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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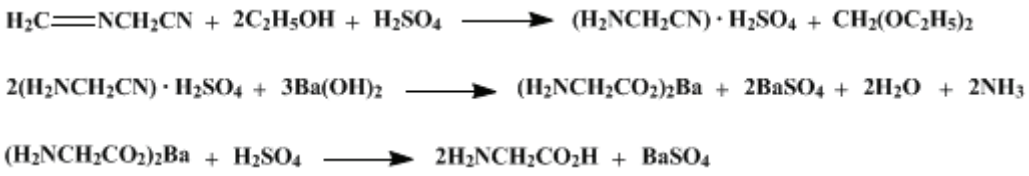
GLYCINE

[(*A*) (*from Methyleneaminoacetonitrile*)]



$$H_2C{=}NCH_2CN + 2C_2H_5OH + H_2SO_4 \longrightarrow (H_2NCH_2CN)\cdot H_2SO_4 + CH_2(OC_2H_5)_2$$

$$2(H_2NCH_2CN)\cdot H_2SO_4 + 3Ba(OH)_2 \longrightarrow (H_2NCH_2CO_2)_2Ba + 2BaSO_4 + 2H_2O + 2NH_3$$

$$(H_2NCH_2CO_2)_2Ba + H_2SO_4 \longrightarrow 2H_2NCH_2CO_2H + BaSO_4$$

Submitted by W. K. Anslow and Harold King.
Checked by H. T. Clarke and Letha Davies Behr.

1. Procedure

(*A*) *Alcoholysis of Methyleneaminoacetonitrile*.—To a solution of 51.5 g. (28 cc., 0.5 mole) of 95 per cent sulfuric acid in 125 cc. of 95 per cent ethyl alcohol at 45–50°, contained in a wide-mouthed 250-cc. conical flask, is added 34 g. (0.5 mole) of methyleneaminoacetonitrile (p. 355) (Note 1). The flask is closed with a rubber stopper (Note 2) and vigorously shaken by hand. Solution takes place with evolution of heat, the temperature rising about 10–15° (Note 3). The liquid separates into two layers, the upper one consisting of methylene diethyl ether; crystallization of the aminoacetonitrile hydrogen sulfate sets in rapidly. The mixture is shaken vigorously at intervals to prevent the formation of a hard cake of crystals. After the mass has stood overnight in the refrigerator at 0–5°, the salt is filtered off and washed with a minimum quantity (20–25 cc.) of ice-cold alcohol. The yield is 57–62 g. (75–81 per cent of the theoretical amount) (Note 4).

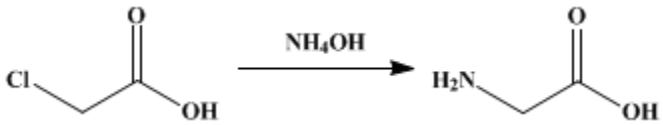
(*B*) *Preparation of Glycine*.—To a boiling suspension of 253 g. (0.8 mole) of barium hydroxide octahydrate in 500 cc. of water in a 1-l. beaker is added, in portions, 61.6 g. (0.4 mole) of aminoacetonitrile hydrogen sulfate at such a rate that the mixture does not froth over. The beaker is then covered with a 1-l. round-bottomed flask containing cold running water, and boiling is continued until no more ammonia is evolved. This requires six to eight hours. The barium is then quantitatively precipitated by the addition of exactly the necessary amount of 50 per cent sulfuric acid (Note 5). The filtrate is concentrated on a water bath to a volume of 50–75 cc.; on chilling, crude glycine crystallizes and is filtered off. The filtrate is again concentrated and chilled and the crystals removed. This process is continued until the final filtrate amounts to about 5 cc. The yield of crude glycine so obtained amounts to 25–27 g. This is systematically recrystallized from water, decolorizing with Norite and collecting the material which melts (with decomposition) at 246° (corr.) or above. Washing of the successive crops with 50 per cent ethyl alcohol is of great assistance in freeing the crystals of mother liquor. The yield of pure glycine is 20–26 g. (67–87 per cent of the theoretical amount).

2. Notes

1. The yields obtained with the crude material are as good as those with the recrystallized nitrile. Recrystallization of the nitrile is attended with considerable loss, only 65–70 per cent of the original weight being recovered.
2. Moistening of the portion of the stopper in contact with the glass should be avoided as this lubrication tends to permit the stopper to escape unless forcibly held down.
3. If the initial temperature of the acid mixture is below that indicated, there is a tendency for the aminoacetonitrile hydrogen sulfate to separate before the nitrile is completely dissolved; if the temperature is too high, there is danger that the alcohol may boil.
4. The mother liquor contains a further quantity of aminoacetonitrile hydrogen sulfate which cannot, however, be recovered as such; in one experiment it yielded 2.3 g. of crude glycine on hydrolysis with excess barium hydroxide.
5. It is well to add a very slight excess of sulfuric acid, heat on the water bath until the precipitate filters readily, and finally complete the operation by adding dilute barium hydroxide solution until no further

precipitation takes place. It is also feasible to finish with a slight excess of barium hydroxide and to remove this by the addition of ammonium carbonate to the boiling solution.

[(*B*) (*from Chloroacetic Acid*)]



Submitted by James M. Orten and Robert M. Hill.
Checked by C. S. Marvel and C. F. Woodward.

1. Procedure

In a 12-l. round-bottomed flask is placed 8 l. (120 moles) of aqueous ammonia (sp. gr. 0.90) and to it is gradually added, with stirring, 189 g. (2 moles) of monochloroacetic acid. The solution is stirred until the chloroacetic acid is dissolved and is then set aside for about forty-eight hours at room temperature. The solution, which is colorless or faintly yellow, is concentrated on a water bath under reduced pressure (Note 1) to a volume of about 200 cc.

The concentrated solution of glycine and ammonium chloride is transferred to a 2-l. beaker, the flask is rinsed with a little water, and this is added to the main portion. The volume of the solution is finally brought to 250 cc. with water, and the glycine is precipitated by the gradual addition of 1500 cc. of methyl alcohol (Note 2). The solution is well stirred during the addition of the methyl alcohol and is cooled in an ice box for four to six hours to allow complete crystallization. The solution is filtered, and the glycine crystals are washed by suspending them in 500 cc. of 95 per cent methyl alcohol; they are again collected on the filter and washed with a little methyl alcohol and then with ether. After air drying the yield is 108–112 g. of glycine.

This product contains small amounts of chloride and ammonia. For purification it is dissolved in 200 to 215 cc. of water with warming. This solution is shaken with 10 g. of permutit (Note 3) and filtered. The glycine is then precipitated by the addition of approximately five volumes (about 1250 cc.) of methyl alcohol. The glycine is collected on a Büchner funnel, washed with methyl alcohol and ether, and dried in the air. The yield is 96–98 g. (64–65 per cent of the theoretical amount) of a product which darkens at 237° and melts at 240° with decomposition. It gives no test for chlorides and is free from ammonium salts as indicated by the test with Nessler's reagent.

2. Notes

1. The distillate can be saved and the aqueous ammonia used in subsequent preparations.
2. The technical grade of methyl alcohol is satisfactory.
3. If permutit is not available, a third crystallization of the glycine from water and methyl alcohol yields a product free from ammonium salts with very little loss. The second crystallization without the use of permutit gives a very good grade of glycine which is pure enough for any ordinary work.

3. Discussion

Glycine hydrochloride can be prepared by the action of hydrochloric acid on hippuric acid,[1] aminoacetonitrile,[2] methyleneaminoacetonitrile,[3] and on ethyl phthaliminoacetate.[4] Aniline has been recommended for its conversion into free glycine.[5] Glycine can also be prepared by the interaction of chloroacetic acid and ammonia;[6] by the hydrolysis of methyleneaminoacetonitrile by successive treatments with barium hydroxide and sulfuric acid;[7] and by the hydrolysis of aminoacetonitrile by means of barium hydroxide.[8] A thorough study has been reported for its preparation in improved yields by the sulfuric acid hydrolysis of aminoacetonitrile, and in satisfactory yields from chloroacetic acid and ammonia.[9] Other methods of preparation include the reduction of cyanoformic esters,[10] a modified Curtius degradation of ethyl cyanoacetate,[11] and the hydrolysis of the neck ligaments of cattle.[12]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 11
- Org. Syn. Coll. Vol. 2, 29
- Org. Syn. Coll. Vol. 3, 88

References and Notes

1. Curtius and Goebel, J. prakt. Chem. (2) **37**, 157 (1888).
2. Eschweiler, Ann. **278**, 236 (1894).
3. Jay and Curtius, Ber. **27**, 60 (1894). Clarke and Taylor, Org. Syn. **4**, 31.
4. Gabriel and Kroseberg, Ber. **22**, 428 (1889).
5. Benedict, J. Am. Chem. Soc. **51**, 2277 (1929).
6. Kraut, Ann. **266**, 295 (1891); Tischtschenko, J. Russ. Phys. Chem. Soc. **53**, 300 (1921) [Chem. Zentr. II, 1001 (1923)]; Robertson, J. Am. Chem. Soc. **49**, 2889 (1927); Boutwell and Kuick, ibid. **52**, 4166 (1930); Orten and Hill, ibid. **53**, 2797 (1931); Cheronis and Spitzmueller, J. Org. Chem. **6**, 349 (1941).
7. Ling and Nanji, Biochem. J. **16**, 702 (1922).
8. Eschweiler, Ann. **278**, 237 (1894).
9. Cocker and Lapworth, J. Chem. Soc. 1401 (1931).
10. Ges. für Kohlentechnik m. b. H., Ger. pat. 594,219 [C. A. **28**, 3417 (1934)].
11. Sah, J. Chinese Chem. Soc. **4**, 198 (1936) [C. A. **31**, 659 (1937)].
12. Armour and Co., U. S. pat. 2,098,923 [C. A. **32**, 194 (1938)].

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

nitrile

cyanoformic esters

Nessler's reagent

ethyl alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonium carbonate (506-87-6)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

aniline (62-53-3)

chloroacetic acid,
monochloroacetic acid (79-11-8)

Norite (7782-42-5)

Ethyl cyanoacetate (105-56-6)

barium hydroxide (17194-00-2)

Glycine (513-29-1)

Methyleneaminoacetonitrile (109-82-0)

methylene diethyl ether (142-68-7)

aminoacetonitrile hydrogen sulfate (5466-22-8)

barium hydroxide octahydrate (12230-71-6)

barium (7440-39-3)

Glycine hydrochloride (6000-43-7)

Hippuric acid (495-69-2)

aminoacetonitrile (540-61-4)

ethyl phthaliminoacetate