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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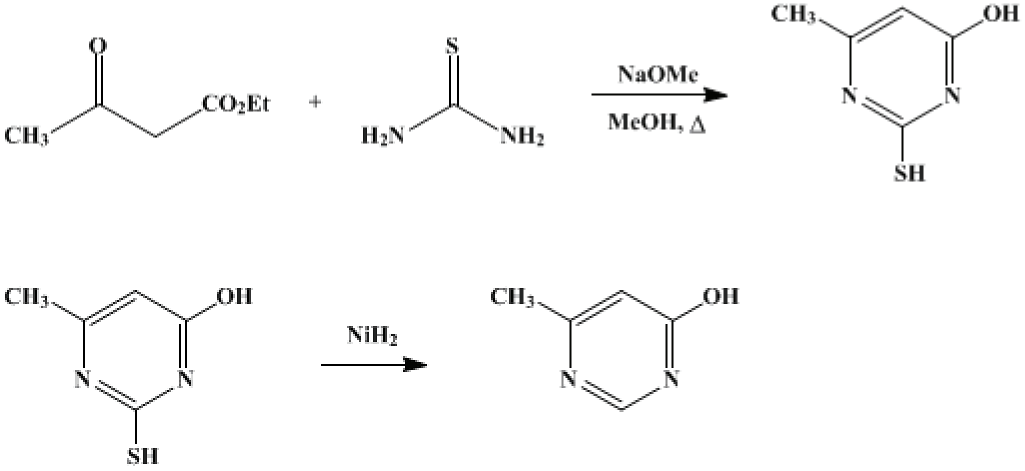
4-METHYL-6-HYDROXYPYRIMIDINE

[4-Pyrimidinol, 6-methyl-]



Submitted by H. M. Foster and H. R. Snyder[1].
Checked by R. T. Arnold and P. E. Throckmorton.

1. Procedure

A. *2-Thio-6-methyluracil*. In a 2-l. flask are placed 76 g. (1 mole) of thiourea, 130 g. (1 mole) of commercial ethyl acetoacetate, 120 g. of commercial sodium methoxide, and 900 ml. of methanol. The reaction mixture is heated gently on the steam bath and is permitted to evaporate to dryness in a hood over a period of about 8 hours. The residue is dissolved in 1 l. of hot water; the solution is treated with a few grams of activated carbon and is filtered. The hot filtrate is carefully treated (Note 1) with 120 ml. of glacial acetic acid. The thiouracil precipitates rapidly and is collected on a 4-in. Büchner funnel. The still wet solid filter cake is suspended in a boiling solution of 1 l. of water and 20 ml. of glacial acetic acid. The slurry is stirred and mixed thoroughly to break up lumps and is then refrigerated.

The product is collected on a 4-in. Büchner funnel and is washed with about 200 ml. of cold water in four portions. The solid is permitted to drain (with suction) for several hours and is then transferred to an oven at 70° for more complete drying. The yield of oven-dried 2-thio-6-methyluracil is 98–119 g. (69–84%). This material is sufficiently pure for the desulfurization reaction (Note 2).

B. *4-Methyl-6-hydroxypyrimidine*. To a hot solution of 10 g. (0.07 mole) of 2-thio-6-methyluracil in 200 ml. of distilled water and 20 ml. of concentrated aqueous ammonia in a 500-ml. round-bottomed flask is added 45 g. (wet paste) of Raney nickel catalyst (Note 3). About 30 ml. of distilled water is used to wash all the nickel catalyst into the reaction flask. The mixture is heated under reflux in a hood for about 1.5 hours. The catalyst is permitted to settle, and the clear solution is decanted and filtered by gravity. The catalyst is washed with two 75-ml. portions of hot water and is discarded (Note 4). The combined filtrate and washings (Note 5) are evaporated to dryness on a steam bath. The residue is placed in an oven at 70° to complete the drying process (Note 6). The yield of crude pyrimidine, m.p. 136–142°, is 7.0–7.2 g. (90–93%).

The crude product is best purified by sublimation under reduced pressure (100–110°/1 mm.) (recovery 90–95%). Purification can also be effected by recrystallization from acetone (recovery 80–90%), ethyl acetate (recovery 70–80%), or ethanol (recovery 60–70%). The purified 4-methyl-6-hydroxypyrimidine melts at 148–149°.

2. Notes

1. The hot solution tends to foam and froth badly when the acetic acid is added, and if care is not taken mechanical loss of product may result.
2. 2-Thio-6-methyluracil does not possess a clearly defined melting point but shows marked decomposition above 280°.[2]
3. The activity of the Raney nickel catalyst greatly affects the yield of the desulfurized pyrimidine. A catalyst described by Brown[3] gave very satisfactory results. A Raney nickel C described by Hurd and Rudner[4] is perhaps a more reactive catalyst; however, the yield of desulfurized pyrimidine was not sufficiently better to warrant its use.
4. Care must be taken not to allow the nickel to dry too completely lest it ignite.
5. The filtrate and washings should be clear and colorless. If the solution is blue or green (indicative of the presence of dissolved nickel) the solution should be treated with hydrogen sulfide, or better with dimethylglyoxime and ammonia, to precipitate the nickel.
6. The 4-methyl-6-hydroxypyrimidine is surprisingly volatile, and loss of product may occur if the material is heated on the steam bath for an appreciable period of time.

3. Discussion

4-Methyl-6-hydroxypyrimidine can be prepared by heating 2,6-dichloro-4-methylpyrimidine with red phosphorus and hydriodic acid[5] and by treating 2-thio-6-methyluracil with hydrogen peroxide.[6] The present synthesis is modeled after the work of Brown,[3] who has described the desulfurization of several thiopyrimidines.

The procedure for the synthesis of 2-thio-6-methyluracil is a modification of the method described by Wheeler and Merriam[7] for the preparation of 2-methylthio-6-methyluracil.

References and Notes

1. University of Illinois, Urbana, Illinois.
2. List, *Ann.*, **236**, 6 (1886).
3. Brown, *J. Soc. Chem. Ind. (London)*, **69**, 355 (1950).
4. Hurd and Rudner, *J. Am. Chem. Soc.*, **73**, 5158 (1951).
5. Gabriel and Colman, *Ber.*, **32**, 2931 (1899).
6. Williams, Ruehle, and Finkelstein, *J. Am. Chem. Soc.*, **59**, 526 (1937).
7. Wheeler and Merriam, *Am. Chem. J.*, **29**, 486 (1903).

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

red phosphorus

2-Thio-6-methyluracil

ethanol (64-17-5)

acetic acid (64-19-7)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

hydrogen sulfide (7783-06-4)

nickel,
Raney nickel (7440-02-0)

acetone (67-64-1)

sodium methoxide (124-41-4)

carbon (7782-42-5)

hydrogen peroxide (7722-84-1)

hydriodic acid (10034-85-2)

Ethyl acetoacetate (141-97-9)

thiourea (62-56-6)

DIMETHYLGLYOXIME (95-45-4)

4-Methyl-6-hydroxypyrimidine,
4-Pyrimidinol, 6-methyl- (3524-87-6)

2,6-dichloro-4-methylpyrimidine (5424-21-5)

2-methylthio-6-methyluracil