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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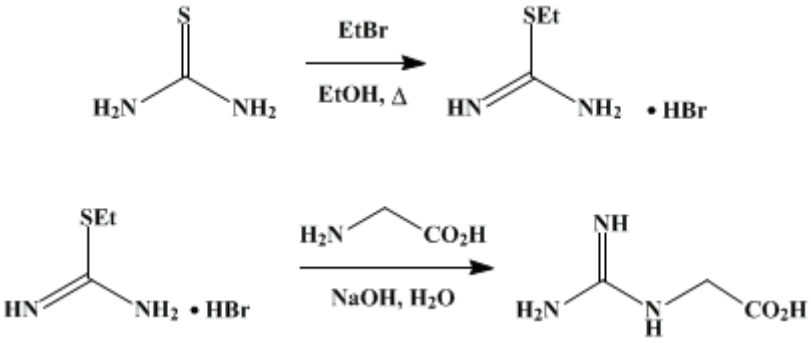
Organic Syntheses, Coll. Vol. 3, p.440 (1955); Vol. 22, p.59 (1942).

GUANIDOACETIC ACID

[Glycocyamine]



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1. Procedure

A. *S-Ethylthiourea hydrobromide.* A mixture of 150 g. of powdered thiourea (1.97 moles) (Note 1), 250 g. of ethyl bromide (2.29 moles), and 200 ml. of absolute ethanol is placed in a 1-l. round-bottomed flask equipped with an efficient condenser. The mixture is warmed on a water bath (bath temperature 55–65°) for 3 hours, with occasional shaking. During this time all the thiourea dissolves. The reflux condenser is replaced by one set for downward distillation, and the ethanol and excess ethyl bromide are removed under the vacuum of a water pump. During the distillation, the temperature of the bath is slowly raised to the boiling point (Note 2). The residual oil is poured into a 500-ml. beaker and allowed to crystallize (Note 3). The solid is pulverized and dried in a desiccator (Note 4) and (Note 5). The yield is 340–360 g. (93–99%).

B. *Guanidoacetic acid.* This reaction should be carried out in a well-ventilated hood, as considerable amounts of ethyl mercaptan are evolved. In a 1-l. Erlenmeyer flask is placed 92.5 g. (0.50) mole of S-ethylthiourea hydrobromide. The flask is immersed in an ice bath, and 252 ml. of 2 *N* sodium hydroxide solution is added. A hot (80+°) solution of 41 g. of glycine in 90 ml. of water is added rapidly. When the temperature reaches 25° (Note 6), the flask is removed from the ice water. After about 30 minutes crystallization begins; then approximately 100 ml. of ether is added, and the mixture is left in the hood overnight (Note 7). The mixture is then chilled for 2 hours in an ice bath, the ether layer is decanted, and the solid is filtered with suction. The crystals are washed on the funnel successively with two 20-ml. portions of ice water (Note 8), two 150-ml. portions of 95% ethanol, and two 150-ml. portions of ether. The yield of air-dried guanidoacetic acid is 47–53 g. (80–90%). This product is pure enough for most purposes (Note 9); it melts with decomposition at 280–284°.

2. Notes

1. Commercial thiourea is usually sufficiently finely divided so that it may be used directly.
2. The last traces are more quickly removed if the vacuum line is attached directly to the flask.
3. If the product is inoculated, the liquid solidifies at once.
4. The crude product is sufficiently pure for the subsequent reaction. If kept in a cool place in the absence of air, it is stable for several months.
5. This is a general method for preparing S-alkylthiourea hydrobromides and hydriodides. The yields are always over 90%. The hydrochlorides are not so readily prepared; it is necessary to determine, by experiment, the optimum conditions for each hydrochloride.
6. The temperature may rise or fall to 25°, depending upon the temperatures of the component solutions.
7. The yield is slightly lower (45 g.) if the mixture is filtered after standing for only 3 hours.

8. The product is appreciably soluble in water.
9. Further purification of this product may be accomplished by (a) recrystallizing it from hot water (125 ml. per 5 g.), or (b) dissolving it in slightly more than the calculated amount of 2 *N* hydrochloric acid and reprecipitating by adding an equivalent quantity of 2 *N* sodium hydroxide. Analytical values for nitrogen (Dumas) given by the crude and purified products were as follows: Calculated: 35.9%. Found: acid as prepared, 35.4%; once recrystallized, 35.9%; reprecipitated, 35.7%.

3. Discussion

S-Ethylthiourea has been prepared as the hydrobromide[1,2,3] and hydriodide.[2,4] Guanidoacetic acid has previously been made from S-ethylthiourea hydriodide[2] and from S-methylthiourea.[5]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 449
- Org. Syn. Coll. Vol. 5, 612

References and Notes

1. Claus, *Ber.*, **7**, 236 (1874).
2. Wheeler and Merriam, *Am. Chem. J.*, **29**, 483 (1903).
3. Schotte, Priewe, and Roescheisen, *Z. physiol. Chem.*, **174**, 119 (1928).
4. Claus, *Ber.*, **8**, 41 (1875).
5. Mourgue, *Bull. soc. chim. France*, **1948**, 181.

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

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Ethyl bromide (74-96-4)

Glycine (513-29-1)

thiourea (62-56-6)

Guanidoacetic acid (352-97-6)

ethyl mercaptan (75-08-1)

S-ethylthiourea hydrobromide (1071-37-0)

S-Ethylthiourea

S-ethylthiourea hydriodide

S-methylthiourea