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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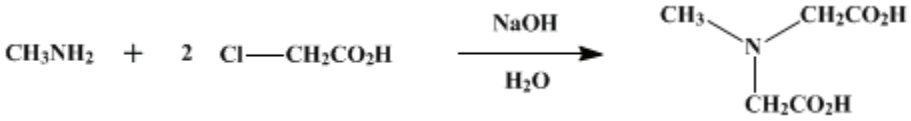
METHYLIMINODIACETIC ACID

[Acetic acid, methyliminodi-]



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1. Procedure

In a 2-l. flask, provided with a mechanical stirrer, separatory funnel, and thermometer, are placed 189 g. (2 moles) of chloroacetic acid and 150 cc. of water. The flask is cooled in ice water, and a cold solution of 160 g. (4 moles) of sodium hydroxide in 500 cc. of water is added, with stirring, at such a rate that the temperature does not exceed 30° (Note 1). After all the alkali has been added, the cooling bath is removed and an aqueous solution (Note 2) containing 31 g. (1 mole) of methylamine is added slowly. The reaction is exothermic, and the temperature is kept below 50° by occasional immersion of the flask in ice water. After all the methylamine has been added, the solution is allowed to stand for two hours to complete the reaction.

A solution of 257 g. (1.05 moles) of barium chloride dihydrate in about 500 cc. of hot water is added to the reaction mixture, with vigorous shaking, and the mixture is heated on a steam bath for one-half hour. A heavy precipitate of the barium salt of the amino acid separates at once. After cooling to room temperature, the barium salt is collected on a suction filter, transferred to a beaker, and washed with two 250-cc. portions of hot water (80°). After drying at 100°, the barium salt weighs 225–230 g. (80–82 per cent of the theoretical amount).

The dry barium salt is placed in a 2-l. flask provided with a mechanical stirrer, 600 cc. of water is added, and the mixture heated to boiling. The calculated quantity of 5 *N* sulfuric acid (Note 3) is introduced gradually from a separatory funnel into the well-stirred mixture over a period of about one hour. The mixture is then centrifuged or filtered with suction (Note 4) through a thin layer of fuller's earth. The barium sulfate precipitate is transferred to a beaker and extracted with two 250-cc. portions of boiling water. The filtrate and washings are transferred to a distilling flask placed in a water bath and concentrated under reduced pressure to a volume of 175–200 cc. (Note 5). The syrupy residue is poured into a large beaker and treated with 500 cc. of absolute methyl alcohol. Crystals of the acid begin to appear at once. The mixture is allowed to stand for three or four hours in an ice bath to complete the precipitation, and the crystalline solid is separated by filtration with suction. After being washed with two 75-cc. portions of methyl alcohol, the product is dried at 100°. The methyliminodiacetic acid forms fine, white crystals, m.p. 215°, and weighs 92–105 g. (63–71 per cent of the theoretical amount).

If an especially pure product is desired, the acid may be reprecipitated by dissolving in an equal weight of warm water and adding three volumes of methyl alcohol. The loss in purification is 4–5 per cent.

2. Notes

1. The temperature must be controlled to avoid formation of glycolic acid. One-half of the alkali is sufficient to neutralize the acid, and the remainder may be added rapidly without danger of raising the temperature.
2. Technical aqueous methylamine solution (28–33 per cent) may be used. The amine content should be determined by titration with standard acid.
3. The barium salt requires 1.416 cc. of 5 *N* sulfuric acid per gram. The acid should be titrated before use.

4. If unchanged barium methyliminodiacetate remains in solution, it peptizes the barium sulfate and the filtration is likely to be trouble-some. If colloidal barium sulfate is encountered, it is advisable to add a slight excess (less than 1 per cent) of sulfuric acid and continue the heating for twenty minutes longer. Traces of sulfate in the final product may be removed, if necessary, by reprecipitation of the acid with methyl alcohol.
5. The residue should have a syrupy consistency but should be fluid enough to be poured freely from the flask.

3. Discussion

Methyliminodiacetic acid has hitherto been prepared by the action of methylamine on formaldehyde cyanohydrin with subsequent hydrolysis of the resulting dinitrile.[1] This method was found by the submitter to be much less satisfactory than the procedure given above.

References and Notes

1. Eschweiler, Ann. **279**, 39 (1894); I. G. Farbenind. A.-G., Fr. pat. 804,497 [C. A. **31**, 3505 (1937)].

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

barium salt of the amino acid

sulfuric acid (7664-93-9)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

chloroacetic acid (79-11-8)

barium sulfate (7727-43-7)

methylamine (74-89-5)

formaldehyde cyanohydrin (107-16-4)

Methyliminodiacetic acid,
Acetic acid, methyliminodi- (4408-64-4)

barium chloride dihydrate (10326-27-9)

glycolic acid (79-14-1)

barium methyliminodiacetate