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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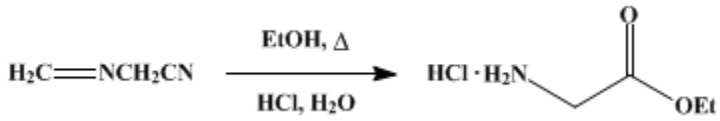
Organic Syntheses, Coll. Vol. 2, p.310 (1943); Vol. 14, p.46 (1934).

GLYCINE ETHYL ESTER HYDROCHLORIDE



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1. Procedure

In a 3-l. round-bottomed flask are placed 500 cc. (400 g., 8.7 moles) of absolute alcohol which has been saturated in the cold with hydrochloric acid gas (Note 1), 870 cc. (680 g., 14.8 moles) of 96 per cent alcohol (Note 2), and 70 g. (1.03 moles) of methyleneaminoacetonitrile (Note 3). This mixture is refluxed on a steam bath for three hours (Note 4). During the refluxing, ammonium chloride separates. After the reaction is complete, the hot alcohol solution is filtered with suction and the filtrate cooled, thus allowing the glycine ester hydrochloride to separate in fine white needles. The product is filtered with suction, sucked as dry as possible on the filter, and then allowed to dry in the air. The yield is about 110 g. The alcohol from the filtrate is distilled (Note 5) until about one-third of its volume is left; it is cooled again, when a second crop of crystals is obtained. The total yield of product, m.p. 142–143°, varies from 125 to 129 g. (87–90 per cent of the theoretical amount). If a very pure product is desired, the material may be re-crystallized from absolute alcohol.

2. Notes

1. The 500 cc. of absolute alcohol is cooled in an ice bath and treated with dry hydrogen chloride until 163 g. has been added, an amount sufficient for saturation. The solution should be protected from the moisture of the air with a calcium chloride tube.
2. It is important to use the strengths of alcohol specified in the directions if the best yields are to be obtained, and it is advisable to test the alcohol with a hydrometer just before using. The 870 cc. of 96 per cent alcohol contains just enough water for the hydrolysis. If, therefore, a less concentrated alcohol is used, the glycine ester hydrochloride does not form so readily and does not separate so easily from solution. Experiments using 96 per cent alcohol saturated with hydrochloric acid and 870 cc. of 96 per cent alcohol gave about 8 to 10 g. less product. A more dilute alcohol than 96 per cent gives a much poorer grade and yield of the glycine ester hydrochloride.
3. The crude material as described in Org. Syn. Coll. Vol. I, **1941**, 355, is satisfactory.
4. A cork and not a rubber stopper should be used during the refluxing, as rubber stoppers will cause the product to be colored.
5. It is important that no water get into the alcohol, as glycine ester hydrochloride is quite soluble in water. Concentration of the filtrate on the steam bath should not be done in an open vessel because the solution will take up moisture and the product will not crystallize.

3. Discussion

Glycine ethyl ester hydrochloride has been prepared by the action of absolute alcohol and hydrogen chloride on glycine;[1] from glycyl chloride and alcohol;[2] by the action of ammonia[3] or hexamethylenetetramine[4] on chloroacetic acid, and subsequent hydrolysis with alcoholic hydrochloric acid; by the action of hydrogen chloride and alcohol on methyleneaminoacetonitrile;[5] and by the reduction of ethyl cyanoformate[6] or the corresponding imido ester hydrochloride.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 424

References and Notes

1. Curtius and Goebel, J. prakt. Chem. (2) **37**, 159 (1888); Harries and Weiss, Ann. **327**, 365 (1903).
2. Fischer, Ber. **38**, 2916 (1905).
3. Hantzsch and Silberrad, ibid. **33**, 70 (1900); Hantzsch and Metcalf, ibid. **29**, 1681 (1896).
4. Auger, Bull. soc. chim. (3) **21**, 6 (1899); Locquin, ibid. **23**, 662 (1900).
5. Jay and Curtius, Ber. **27**, 60 (1894); Klages, ibid. **36**, 1508 (1903).
6. Ges. für Kohlentechnik m.b. H., Ger. pat. 594,219 [C. A. **28**, 3417 (1934)]; 638,577 [C. A. **31**, 3066 (1937)]; E. Merck, Ger. pat. 597,305 [C. A. **28**, 5078 (1934)].
7. Ges. für Kohlentechnik m.b. H., Ger. pat. 604,277 [C. A. **29**, 812 (1935)].

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

glycine ester hydrochloride

alcohol (64-17-5)

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

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

chloroacetic acid (79-11-8)

Glycine (513-29-1)

Methyleneaminoacetonitrile (109-82-0)

hexamethylenetetramine (100-97-0)

Glycine ethyl ester hydrochloride (623-33-6)

glycyl chloride

ethyl cyanoformate (623-49-4)