



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.

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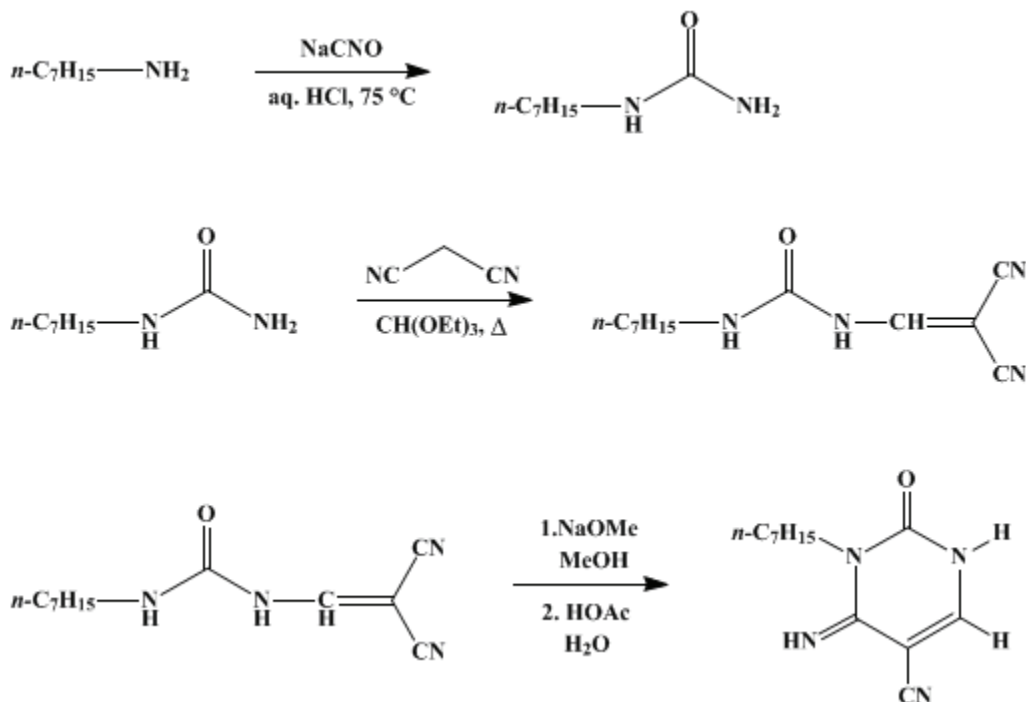
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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3-*n*-HEPTYL-5-CYANOCYTOSINE

[2(1H)-Pyrimidinone, 5-cyano-3-heptyl-4(3)-imino-]



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1. Procedure

A. *N-n-Heptylurea*. To a mixture of 24.1 g. (0.21 mole) of *n*-heptylamine (Note 1), 35 g. of cracked ice, and 150 ml. of ice-cold water is added 38 ml. of 5*N* hydrochloric acid (Note 2) with stirring. The mixture is heated on the steam bath at 70–80°, and 14.3 g. (0.22 mole) of sodium cyanate is added portion-wise. After 2–4 hours of continued heating, two layers separate. The product crystallizes on standing overnight at room temperature. It is collected on a Büchner funnel, washed with 100 ml. of cold water, and drained as dry as practical by suction. This solid is dissolved in 125 ml. of boiling ethyl acetate, and the resulting solution is cooled to room temperature. The white crystalline *N-n*-heptylurea is filtered and dried on a porcelain plate at room temperature. A yield of 28.5–29.5 g. (86–88%) of product melting at 110–111° is obtained (Note 3).

B. *3-n-Heptylureidomethylenemalononitrile*. In a 250-ml. round-bottomed flask fitted with a heating mantle and a reflux condenser are placed 28.5 g. (0.18 mole) of *N-n*-heptylurea, 11.9 g. (0.18 mole) of malononitrile (Note 4), and 26.7 g. (0.18 mole) of triethyl orthoformate (Note 4). The mixture is heated under reflux for 2 hours and then cooled in ice. The solid product is collected by suction filtration on a Büchner funnel. The filtrate is concentrated on the steam bath to incipient crystallization, cooled, and filtered. The two lots of tan solid, 41–42 g., thus obtained are dissolved in 75 ml. of 75% ethyl alcohol in a 250-ml. beaker, 2 g. of decolorizing carbon is added, and the mixture is boiled for 2–3 minutes with constant stirring (necessary to avoid vigorous bumping). The hot solution is filtered by gravity into a 250-ml. Erlenmeyer flask through fluted filter paper. The flask is stoppered and cooled in the refrigerator for 4 hours. The solid product is collected by suction filtration on a Büchner funnel and washed four times with 10-ml. portions of distilled water. The white crystalline *3-n*-heptylureidomethylenemalononitrile is dried at 50° in a vacuum oven. It melts at 130–132° and amounts to 33.8–34.8 g. (80–83%) (Note 5).

C. *3-n-Heptyl-5-cyanocytosine*. In a 250-ml. Erlenmeyer flask are placed 33.8 g. (0.145 mole) of *3-n-heptylureidomethylenemalononitrile* and 70 ml. of *methanol*; then 8.5 g. (0.16 mole) of *sodium methoxide* (Note 6) is added carefully in small portions (Note 7). The resulting solution is allowed to stand at room temperature for 3 days in the stoppered flask. The contents of the flask are dissolved in 300 ml. of cold water in an 800-ml. beaker, and the solution is stirred as 11 ml. of glacial *acetic acid* is added. The precipitated solid is collected by suction filtration on a Büchner funnel and washed with three 40-ml. portions of distilled water. The undried product is dissolved in 600 ml. of hot *ethyl alcohol*; then the solution is filtered into a 1-l. flask by gravity through a fluted filter paper, concentrated on the steam bath to 200 ml., and cooled in the refrigerator for 4 hours. The *3-n-heptyl-5-cyanocytosine* crystallizes in white needles, melts at 192–197° (Note 8), and amounts to 29.7–31.1 g. (88–92%) (Note 9).

Recrystallization of 20 g. of this product from 230 ml. of hot *ethyl alcohol* affords 17.8 g. of fine colorless needles, m.p. 199.5–202.5°.

2. Notes

1. *n-Heptylamine* is available from Sapon Laboratories, P. O. Box 599, Lynbrook, New York, and from Distillation Products Industries, Rochester 3, New York.
2. If excess acid is present, considerable foaming may occur on addition of *sodium cyanate*.
3. The melting point for *N-n-heptylurea* given in the literature² is 110–111°.
4. Commercially available reagents were employed.
5. The melting point for *n-heptylureidomethylenemalononitrile* is reported³ to be 130–132°. An additional 1–1.5 g. may be obtained by evaporating the filtrate to a volume of 100 ml.
6. *Sodium methoxide* is available from Mathieson Chemical Corporation, Niagara Falls, New York. Alternatively, a solution prepared by dissolving 3.6 g. of *sodium* in 70 ml. of *methanol* may be used.
7. Upon addition of *sodium methoxide* to the *methanol* solution considerable heat is evolved.
8. The melting point of *3-n-heptyl-5-cyanocytosine* is given in the literature⁴ as 200°.
9. The submitters obtained comparable yields in all steps using 144.2 g. (1.25 moles) of *heptylamine* and correspondingly larger amounts of all reagents.

3. Discussion

N-n-Heptylurea has been prepared by the action of *nitrourea* on *n-heptylamine*.⁵

3-n-Heptyl-5-cyanocytosine has been prepared by a variation of this procedure by Whitehead.⁴

The procedure described here has given equally good yields of other 3-alkyl-5-cyanocytosines and 3-cycloalkyl-5-cyanocytosines; however, it does not yield 3-aryl-5-cyanocytosines from arylureas.

References and Notes

1. Eli Lilly & Company, Indianapolis, Indiana.
2. Forselles and Wahlforss, *Ber.*, **25** Referate, 636 (1892).
3. Whitehead, *J. Am. Chem. Soc.*, **75**, 674 (1953).
4. Whitehead and Traverso, *J. Am. Chem. Soc.*, **77**, 5871 (1955).
5. Tseng and Ho, *J. Chinese Chem. Soc.*, **4**, 335 (1936) [*C. A.*, **31**, 1011 (1937)].

Appendix

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

ethyl alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

sodium methoxide (124-41-4)

decolorizing carbon (7782-42-5)

sodium (13966-32-0)

triethyl orthoformate (122-51-0)

Nitrourea (556-89-8)

Malononitrile (109-77-3)

sodium cyanate (917-61-3)

2(1H)-Pyrimidinone, 5-cyano-3-heptyl-4(3)-imino-

heptylamine,
n-heptylamine (111-68-2)

3-n-HEPTYL-5-CYANOCYTOSINE (53608-90-5)

N-n-heptylurea (42955-46-4)

3-n-heptylureidomethylenemalononitrile

n-heptylureidomethylenemalononitrile