



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](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.

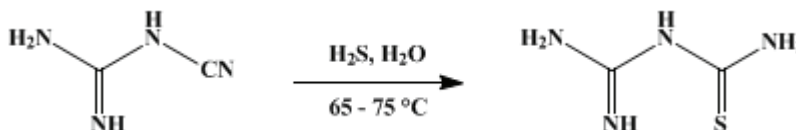
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 4, p.502 (1963); Vol. 35, p.69 (1955).*

## GUANYLTHIOUREA

[Urea, 1-amidino-2-thio-]



Submitted by Frederick Kurzer<sup>1</sup>

Checked by John C. Sheehan, George Buchi, and David Knutson.

### 1. Procedure

A 500-ml. three-necked round-bottomed flask, supported in a water bath equipped with a thermostat, is fitted with a vertical air-condenser and, on the side necks, with a thermometer and a gas delivery tube, both of which nearly reach the bottom of the vessel. The flask contains a solution of 42 g. (0.5 mole) of N-cyanoguanidine (dicyandiamide) (Note 1) in 200 ml. of water (Note 2). This is kept at 75° during 12 hours, and at 65–70° during an additional 25–30 hours (Note 3) while a fairly slow stream (Note 4) of hydrogen sulfide is passed through (Note 5). The resulting deep yellow liquid is allowed to cool to 45° while passage of hydrogen sulfide is continued; it is made strongly alkaline with 15 ml. of 40% aqueous sodium hydroxide and is freed from suspended impurities (consisting usually of finely divided black particles) by rapid filtration under reduced pressure (Note 6). The clear, yellow filtrate is allowed to cool slowly to room temperature, when lustrous prismatic leaflets separate gradually. Crystallization is completed by storing the flask and contents at 0° for 24 hours. The crystalline mass is broken up with a spatula, collected by filtration, and washed with three 20-ml. portions of ice water, the second and third portions of washing liquid being collected separately and discarded (Note 7). The yield of crude guanylthiourea, forming large, nearly colorless prisms, m.p. 160–164° (dec., with previous sintering at 154–158° or somewhat lower) (Note 8), varies between 29.5 and 32.5 g. (50–55%).

The material is purified as follows: The large crystals are powdered (Note 9) and boiled with successive portions of methanol until solution is complete, the saturated extracts being decanted and collected; approximately 8–9 ml. of methanol per gram of crude solid is required. The combined hot solution is filtered, if necessary, with suction, is allowed to cool slowly to room temperature, and is then stored at 0° overnight. Almost pure guanylthiourea, forming colorless prisms, m.p. 170–172° (dec., with previous sintering in the range 166–170°), is collected by filtration and washed with a little methanol. The recovery, per crystallization, varies from 65% to 70%. Most of the material contained in the mother liquors may be obtained by evaporation to small volume (Note 10) and forms one or two crops of satisfactory quality (melting point ranging between 166° and 170°).

### 2. Notes

1. A good reagent grade of N-cyanoguanidine is satisfactory in this synthesis.
2. The smallest possible volume of water is employed to ensure direct crystallization of the product when the solution is finally allowed to cool. Smaller volumes than the stated amount of water, however, tend to block the delivery tube with separated crystalline material, particularly in the beginning stages of the reaction, when much of the less-soluble reactant is still present.
3. The total time of heating may be made up of several shorter periods. On being cooled overnight the reaction mixture deposits a thick crust of crystalline solid on the walls of the flask. After 8 hours, large, spikelike prisms of unchanged N-cyanoguanidine predominate, but later the separated mass consists of massive rhombic prisms of guanylthiourea, with small needles of 2,4-dithiobiuret filling the spaces between the prisms. Solution is once again rapidly effected when the temperature is raised to 70°, with passage of hydrogen sulfide.
4. A rate of 3–4 bubbles of hydrogen sulfide per second is satisfactory. Toward the end of the time of reaction, a slower stream suffices.

5. Since [hydrogen sulfide](#) is only slowly absorbed, most of the gas escapes through the air condenser. The reaction must therefore be performed in an efficient hood.
6. A preheated Büchner flask and filter of 5- to 7-cm. diameter carrying a double layer of filter paper are employed.
7. [2,4-Dithiobiuret](#) may be isolated from the alkaline filtrate as follows: The stirred alkaline filtrate is acidified to Congo red with 25–30 ml. of concentrated [hydrochloric acid](#). A pale yellow powdery solid is rapidly precipitated, with evolution of [hydrogen sulfide](#); after storage at 0°, the solid (dry weight 7.5–9.0 g.) is collected by filtration, washed three times with 30-ml. portions of ice water, and pressed semidry. This material is added to boiling water (100 ml.) and stirred at 95–100° for 2 minutes, and the undissolved yellow powdery impurities (1.0–1.5 g., consisting largely of [sulfur](#)) are quickly removed by filtration with suction through a preheated funnel. The clear, pale yellow filtrate is rapidly filled with crystals, which are collected after storage at 0° for 12 hours. The yield of crude [2,4-dithiobiuret](#), forming small yellow needles, m.p. 178–180° (dec., previously sintering at 172–175°) is 5.5–7.0 g. (8–10%) ([Note 11](#)). Two crystallizations from boiling water (12 ml. per gram, recovery per crystallization: 80–90%) ([Note 12](#)), one with addition of [carbon](#), affords nearly white lustrous needles of [2,4-dithiobiuret](#), m.p. 180–182° (dec., previously sintering slightly at 178–180°) ([Note 13](#)).
8. Colorless [guanylthiourea](#) melts to a pale yellow liquid, which resolidifies to a yellow crystalline mass on cooling; partial rearrangement to [guanidine thiocyanate](#) occurs during the fusion.
9. When ground in a mortar, the crude [guanylthiourea](#) evolves small quantities of occluded [hydrogen sulfide](#).
10. The methanolic filtrates are rapidly distilled to approximately half volume at low temperature in a good vacuum. The solution is likely to froth considerably, and the use of a relatively large distilling flask is recommended. Small quantities of solid separating on the walls of the flask are redissolved by heating the residual liquid once again on a steam bath.
11. The yield of [dithiobiuret](#) increases on lengthening the time of reaction. After 100 hours' passage of [hydrogen sulfide](#) the yields of [guanylthiourea](#) and [dithiobiuret](#) were 25–35% and 15–18%, respectively.
12. Crystallization is carried out by adding the solid to the appropriate volume of boiling water, stirring at 95–100° for about 1 minute, and removing small quantities of suspended yellow impurities by filtration under reduced pressure using carefully preheated apparatus. When cooled slowly, the clear filtrate deposits the product in the form of large, lustrous needles.
13. On analysis, this material gives [carbon](#), [hydrogen](#), [nitrogen](#), and [sulfur](#) percentages in excellent agreement with the calculated values. Two additional crystallizations from [ethanol](#)-water (10 ml. each, per gram) raise the melting point to 183–185° (dec.). These decomposition temperatures are somewhat influenced by the rate of heating; the quoted values are observed when the specimen is inserted at 160° and the bath temperature is raised at the approximate rate of 8° per minute.

### 3. Discussion

[Guanylthiourea](#) has been prepared by the prolonged interaction of saturated aqueous [hydrogen sulfide](#) with [N-cyanoguanidine](#)<sup>2,3</sup> or an amidinourea salt<sup>4</sup> at 60–80°. It is formed in small quantities when [thiourea](#) is heated with [thiophosgene](#) or [phosphorus pentachloride](#) at 100–110°. <sup>5</sup> [Guanylthiourea](#) also results from the acid hydrolysis of [4,6-diamino-2-thio-1,3,5-thiadiazine](#).<sup>6,7</sup> In all these syntheses the product is collected as a sparingly soluble salt, the base being subsequently isolated by comparatively laborious methods, e.g. from the oxalate<sup>2</sup> or the phosphate.<sup>7</sup> The present procedure,<sup>8</sup> based on Bamberger's method,<sup>2</sup> allows the direct isolation of the base. Small quantities of [2,4-dithiobiuret](#), which are also formed in this reaction as a by-product, are readily separated.

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### References and Notes

1. Royal Free Hospital School of Medicine, University of London, England.
2. Bamberger, *Ber.*, **16**, 1460 (1883).
3. Slotta and Tschesche, *Ber.*, **62**, 1402 (1929).
4. Bamberger, *Ber.*, **16**, 1461 (1883).
5. Rathke, *Ber.*, **11**, 962 (1878).
6. Thurston and Sperry, U. S. pat. 2,364,594 [*C. A.*, **39**, 4630 (1945)].

7. Birtwell, Curd, Hendry, and Rose, *J. Chem. Soc.*, **1948**, 1653.  
8. Kurzer, *J. Chem. Soc.*, **1955**, 1.
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**Appendix**  
**Chemical Abstracts Nomenclature (Collective Index Number);**  
**(Registry Number)**

N-cyanoguanidine (dicyandiamide)

amidinourea salt

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

phosphorus pentachloride (10026-13-8)

hydrogen sulfide (7783-06-4)

nitrogen (7727-37-9)

sulfur (7704-34-9)

carbon (7782-42-5)

Thiophosgene (463-71-8)

guanidine thiocyanate

thiourea (62-56-6)

Guanylthiourea,  
Urea, 1-amidino-2-thio- (2114-02-5)

N-cyanoguanidine (461-58-5)

2,4-dithiobiuret,  
dithiobiuret (541-53-7)

4,6-diamino-2-thio-1,3,5-thiadiazine