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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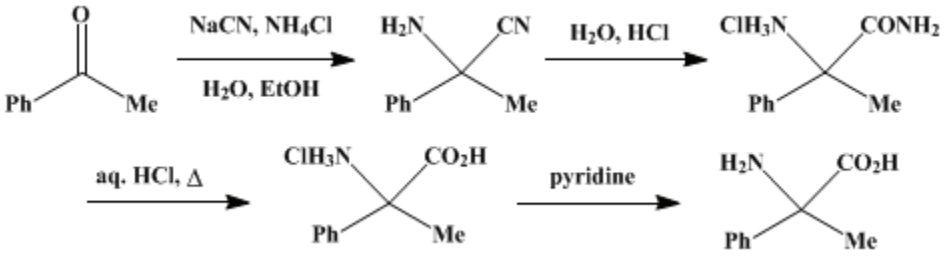
dl-α-AMINO-α-PHENYLPROPIONIC ACID

[Alanine, α-phenyl-, *dl*-]



Submitted by Robert E. Steiger
Checked by R. L. Shriner and S. P. Rowland.

1. Procedure

In a 2-l. round-bottomed flask are placed, in the order mentioned, 50 g. (1 mole) of 98% sodium cyanide in 100 ml. of water, 58.9 g. (1.1 moles) of ammonium chloride in 140 ml. of lukewarm water (about 35°), and 134 ml. (2 moles) of aqueous ammonia (sp. gr. 0.90). The mixture is shaken while 120 g. (1 mole) of acetophenone in 300 ml. of 95% ethanol is added. The flask is stoppered with a rubber stopper, which is wired in place (Note 1), and is then immersed in a water bath maintained at 60°. The flask is shaken from time to time, and a homogeneous solution results within 30 minutes. The reaction mixture is heated for 5 hours at 60°, then well cooled in an ice-water mixture, and poured, with precautions (under a well-ventilated hood), into a 5-l. round-bottomed flask which is immersed up to the neck in an ice-water mixture and which contains 800 ml. of concentrated hydrochloric acid (sp. gr. 1.18–1.19). The reaction flask is rinsed with two 25-ml. portions of water, which are added to the hydrochloric acid solution. The solution of the aminonitrile is saturated at 0–5° with dry hydrogen chloride (Note 2) and is then set aside overnight in the ice-water bath, which is allowed to melt and come to the temperature of the room. The mixture of solid and liquid material is diluted with 1 l. of water and boiled vigorously for 2.5 hours under a reflux condenser in a well-ventilated hood (Note 3). The dark hydrolysate is concentrated under reduced pressure to remove the acetophenone and other volatile impurities. The solution is finally transferred to a 10-in. evaporating dish and is stirred occasionally while it is evaporated almost to dryness. Once a heavy deposit of inorganic salts has formed, very little bumping occurs. The solid residue is evaporated on a water bath twice with 100-ml. portions of water in order to remove as much hydrochloric acid as possible. The residue is crushed, and 600 ml. of absolute ethanol is added. The suspension is warmed for a short time on a steam bath; it is shaken thoroughly and then chilled in an ice-water mixture. The inorganic salts are removed by filtration through a 15-cm. Büchner funnel, and the cake is washed with small portions of absolute ethanol until 600 ml. has been used. The combined filtrates and washings are placed in a 3-l. beaker, and pyridine is added while the mixture is stirred by hand with a thick glass rod. The addition of pyridine is continued until the solution is nearly neutral to Congo red paper, and then an additional 50 ml. is added; the total amount of pyridine required is 80–100 ml. (Note 4).

The resulting rather stiff paste is chilled in an ice-water mixture for 1 hour. The solid is collected on a 15-cm. Büchner funnel and washed with 25-ml. portions of absolute ethanol until it is white and until the filtrate becomes colorless (100–200 ml. of ethanol is required). The fluffy material, after it is dried in a vacuum desiccator over flake sodium hydroxide, weighs 66 g. (40%).

The amino acid contains a small amount of ammonium chloride, which can be removed by dissolving the product in 21 times its weight of water and precipitating it by the addition of 42 times its weight of absolute ethanol (Note 5). The mixture is allowed to stand overnight in a refrigerator. The amino acid is collected on a Büchner funnel and washed with an ethanol-water mixture containing 80% by weight of ethanol. The amino acid is dried in a vacuum desiccator over flake sodium hydroxide. The

recovery is about 70% (Note 6).

2. Notes

1. A flask fitted with a ground-glass stopper is convenient for carrying out this step. The ground-glass stopper should be slightly lubricated with stopcock grease. It must be firmly secured in place by means of adhesive tape, as some pressure develops when the reaction mixture is heated.
2. From 500 to 600 g. of dry hydrogen chloride gas is required. Since this gas is very rapidly absorbed, a high-speed generator can be used.
3. The hydrolysis of the aminonitrile must be carried out under a good hood. The top of the reflux condenser should be connected with the ventilating pipe by means of a piece of glass tubing.
4. The minimum amount of pyridine necessary is determined by the amount of hydrochloric acid remaining in the residue.
5. The material does not readily become wet in contact with water, and it dissolves very slowly. The finely powdered material is best suspended in a large excess of water, e.g., about 30 times its weight. The suspension is boiled under a reflux condenser and frequently shaken until the solid is dissolved. The excess water is then boiled off at atmospheric pressure until a solution of the amino acid in 21 times its weight of water is obtained. The solution is then cooled and treated with absolute ethanol.
6. The amino acid does not have a sharp melting point. It sublimes with decomposition at about 265–270°.

3. Discussion

α-Amino-α-phenylpropionitrile has been prepared by heating acetophenone cyanohydrin for 6–8 hours in a closed vessel with 1 equivalent of ethanolic ammonia at 70°;[1,2] and by heating acetophenone for 4 hours in a closed vessel with an ethanolic solution of ammonium cyanide to 80°.[3] α-Amino-α-phenylpropionitrile has been hydrolyzed by the action of, first, fuming hydrochloric acid at room temperature, and then dilute hydrochloric acid at boiling temperature, in the presence of some ethanol. This procedure gives a good yield of the amino acid hydrochloride. The amino acid has usually been liberated from its hydrochloride by means of ammonium hydroxide.[1,2,3] The process of isolating the amino acid by treating an ethanolic solution of its hydrochloride with pyridine is essentially the same as that developed for the preparation of glycine[4] and of α-aminoisobutyric acid.[5]

References and Notes

1. Tiemann and Köhler, *Ber.*, **14**, 1981 (1881).
2. McKenzie and Clough, *J. Chem. Soc.*, **101**, 395 (1912).
3. Jawelow, *Ber.*, **39**, 1195, 1197 (1906).
4. Clarke and Taylor, *Org. Syntheses*, **4**, 31 (1925); Coll. Vol. **1**, 298 (1941).
5. Clarke and Bean, *Org. Syntheses*, **11**, 4 (1931); Coll. Vol. **2**, 29 (1943).

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

ethanolic ammonia

ethanol (64-17-5)

hydrogen chloride,
hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

ammonium cyanide

aminonitrile (7727-37-9)

Acetophenone (98-86-2)

pyridine (110-86-1)

ammonium hydroxide (1336-21-6)

Glycine (513-29-1)

α-Aminoisobutyric acid (62-57-7)

α-Amino-α-phenylpropionitrile

acetophenone cyanohydrin

DL-α-Amino-α-phenylpropionic acid (6945-32-0)

Alanine, α-phenyl-, dl-