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.

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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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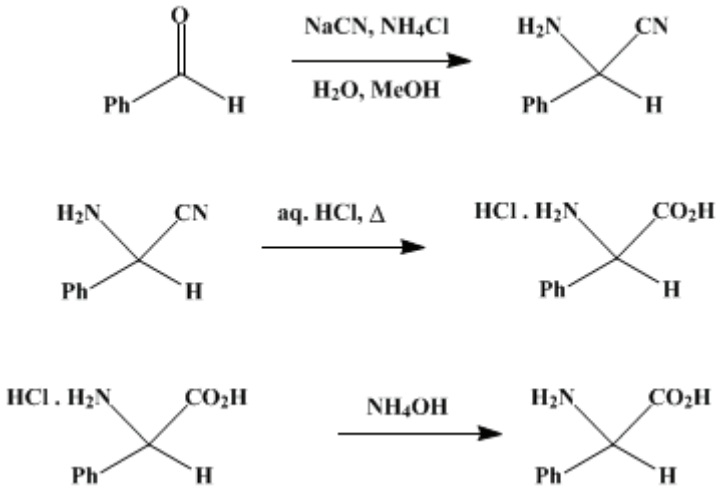
dl-α-AMINOPHENYLACETIC ACID

[Glycine, α-phenyl-]



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1. Procedure

To a solution of 100 g. (2.0 moles) of 98% sodium cyanide in 400 ml. of water, contained in a 3-l. round-bottomed flask fitted with a Hershberg stirrer, is added 118 g. (2.2 moles) of ammonium chloride. The mixture is stirred at room temperature under a properly ventilated hood. When the ammonium chloride has dissolved, a solution of 212 g. (2.0 moles) of benzaldehyde in 400 ml. methanol is added in one portion. The reaction begins rapidly, the temperature rising to about 45°. Stirring is continued for 2 hours. The heterogeneous mixture, after dilution with 1 l. of water, is extracted with 1 l. of benzene, and the aqueous layer is discarded. The benzene layer is washed with three 50-ml. portions of water, and the aminonitrile is extracted, in the form of its hydrochloride, by shaking the benzene solution with 6 *N* hydrochloric acid, first with one 600-ml. portion and then with two 300-ml. portions.

The combined acid extracts are placed in a 3-l. round-bottomed flask and refluxed for 2 hours (Note 1). The hydrolysate is diluted with water to bring its volume to about 2 l. and is then subjected to distillation under reduced pressure (20–30 mm.) to remove all benzaldehyde and other volatile substances (Note 2). To remove some resinous matter deposited in the course of the hydrolysis, the mixture is treated with 10 g. of Norit and filtered through a Büchner funnel. The yellow filtrate is transferred to a 3-l. beaker. It is stirred by hand with a thick glass rod while ammonium hydroxide (sp. gr. 0.90) is added through a dropping funnel until the liquid is faintly alkaline to litmus (Note 3). The mixture becomes quite hot and acquires a strong odor of benzaldehyde. The amino acid separates in the form of yellow crystals. The mixture is cooled to room temperature, and the crystals are collected on a 15-cm. Büchner funnel. After washing with about 1 l. of water in small portions to remove the ammonium chloride, the solid is washed successively with 150 ml. of ethyl ether, three 50-ml. portions of hot 95% ethanol, and finally with about 500 ml. of water. The crystals, when dried by suction, weigh 220 to 240 g. (Note 4). Drying is completed in a vacuum desiccator over phosphorus pentoxide. The yield of crude amino acid is 102–116 g. (34–39%).

For purification, the product is dissolved in 800 ml. of 1 *N* sodium hydroxide, 500 ml. of ethanol is added, and the solution is filtered. The filtrate is transferred to a 2-l. beaker and is heated to the boiling point. Then 160 ml. of 5 *N* hydrochloric acid is slowly added, through a dropping funnel, while stirring by hand. The mixture is cooled to room temperature and is filtered with suction. The product is washed with 100 ml. of ethanol, then with 200 ml. of water, and is dried in a vacuum desiccator over

phosphorus pentoxide. The nearly white, lustrous platelets have no definite melting point (Note 5). The yield of pure amino acid is 98–112 g. (33–37%) (Note 6).

2. Notes

1. The hydrolysis of the aminonitrile should be carried out under a hood, since some hydrocyanic acid is liberated.
2. During this process, the volume of the solution must be maintained at about 2 l. by the frequent addition of water through a dropping funnel. Otherwise the hydrochloride of *dl*-phenylglycine, which is sparingly soluble in concentrated hydrochloric acid, may separate.
3. From 375 to 425 ml. of ammonium hydroxide of sp. gr. 0.90 is required.
4. This crude product is hydrated.
5. The decomposition range was about 270–280° with sintering at 258°. A new sample, when placed in the melting-point bath at 280–300°, sintered, and then decomposed at 300–302°.
6. Increasing the quantities of cyanide and ammonium chloride to 3 moles does not markedly improve the yields.

3. Discussion

dl-Phenylglycine has been prepared by heating α-bromophenylacetic acid with three times its weight of ammonium hydroxide (sp. gr. 0.90) to 100–110°;[1] by hydrolysis of α-aminophenylacetonitrile with dilute hydrochloric acid;[2,3] and by reduction of benzoylformic acid phenylhydrazone with sodium amalgam in dilute sodium hydroxide.[4] The method described above is, with some modifications and additions, the procedure used by Marvel and Noyes.[3,5]

References and Notes

1. Stöckenius, *Ber.*, **11**, 2002 (1878).
2. Tiemann, *Ber.*, **13**, 383 (1880); Ulrich, *Ber.*, **37**, 1688 (1904); Zelinsky and Stadnikoff, *Ber.*, **39**, 1725 (1906); **41**, 2062 (1908); Ingersoll and Adams, *J. Am. Chem. Soc.*, **44**, 2933 (1922).
3. Marvel and Noyes, *J. Am. Chem. Soc.*, **42**, 2264 (1920).
4. Elbers, *Ann.*, **227**, 343 (1885).
5. Dr. D. Stetten, Jr. (private communication), found that when the synthesis is carried out according to Zelinsky and Stadnikoff, *Ber.*, **41**, 2062 (1908), and the amino acid is isolated in the fashion described above, the yield is not appreciably higher than the one recorded here.

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

hydrochloride of dl-phenylglycine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

methanol (67-56-1)

ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

hydrocyanic acid (74-90-8)

aminonitrile (7727-37-9)

benzaldehyde (100-52-7)

Norit (7782-42-5)

sodium (13966-32-0)

ammonium hydroxide (1336-21-6)

Glycine, α-phenyl- (2935-35-5)

α-Bromophenylacetic acid (4870-65-9)

α-aminophenylacetonitrile

benzoylformic acid phenylhydrazone

dl-phenylglycine (103-01-5)

phosphorus pentoxide (1314-56-3)

DL-α-Aminophenylacetic acid (2835-06-5)