition (Note 8).

## 2. Notes

1. Suitable material is available from Pfanstiehl Laboratories, Waukegan, Illinois. It may also be prepared from the hydrochloride of 2-amino-2-deoxy-D-glucose (D-glucosamine) in 95% yield by a facile procedure.<sup>2</sup> The 2-acetamido-2-deoxy-D-glucose should be dried at 25° (1 mm.) for at least 12 hours before use. If this material is in the form of a powder rather than compact crystals, more acetyl chloride may

have to be added in order to get a stirrable mixture; the checkers found that an extra 50 ml. of acetyl chloride did not lower the yield.

2. The reaction mixture may be left for longer periods, as over a weekend, without adverse effect. If the ambient temperature is too low, undissolved material may be present after 16 hours, in which case a longer period of stirring is indicated, or the reaction mixture may be gently heated (not above 30°).

3. It is essential that isolation of the product be conducted rapidly and at 0° throughout, especially while the solution is acidic. All apparatus and solutions should be at hand before the reaction mixture is poured on ice. The product reacts fairly rapidly with water in the presence of an acid catalyst, undergoing acetyl migration to give the water-soluble 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy- $\alpha$ -D-glucopyranose hydrochloride.

4. An extended period of drying is unnecessary and should be avoided.

5. Commercial methylene chloride is usually sufficiently dry to use without pretreatment in place of dry, alcohol-free chloroform. The checkers used a pressure funnel under dry nitrogen for the filtration; filtration was rapid and exposure to atmospheric moisture was slight.

6. The solution must not be evaporated to a volume that permits crystallization to begin before the ether is added. The addition of ether should be sufficiently rapid that the heavy syrup is diluted to a clear, homogeneous solution before crystallization begins.

7. The checkers observed m.p. 118–119° when an open capillary tube containing a sample of analytical purity was placed in a stirred oil bath at 100° with the temperature rising several degrees a minute. The melting point of benzoic acid, determined simultaneously, was 122–123°. The checkers found  $[\alpha]^{24D} +110^\circ$  (c. 1, CHCl<sub>3</sub>); literature values range from +109.7° to +118°.

8. Material of lesser purity may decompose within a much shorter time. If the product is exposed to moist air, it is converted into 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy- $\alpha$ -D-glucopyranose hydrochloride, which is insoluble in chloroform.

### 3. Methods of Preparation

The direct one-step preparation of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy- $\alpha$ -D-glucopyranosyl chloride was reported by Micheel and co-workers,<sup>3</sup> and the described procedure is essentially the method of Horton and Wolfrom.<sup>4</sup> The product was first prepared through a two-step route from 2-amino-2-deoxy-D-glucose hydrochloride by Baker and co-workers,<sup>5</sup> and a number of adaptations of this method have been described.<sup>6-8</sup>

### 4. Merits of the Preparation

The procedure permits acetylation of the sugar and replacement of the 1-acetoxy group by chlorine in one operation in only 2-3 hours of working time, gives good yields of pure product, and does not require gaseous hydrogen chloride. The two-step procedure from 2-amino-2-deoxy-D-glucose hydrochloride<sup>5-7</sup> is time-consuming, and yields are very low if the acetylated intermediate is isolated.<sup>8</sup> The yield is better when the second stage is performed without isolation of the intermediate,<sup>9</sup> but gaseous hydrogen chloride is required, and the preparation takes considerably more working time than the method described.

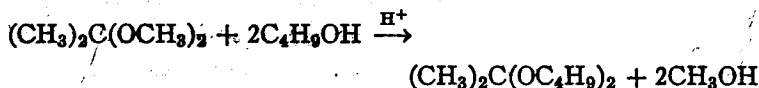
The product is used in the preparation of glycoside, thioglycoside, oligosaccharide, and glycosylamine derivatives of 2-acetamido-2-deoxy-D-glucose.<sup>10</sup> A number of these compounds are of current interest; several seem to be involved in viral penetration of cells, and others are of interest in the synthesis of model substrates for enzymes. The product has the  $\alpha$ -D configuration and normally reacts to give glycosides with the  $\beta$ -D configuration, presumably through participation of the acetamido group in a bicyclic, closed-ion intermediate. Under controlled conditions it reacts with water to give 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy- $\alpha$ -D-glucopyranose hydrochloride.<sup>11</sup>

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## ACETONE DIBUTYL ACETAL\*

(Propane, 2,2-dibutoxy-)

Submitted by N. B. LORETTE and W. L. HOWARD.<sup>1</sup>

Checked by MAX TISHLER and STANLEY NUSIM.

## 1. Procedure

A mixture of 312 g. (3 moles) of acetone dimethyl acetal (Note 1), 489 g. (6.6 moles) of butanol, 1.0 l. of benzene, and 0.2 g. of *p*-toluenesulfonic acid is placed in a 3-l. flask. The flask is connected to a packed fractionating column and the solution distilled until the azeotrope of benzene and methanol, boiling at 58°, is completely removed (Note 2). The contents of the boiler are then cooled below the boiling point and a solution of 0.5 g. of sodium methoxide in 20 ml. of methanol (Note 3) is added all at once with stirring. The flask is replaced for further distillation, and most of the remaining benzene is distilled at atmospheric pressure. The pressure is then reduced, and the remaining benzene and unreacted butanol are removed (Note 4). Finally, the pressure is reduced to 20 mm., the last traces of low-boiling materials are taken to the cold trap, and the product is distilled. After a small fore-run, acetone dibutyl acetal is collected at 88–90°/20 mm. The yield is 421–453 g. (74.6–80.3%),  $n_D^{25}$  1.4105,  $d_4^{25}$  0.8315.



## 2. Notes

1. Commercial acetone dimethyl acetal (2,2-dimethoxypropane) from the Dow Chemical Company was used without further treatment.

2. About 570 ml. of this azeotrope is obtained. The methanol produced may be estimated by washing an aliquot with about two volumes of water in a graduated cylinder. The methanol content is approximately the difference between the initial volume and that of the residual benzene phase, and about 230 ml. is obtained, depending on the efficiency of fractionation. Other hydrocarbons, e.g., hexane or cyclohexane, can be used for the removal of methanol.

The submitters' distillation was carried out in a 19 x 1200-mm. vacuum-jacketed silvered column fitted with a magnetically operated vapor-takeoff head controlled by a timed relay. The checkers found that a 19 x 340-mm. vacuum-jacketed column fitted with a magnetically operated liquid takeoff and packed with  $\frac{1}{4}$ -in. glass Raschig rings was sufficient for carrying out the distillation. The checkers, using a reflux ratio of 2.7 to 1 throughout the distillation, found the total time required to be 19 hours.

Since the required separations are not difficult, any reasonably efficient fractionating column may be used.

3. Other soluble non-volatile bases may be used.

4. It is best to keep the temperature of the distilland below 125–150°, because pyrolysis of the product becomes progressively more serious at higher temperatures. The pressure is reduced to a convenient value when the distilland temperature reaches 125°. For example, a pressure of 200 mm. will allow the condensation of the benzene without resort to special cooling.

## 3. Methods of Preparation

Acetone dibutyl acetal has been prepared from isopropenyl acetate and butanol,<sup>2</sup> from butanol and isopropenyl butyl ether obtained from the reaction of butanol with propyne,<sup>3</sup> and by orthoformic ester synthesis.<sup>4,5</sup>