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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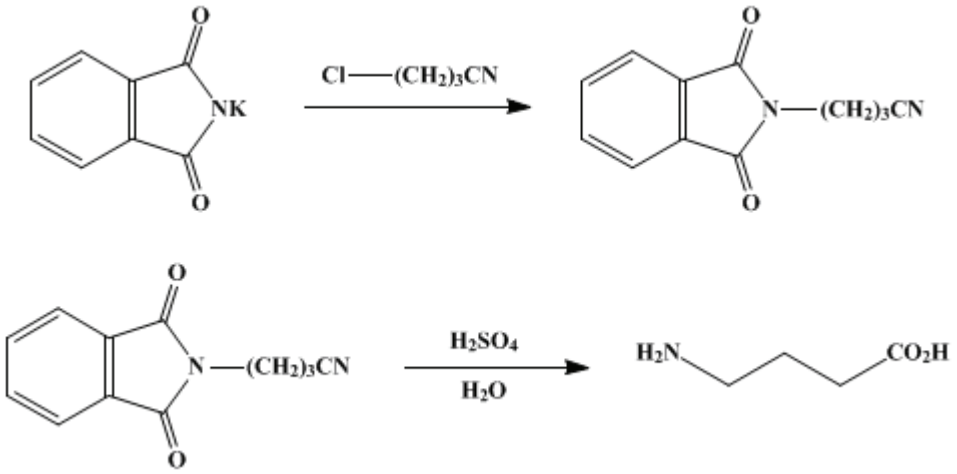
γ-AMINOBUTYRIC ACID

[Butyric acid, γ-amino-]



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1. Procedure

In a 1-l. round-bottomed flask fitted with a tightly fitting cork stopper carrying an air condenser are placed 100 g. (0.54 mole) of finely powdered potassium phthalimide (Org. Syn. Coll. Vol. I, **1941**, 119) and 52 g. (0.5 mole) of γ-chlorobutyronitrile (Org. Syn. Coll. Vol. I, **1941**, 156). The flask is heated in an oil bath maintained at 150–180° for one and one-half hours (Note 1) and then allowed to cool. The excess potassium phthalimide and the potassium chloride formed are removed by extraction with several portions of boiling distilled water until the wash water gives no test for chloride ion. The flask is then cooled and the product caused to solidify, and the remaining water is decanted as completely as possible. The solid is treated with 140 cc. of concentrated sulfuric acid, and the mixture is warmed gently in an oil bath under a reflux condenser until all the γ-phthalimidobutyronitrile is brought into solution. Through the reflux condenser 200 cc. of distilled water is added carefully and the solution is refluxed vigorously for three hours. The mixture is cooled and allowed to stand overnight, and the phthalic acid is filtered. The filtrate is transferred to a large evaporating dish, 1 l. of distilled water is added, and then an excess of barium carbonate (about 550 g.) is added in small portions (Note 2). The mixture is evaporated nearly to dryness on the steam bath, and the residue is stirred throroughly with 1 l. of distilled water and again evaporated (Note 3). Finally 1 l. of distilled water is stirred with the solid and the mixture is filtered on a large Büchner funnel. The precipitate is washed with three 200-cc. portions of hot distilled water, and the filtrate and washings are concentrated to a volume of 200 cc. on the steam bath. After the addition of 2 g. of activated carbon the solution is filtered by suction, using a No. 42 Whatman paper, and the charcoal is washed with several small portions of hot distilled water. The filtrate is concentrated on the steam bath to the point of crystallization (about 75 cc.), and 375–500 cc. of absolute alcohol is added to precipitate the amino acid. The mixture is stirred well so that the yellow impurities are retained in the solvent, and, after cooling, the colorless, crystalline product is collected and washed with absolute alcohol.

The alcoholic filtrate is evaporated to 50 cc., and 50 g. of barium hydroxide and 150 cc. of distilled water are added (Note 4). The mixture is refluxed for two hours and the excess barium hydroxide is precipitated with carbon dioxide. The barium carbonate is removed by filtration and washed with hot distilled water. A slight excess of sulfuric acid is added to the filtrate to liberate the amino acid from its barium salt, and an excess of barium carbonate is added to remove sulfate ion. The mixture is digested on the steam bath until effervescence ceases, and then it is filtered and the precipitate is washed with hot

distilled water. The filtrate and washings are concentrated on the steam bath to a volume of 100 cc., decolorized with 1 g. of active carbon, filtered, and concentrated to the point of crystallization (about 25 cc.). The amino acid is precipitated by the addition of 150 cc. of absolute alcohol, and the product is collected and washed with absolute alcohol.

The combined yield is 24–32 g. (47–62 per cent on the basis of the γ-chlorobutyronitrile used). The amino acid may be recrystallized by dissolving it in the least possible amount of distilled water and adding 5 to 7 volumes of absolute alcohol.

2. Notes

1. It is advisable to interrupt the heating after about forty-five minutes and thoroughly mix the pasty material by means of a glass rod. Longer heating of the reaction mass, although unnecessary, does no harm.
2. The reagent neutralizes the sulfuric acid and decomposes the ammonium sulfate, but it does not react with the amino acid.
3. Usually the ammonia is removed completely by these two treatments, but if it is not the thorough mixing of the solid with water and the subsequent evaporation must be repeated.
4. The alcoholic filtrate contains appreciable amounts of pyrrolidone. The treatment with excess barium hydroxide converts this into the barium salt of the amino acid.[1], [2]

3. Discussion

γ-Aminobutyric acid has been prepared by the electrolytic reduction of succinimide to pyrrolidone and hydrolysis of the pyrrolidone by means of barium hydroxide;[1] by the oxidation of piperylurethan with fuming nitric acid and treatment of the resulting product with concentrated hydrochloric acid in sealed tubes at 100°;[3] by the hydrolysis of the condensation product of N-(β-bromoethyl)-phthalimide and sodiomalonic ester;[4] and by the method described above which is a slight modification of that of Gabriel.[2]

References and Notes

1. Tafel and Stern, Ber. **33**, 2224 (1900).
2. Gabriel, ibid. **22**, 3335 (1889); **23**, 1771 (1890).
3. Schotten, ibid. **16**, 643 (1883).
4. Aschan, ibid. **24**, 2450 (1891).

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

piperylurethan

sodiomalonic ester

alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

nitric acid (7697-37-2)

carbon dioxide (124-38-9)

carbon (7782-42-5)

Potassium Phthalimide (1074-82-4)

γ-Chlorobutyronitrile (628-20-6)

barium hydroxide (17194-00-2)

barium carbonate (513-77-9)

ammonium sulfate (7783-20-2)

phthalic acid (88-99-3)

Succinimide (123-56-8)

γ-Aminobutyric acid,
Butyric acid, γ-amino- (56-12-2)

potassium chloride (7447-40-7)

γ-phthalimidobutyronitrile

pyrrolidone (616-45-5)

N-(β-bromoethyl)-phthalimide (574-98-1)