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.

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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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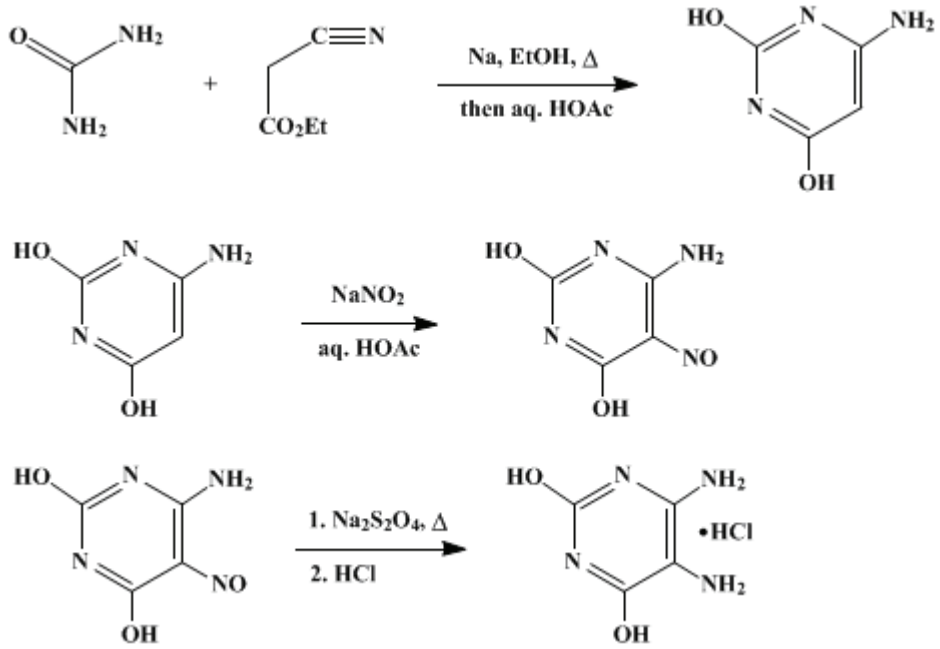
DIAMINOURACIL HYDROCHLORIDE

[Uracil, 5,6-diamino-, hydrochloride]



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1. Procedure

In a 3-l., three-necked flask (Note 1) equipped with a reflux condenser and an efficient stirrer is placed 1 l. of absolute (99.8%) ethanol. To this is added 39.4 g. (1.72 g. atom) of sodium, and, after solution is complete (Note 2), 91.5 ml. (97.2 g., 0.86 mole) of ethyl cyanoacetate (Note 3) and 51.5 g. (0.86 mole) of urea are added. The mixture is heated under reflux on a steam bath with vigorous stirring for 4 hours. After about 2 hours, the reaction mixture becomes practically solid, and the stirrer may have to be stopped. At the end of the reaction time, 1 l. of hot (80°) water is added to the reaction mixture, and stirring is resumed. After complete solution has taken place, the stirred mixture is heated at 80° for 15 minutes and is then neutralized to litmus with glacial acetic acid (Note 4). Additional glacial acetic acid (75 ml.) is added, followed by cautious addition of a solution of 64.8 g. (0.94 mole) of sodium nitrite dissolved in 70 ml. of water. The rose-red nitroso compound separates almost immediately as an expanded precipitate which almost stops the stirrer. After a few minutes the nitroso compound is removed by filtration and washed twice with a small amount of ice water. The moist material is transferred back to the 3-l. flask, and 430 ml. of warm water (50°) is added.

This procedure should be conducted in a good hood. The slurry is stirred while being heated on a steam bath, and solid sodium hydrosulfite is added until the red color of the nitroso compound is completely bleached (Note 5). Then an additional 30 g. of sodium hydrosulfite is added; the light tan suspension is stirred with heating for 15 minutes more and is allowed to cool. The dense diaminouracil bisulfite is filtered from the cooled solution, washed well with water, and partially dried.

The crude product is readily purified by conversion to its hydrochloride salt. The bisulfite salt is transferred to a wide-mouthed 1-l. flask, and concentrated hydrochloric acid is added until the consistency of the resulting mixture is such as to permit mechanical stirring (100 to 200 ml. of acid). The slurry is heated on a steam bath with stirring for 1 hour (*Hood!*). The tan diaminouracil hydrochloride is filtered on a sintered glass funnel, washed well with acetone, and vacuum-dried over

phosphorus pentoxide. The yield of diaminouracil hydrochloride is 104–124 g. (68–81%) (Note 6) and (Note 7).

2. Notes

1. Since the reaction mixture becomes almost solid after nitrosation, one of the necks of the flask should be of large diameter to facilitate removal of the product.
2. The usual precautions must be observed with respect to the hydrogen evolved. The reflux condenser is capped with a drying tube after hydrogen evolution ceases. The sodium ethoxide must be used immediately after its preparation, for it discolors rapidly and in this state leads to an impure product.
3. Eastman Kodak white label grade, Dow Chemical, and Kay-Fries ethyl cyanoacetate were all used with equal success.
4. Caution must be exercised in the addition of the glacial acetic acid in order to avoid frothing of the hot solution. The frothing becomes most vigorous as the 6-aminouracil begins to precipitate from the solution. The heating and subsequent neutralization assure cyclization of the initially formed cyanoacetylurea to 6-aminouracil. The nitrosation is carried out on the two-phase (solid-liquid) system.
5. The amount of sodium hydrosulfite used depends on its age and quality. The submitters never had to use more than 250 g. per run.
6. The preparation may be interrupted after the nitroso compound has been separated or after the crude bisulfite salt has been isolated. This preparation has been satisfactorily carried out on a scale seven times that given.
7. If placed in a preheated melting-point block, the product melts with decomposition in the range 300–305°. Diaminouracil hydrochloride in 0.1*N* hydrochloric acid has a well-defined absorption peak at 260 mμ, log ε = 4.24. Satisfactory analyses for nitrogen and chlorine are difficult to obtain with this type of compound although good results are obtained for carbon and hydrogen.

3. Discussion

The procedure for the formation of diaminouracil bisulfite is slightly modified from that of Cain, Mallette, and Taylor,[2] which in turn is derived from preparations of Bogert and Davidson,[3] and Traube.[4] The sulfate salt may be formed in lower yield than the hydrochloride described here by dissolving the bisulfite salt in aqueous base and precipitating with sulfuric acid.[3,4] The hydrochloride is appreciably soluble in water, while the sulfate salt is only slightly soluble.

Other methods of reducing the nitroso compound include the use of ammonium sulfide[4] and hydrogenation utilizing Adams catalyst.[5]

Bredereck, Hennig, and Pfleiderer[6] describe a method for the formation of diaminouracil from uric acid which involves acetylation and subsequent hydrolysis of the acetyl derivative. This preparation was attempted on a large scale by the submitters without success (even when the acetylation step was carried out twice on the same material).

References and Notes

1. University of Illinois, Urbana, Illinois.
2. Cain, Mallette, and Taylor, *J. Am. Chem. Soc.*, **68**, 1996 (1946).
3. Bogert and Davidson, *J. Am. Chem. Soc.*, **55**, 1668 (1933).
4. Traube, *Ber.*, **33**, 1371 (1900).
5. E. C. Taylor, Jr., unpublished results.
6. Bredereck, Hennig, and Pfleiderer, *Ber.*, **86**, 321 (1953).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

sodium hydrosulfite (7775-14-6)

acetone (67-64-1)

carbon (7782-42-5)

chlorine (7782-50-5)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

urea (57-13-6)

Ethyl cyanoacetate (105-56-6)

ammonium sulfide

uric acid

Diaminouracil hydrochloride (53608-89-2)

Uracil, 5,6-diamino-, hydrochloride

diaminouracil bisulfite

6-aminouracil

cyanoacetylurea (1448-98-2)

diaminouracil

phosphorus pentoxide (1314-56-3)