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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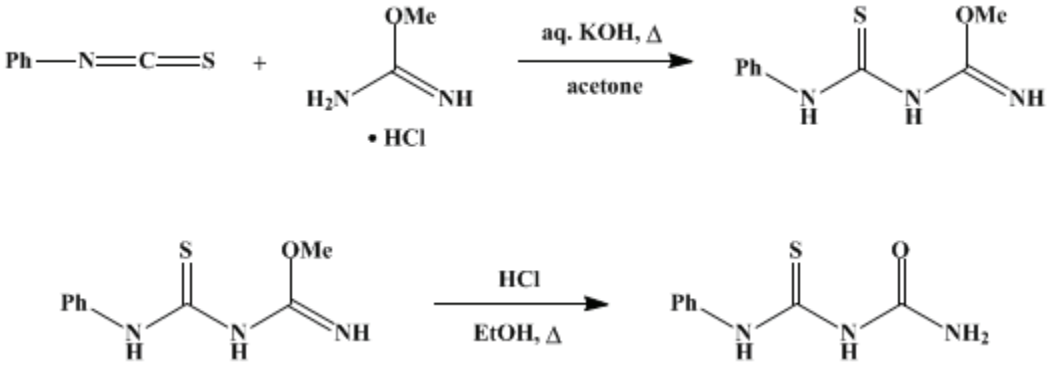
Organic Syntheses, Coll. Vol. 5, p.966 (1973); Vol. 42, p.87 (1962).

1-PHENYL-2-THIOBIURET

[Biuret, 1-phenyl-2-thio-]



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1. Procedure

A. *1-Phenyl-2-thio-4-methylisobiuret*. Into a 500-ml. three-necked flask fitted with a Hershberg stirrer[2] and reflux condenser are introduced a solution of 23.0 g. (0.35 mole) of 85% potassium hydroxide in 75 ml. of water, followed by 38.7 g. (0.35 mole) of methylisourea hydrochloride (Note 1). The clear liquid is diluted with 150 ml. of acetone, and the resulting suspension, containing finely divided crystalline solid, is treated with 27.0 g. (24 ml., 0.2 mole) of recently distilled phenyl isothiocyanate.

After the additions have been completed, the third neck of the flask is closed and the temperature of the stirred reaction mixture is raised to its boiling point during 15–20 minutes, then heating under reflux is continued for 10–15 minutes. The contents of the flask, which first change to a greenish yellow clear solution, then later separate into two phases, are kept well mixed by rapid stirring (Note 2). The flask is next disconnected, fitted with a stillhead, and the acetone is distilled rapidly at 25–35° under reduced pressure. The residual semicrystalline suspension, or two-phase mixture containing the crude product in the upper viscous layer, is carefully stirred onto 300–400 g. of crushed ice. This yields the crude isobiuret as a very pale-yellow granular solid, which is collected by suction filtration, washed with successive small portions of water, drained well, and allowed to dry at room temperature. The dry product is dissolved 120–150 ml. of boiling benzene. Small quantities of suspended yellow powdery material (and possibly droplets of water) are removed by gravity filtration through a heated funnel or by suction filtration through a preheated Büchner funnel. The clear yellow filtrate deposits large prismatic crystals of 1-phenyl-2-thio-4-methylisobiuret, which are collected by suction filtration at room temperature, washed with a little benzene, and air-dried. The yield of material having a melting point in the range of 122–128° is 27–31.5 g. (65–75%) (Note 3). Further small quantities (2–4 g.) of less pure material may be obtained by partial vacuum evaporation of the combined mother liquors and washings.

B. *1-Phenyl-2-thiobiuret*. A solution of 20.9 g. (0.1 mole) of 1-phenyl-2-thio-4-methylisobiuret in 200 ml. of hot absolute ethanol is treated with 40 ml. of concentrated hydrochloric acid, and the clear liquid is heated under reflux until to more methyl chloride is evolved (6–12 minutes, (Note 4)). The resulting solution is stirred into 2.1 of water, and the separated crystalline precipitate is collected after storage at 0° for at least 24 hours. The dried product is dissolve in boiling absolute ethanol (5–6 ml. per g.) then the hot solution is quickly filtered by light suction and diluted with half its volume of petroleum ether (b.p. 60–80°). The separated 1-phenyl-2-thiobiuret is collected by suction filtration after storage for 12 hours at room temperature, and rinsed with small portions of a mixture of equal volumes of ethanol and petroleum ether. The yield of product, m.p. 159–161° (Note 5), is 8.8–10.5 g. (45–54%) (Note 6).

2. Notes

1. Methylisourea hydrochloride is accessible from commercially available calcium cyanamide by the method described in *Organic Syntheses*.[3]
2. The reaction is complete when a withdrawn sample of the liquid, stirred on a watch-glass in an air current, solidifies rapidly and smells only very faintly of phenyl isothiocyanate.
3. This product, though still pale yellow, is suitable for most synthetic purposes. Colorless glass-like prisms of m.p. 128–130° (cor.) are obtainable on further crystallization from benzene.
4. The top of the condenser is fitted with a short vertical piece of hard-glass tubing at the mouth of which the escaping methyl chloride may be burned off. The completeness of the reaction is indicated when insufficient gas is evolved to support a *steady* flame. Methyl chloride will continue to diffuse out and produce a flickering flame when a match is held to the outlet. Prolonging the reaction time excessively reduces the yield.
5. Rather variable melting points have been reported for this compound, probably because the melting is accompanied by decomposition. In a bath heated at about 2° per minute, the checkers obtained capillary tube melting points for all samples in the range 149.5–152° (cor.).
6. The submitters report that partial evaporation of the mother liquors gives additional small quantities of low-melting fractions from which additional pure material may be obtained by further crystallizations. In contrast, the checkers obtained nearly one-half the yield in a second crop which had essentially the same melting point as the first crop. This somewhat different behavior may result from a difference in solvent characteristics of different samples of petroleum ether.

3. Discussion

1-Phenyl-2-thiobiuret has been prepared by the pyrolysis, at 75–90°, of 1-phenyl-2-thio-4-methylisobiuret hydrochloride,[4] and by the condensation of carbamyl isothiocyanate with aniline.[5] The method here described, which is based on the former method, is regarded as most convenient. A comprehensive review of syntheses of biurets, thiobiurets, and dithiobiurets is available.[6]

4. Merits of Preparation

This synthesis is generally applicable. For example, condensation of phenyl isothiocyanate and ethylisourea by the procedure above gives 70–80% yield of 1-phenyl-2-thio-4-ethylisobiuret,[4] which forms lustrous massive prisms, m.p. 98–99° (from benzene).

References and Notes

1. Royal Free Hospital School of Medicine, University of London, England.
2. P. S. Pinkney, *Org. Syntheses*, Coll. Vol. **2**, 116 (1943).
3. F. Kurzer and A. Lawson, *Org. Syntheses*, Coll. Vol. **4**, 645 (1963).
4. W. M. Bruce, *J. Am. Chem. Soc.*, **26**, 449 (1904); F. Kurzer and S. A. Taylor, *J. Chem. Soc.*, 379 (1958).
5. L. Birckenbach and K. Kraus, *Ber.*, **71**, 1492 (1938).
6. F. Kurzer, *Chem. Rev.*, **56**, 95 (1956).

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

petroleum ether

calcium cyanamide

1-Phenyl-2-thio-4-methylisobiuret

1-phenyl-2-thio-4-methylisobiuret hydrochloride

1-phenyl-2-thio-4-ethylisobiuret

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

aniline (62-53-3)

methyl chloride (74-87-3)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

PHENYL ISOTHIOCYANATE (103-72-0)

1-Phenyl-2-thiobiuret,
Biuret, 1-phenyl-2-thio- (53555-72-9)

carbamyl isothiocyanate

ethylisourea

Methylisourea hydrochloride