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.

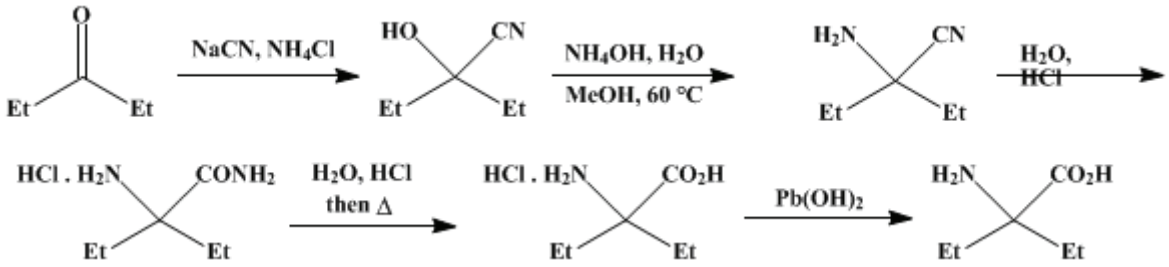
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.022.0013

Organic Syntheses, Coll. Vol. 3, p.66 (1955); Vol. 22, p.13 (1942).

α-AMINODIETHYLACETIC ACID

[Butyric acid, α-amino-α-ethyl-]



Submitted by Robert E. Steiger
Checked by W. E. Bachmann and Yun-Tsung Chao.

1. Procedure

A solution of 50 g. (1 mole) of sodium cyanide (98% purity) in 100 ml. of water is placed in a 2-l. round-bottomed flask (Note 1) fitted with a ground-glass stopper. A solution of 58.9 g. (1.1 moles) of ammonium chloride in 140 ml. of lukewarm water is added, followed by 67 ml. (1 mole) of concentrated ammonium hydroxide (sp. gr. 0.9). This mixture is stirred mechanically and is cooled by a stream of water while a solution of 86.1 g. (1 mole) of diethyl ketone in 160 ml. of methanol (Note 2) is added. The flask is then stoppered (Note 3) and half immersed for 5 hours in a water bath, the temperature of which is kept at 55–60°. The reaction mixture is then cooled in an ice bath and poured (with precautions, i.e., under a properly ventilated hood) into 800 ml. of concentrated hydrochloric acid (sp. gr. 1.18) contained in a 5-l. round-bottomed flask which is surrounded up to the neck by ice and water. The reaction flask is rinsed with two 25-ml. portions of water. The mixture is now saturated at 0–5° with hydrogen chloride gas. After standing overnight under a hood, the mixture is refluxed for 2.5 hours (Note 4).

The solution is evaporated to dryness under reduced pressure on a water bath. In order to remove as much hydrochloric acid as possible, the temperature of the bath is raised to 100° toward the end of the distillation. The residue of amino acid hydrochloride and inorganic salts is suspended in 500 ml. of absolute ethanol. The suspension is boiled on a steam bath for a short time, then cooled to room temperature and filtered on a Büchner funnel. The residue of inorganic salts is washed with 500 ml. of absolute ethanol. To the combined filtrates is added 400 ml. of ethyl ether (U. S. P. quality) in order to precipitate inorganic material. After several hours the mixture is filtered, and the residue is washed with a 5:2 mixture of absolute ethanol and ether. The filtrate is transferred to a 5-l. round-bottomed flask, about 200 ml. of water is added, and the liquids are removed by distillation under reduced pressure. The nearly dry residue is dissolved in 2 l. of water, and the solution is treated with an excess of freshly prepared lead hydroxide (Note 5). The suspension is diluted with water to a volume of about 3.5 l. and is then concentrated under reduced pressure, at as low a temperature as possible, to a volume of about 2 l. The suspension is then filtered with suction (Note 6), and the residue of lead salts is washed thoroughly with water. The cloudy filtrate, which still contains some free ammonia, is concentrated by distillation under reduced pressure to a volume of about 300–400 ml. The mixture is filtered, the filtrate is saturated with hydrogen sulfide gas, and the precipitate of lead sulfide is removed by filtration with suction (Note 6). The solution is now concentrated by distillation under reduced pressure on a water bath, and 1 l. of 95% ethanol is added to the nearly dry residue of the amino acid. The suspension is boiled under a reflux condenser until nearly all the amino acid is dissolved, and the mixture is then allowed to cool to room temperature. The amino acid, which separates in the form of fine needles, is collected on a Büchner funnel and washed with a little 95% ethanol. A second crop of crystals is obtained by evaporating the combined filtrates to dryness, dissolving the residue in the minimum amount of hot water, and treating the solution with 95% ethanol. The amino acid is dried in the air and then in a vacuum desiccator over phosphorus pentoxide. The total yield of product is 58.8–65 g. (39–

43%, assuming that the product contains exactly one molecule of water of crystallization) (Note 7).

2. Notes

1. The checkers used a 1-l. Erlenmeyer flask fitted with a ground-glass stopper.
2. The methanol must be free from acetone since this ketone would give rise to α-aminoisobutyric acid.
3. The ground-glass stopper should be lubricated slightly with stop-cock grease. It must be secured firmly by means of adhesive tape, as some pressure develops when the flask is heated.
4. The hydrolysis must be carried out under a hood. The top of the reflux condenser should be connected with the ventilation pipe by means of a piece of glass tubing. The methanol contained in the reaction mixture escapes in the form of methyl chloride, along with some hydrogen chloride.
5. The lead hydroxide is prepared by adding 1.5 l. of a 2 *N* solution of sodium hydroxide (3 moles) through a dropping funnel to a continuously stirred solution of 569 g. (1.5 moles) of lead acetate, $(CH_3CO_2)_2Pb{\cdot}3H_2O$, in 1.35 l. of water. The precipitate is collected on a 13-cm. Büchner funnel and washed well with water in order to remove water-soluble impurities. The paste of lead hydroxide is transferred to the solution that is to be freed of chloride ions.
6. A Büchner funnel of adequate size is fitted with two pieces of hardened filter paper covered with a thin layer of moistened Norit.
7. The checkers obtained 65 g. of pure amino acid in the first crop; the second crop of 5 g. contained chloride ion. When heated in an open tube, the pure product sublimed at 255° without melting.

3. Discussion

α-Aminodiethylacetic acid has been prepared from α-bromodiethylacetic acid and ammonia;[1] and by hydrolysis of α-aminodiethylacetonitrile with hydrochloric acid.[1,2,3,4] The required nitrile was obtained by heating diethyl ketone cyanohydrin with one equivalent of ethanolic ammonia;[2] by heating diethyl ketone with an ethanolic solution of ammonium cyanide;[3] and by heating diethyl ketone with a solution of potassium cyanide and ammonium chloride.[1, 4] α-Aminodiethylacetic acid has also been obtained from ethyl α-cyanodiethylacetate by partial hydrolysis to ethyl diethylmalonamate and subsequent degradation in alkaline hypobromite.[5]

References and Notes

1. Rosenmund, *Ber.*, **42**, 4472 (1909).
2. Tiemann and Friedländer, *Ber.*, **14**, 1973 (1881).
3. Gulewitsch and Wasmus, *Ber.*, **39**, 1191 (1906).
4. Freytag, *Ber.*, **48**, 649 (1915).
5. Lin and Li, *J. Chinese Chem. Soc.*, **6**, 88 (1938) [*C. A.*, **35**, 5096 (1941)].

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

amino acid hydrochloride

ethanol (64-17-5)

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

ammonia (7664-41-7)

methanol (67-56-1)

ether,
ethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

lead hydroxide

hydrogen sulfide (7783-06-4)

lead sulfide

ammonium cyanide

potassium cyanide (151-50-8)

methyl chloride (74-87-3)

acetone (67-64-1)

lead acetate

ammonium hydroxide (1336-21-6)

α-Aminoisobutyric acid (62-57-7)

diethyl ketone (96-22-0)

α-Aminodiethylacetic acid,
Butyric acid, α-amino-α-ethyl- (2566-29-2)

α-bromodiethylacetic acid (5456-23-5)

α-aminodiethylacetonitrile

diethyl ketone cyanohydrin

ethyl α-cyanodiethylacetate

ethyl diethylmalonamate

phosphorus pentoxide (1314-56-3)