Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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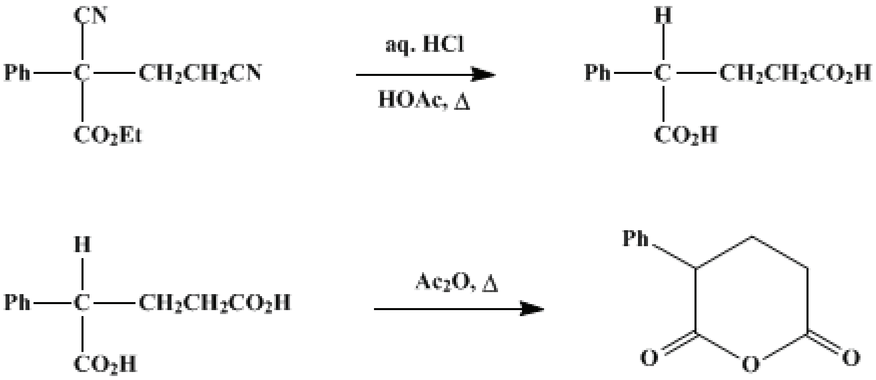
α-PHENYLGLUTARIC ANHYDRIDE

[Glutaric anhydride, 2-phenyl-]



Submitted by E. C. Horning and A. F. Finelli[1].
Checked by William S. Johnson and H. Wynberg.

1. Procedure

In a 500-ml. flask equipped with a reflux condenser are placed 48.4 g. (0.20 mole) of α-phenyl-α-carbethoxyglutaronitrile (p. 776), 225 ml. of hydrochloric acid (sp. gr. 1.19), and 50 ml. of acetic acid. The mixture is heated under reflux for 10 hours. The solution is cooled, transferred to a 1-l. separatory funnel, and diluted with 300 ml. of water. The α-phenylglutaric acid is extracted with five 100-ml. portions of ether-ethyl acetate (1:1) (Note 1). The extracts are combined, washed once with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvents are removed as completely as possible by distillation from a steam bath, and the residue is transferred to a 200-ml. flask. Acetic anhydride (50 ml.) is added, and the solution is heated under gentle reflux for 1 hour. The excess acetic anhydride is removed by distillation at atmospheric pressure, and the residue is distilled under reduced pressure through a short (15-cm.) Vigreux column with an air-cooled side arm. The product is collected at 178–188°/0.5–1 mm. (Note 2). The yield is 31.1–32.7 g. (82–86%); m.p. 90–94°.

This material may be recrystallized by dissolving the product in hot ethyl acetate (2 ml. per g. of the anhydride) and adding an equal volume of hexane or 60–68° petroleum ether slowly to the hot solution. The solution is allowed to cool, and when crystallization occurs (usually at 40–50°) an additional volume (2 ml. per g. of the anhydride) of hexane is added. The mixture is cooled, and the crystalline product is removed by filtration and washed with cold hexane (5 ml. per g. of the anhydride). The recovery of colorless material, m.p. 95–96°, is 90–92%.

2. Notes

1. The extraction may be facilitated by saturation of the aqueous layer with sodium chloride.
2. It is necessary to flame the column and side arm. The product obtained in this way is a light-yellow or cream-colored solid which need not be recrystallized unless a colorless sample is desired. If the final distillation is carried out too slowly or at pressures above 2 mm. considerable decomposition may occur, reducing the yield of the product.

3. Discussion

α-Phenylglutaric acid has been prepared by the hydrolysis and decarboxylation of diethyl α-phenyl-α-carbethoxyglutarate (prepared by the alkylation of diethyl phenylmalonate with ethyl β-iodopropionate) with hydrochloric acid.[2] The anhydride may be obtained from the acid by direct distillation under reduced pressure, although the use of acetic anhydride results in a purer product.

References and Notes

1. University of Pennsylvania, Philadelphia, Pennsylvania.
2. Fichter and Merckens, *Ber.*, **34**, 4175 (1901).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium chloride (7647-14-5)

magnesium sulfate (7487-88-9)

diethyl phenylmalonate (83-13-6)

hexane (110-54-3)

α-Phenyl-α-carbethoxyglutaronitrile (53555-70-7)

α-Phenylglutaric anhydride,
Glutaric anhydride, 2-phenyl- (2959-96-8)

α-phenylglutaric acid

diethyl α-phenyl-α-carbethoxyglutarate

ethyl β-iodopropionate (6414-69-3)