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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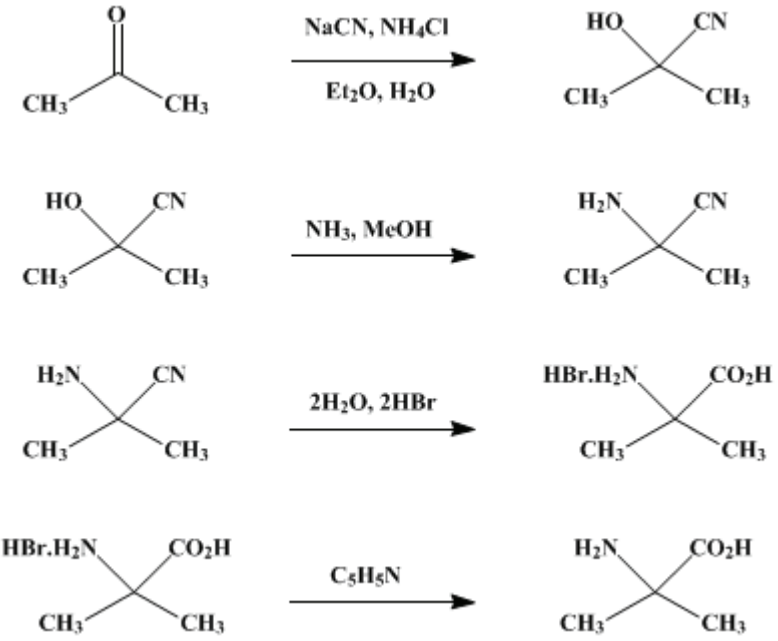
Organic Syntheses, Coll. Vol. 2, p.29 (1943); Vol. 11, p.4 (1931).

α-AMINOISOBUTYRIC ACID

[Isobutyric acid, α-amino-]



Submitted by H. T. Clarke and H. J. Bean.
Checked by C. S. Marvel and C. F. Bailey.

1. Procedure

A filtered solution of 200 g. (3.7 moles) of ammonium chloride in 500 cc. of water is placed in a 3-l. round-bottomed flask. The flask is surrounded by an ice bath and cooled to 5–10°. A solution of 175 g. (3 moles) of acetone in 500 cc. of ether is added with stirring (Note 1). Then a solution of 160 g. (3.2 moles) of sodium cyanide in 350 cc. of water is added, with stirring, at such a rate that the temperature never exceeds 10° (Note 2).

The reaction mixture is stirred for one hour after all the cyanide has been added and then is allowed to stand overnight. The ether layer is separated and the aqueous liquor is extracted with six 300-cc. portions of ether. The ether extracts are combined and the ether is distilled. The residue, which consists mainly of acetone cyanohydrin, is diluted with 800 cc. of methyl alcohol. The solution is cooled and saturated with ammonia gas (Note 3). The reaction mixture is allowed to stand for two or three days (Note 4), and the excess ammonia is expelled by a current of air. The methyl alcohol is removed by distillation as completely as possible, and 600 cc. of water is added to the residue. Then 1 kg. of 48 per cent hydrobromic acid is added and the mixture is refluxed for two hours.

The hydrobromic acid is distilled under reduced pressure on a steam bath. The residue is treated with 400–500 cc. of water, and the solution is again concentrated under reduced pressure to remove as much hydrobromic acid as possible (Note 5).

The residue is dissolved in fifteen to twenty times its weight of methyl alcohol (Note 6) and filtered, and an excess of pyridine (Note 7) is added. The free amino acid separates on standing overnight. It is collected on a Büchner funnel, washed thoroughly with methyl alcohol, and dried. The yield is 92–102 g. (30–33 per cent of the theoretical amount). If a pyridine-free product is desired, it is dissolved in 200 cc. of warm water and filtered, and the filtrate is poured into 2 l. of methyl alcohol (Note 8). There is less than 10 g. of product in the mother liquors. It may be isolated by evaporating to dryness, washing

with methyl alcohol, and purifying by reprecipitation in the same way.

2. Notes

1. Vigorous stirring is necessary to obtain the best results.
2. The reaction temperature may rise to 15° without lowering the yield. If the temperature falls to 0°, the reaction does not take place readily.
3. The excess of ammonia is necessary to cause the formation of the aminonitrile from the acetone cyanohydrin formed in the first stage of the process.
4. In some runs this time was only twenty-four hours and no serious diminution of the yield was noted.
5. After addition of the water and subsequent evaporation almost to dryness it is well to add another small portion of water (25–75 cc.) and again evaporate to dryness to ensure the complete removal of hydrobromic acid. This should be done several times if necessary.
6. The amount of methyl alcohol should not exceed 3 l.; otherwise the amino acid will be precipitated incompletely. Long stirring in the cold may be necessary to effect complete solution, though apparently no difficulty is encountered if the residue does not dissolve completely.
7. The minimum amount of pyridine necessary is determined by the amount of hydrobromic acid remaining in the residue. An excess of pyridine does no harm. If it is desired to use the minimum amount pyridine is added in small portions until the solution is neutral to Congo red, and then an additional 250 g. is added.
8. A further small quantity may be obtained by evaporating the mother liquor to a small volume on a steam bath, allowing it to crystallize, and washing the crystals with methyl alcohol.

3. Discussion

The only satisfactory method of preparing α-aminoisobutyric acid is the Strecker synthesis[1] in one or another of its modifications.[2] The process of isolating the product by treating an alcoholic solution of the hydrobromide with pyridine is essentially the same as that developed for glycine;[3] alternatively, aniline may be used.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 88

References and Notes

1. Strecker, Ann. **75**, 28 (1850).
2. Tiemann and Friedländer, Ber. **14**, 1970 (1881); Marckwald, Neumark, and Stelzner, ibid. **24**, 3283 (1891); Gulewitsch, ibid. **33**, 1900 (1900); Hellsing, ibid. **37**, 1923 (1904); Gulewitsch and Wasmus, ibid. **39**, 1184 (1906); Zelinsky and Stadnikoff, ibid. **39**, 1726 (1906); Cocker and Lapworth, J. Chem. Soc. **1931**, 1391.
3. Org. Syn. **4**, 31 (1925).
4. Benedict, J. Am. Chem. Soc. **51**, 2277 (1929).

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

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

aniline (62-53-3)

sodium cyanide (143-33-9)

HYDROBROMIC ACID,
hydrobromide (10035-10-6)

acetone (67-64-1)

pyridine (110-86-1)

Glycine (513-29-1)

Acetone cyanohydrin (75-86-5)

α-Aminoisobutyric acid,
Isobutyric acid, α-amino- (62-57-7)