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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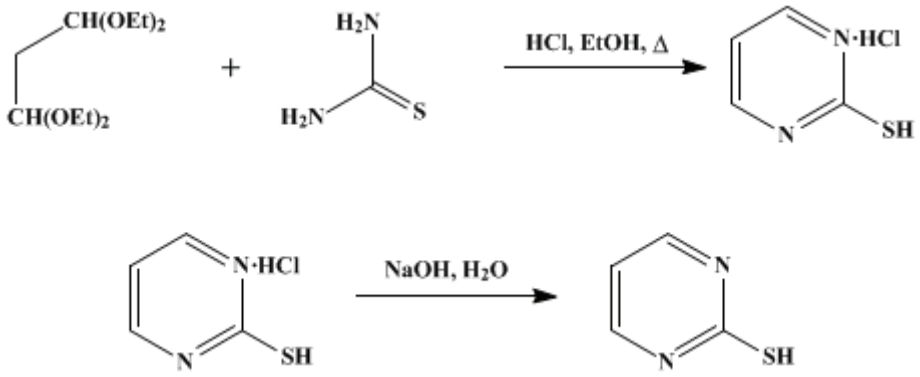
2-MERCAPTOPYRIMIDINE

[2-Pyrimidinethiol]



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1. Procedure

A. *2-Mercaptopyrimidine hydrochloride*. Thiourea (61 g., 0.80 mole) and 600 ml. of ethyl alcohol (Note 1) are placed in a 2-l. three-necked flask equipped with a sealed mechanical stirrer, a reflux condenser, and a stopper. The stirrer is started, and 200 ml. of concentrated hydrochloric acid is added in one portion through the open neck. After several minutes, when the warm mixture has become homogeneous, 176 g. (0.80 mole) of commercial-grade 1,1,3,3-tetraethyoxypropane (Note 2) is added rapidly, the open neck is stoppered, and the yellow solution is boiled for about 1 hour with continuous stirring. During this period the reaction mixture darkens in color and the product separates (Note 3).

The reaction mixture is chilled to about 10° by immersing it in an ice bath for about 30 minutes, and the yellow crystalline precipitate is collected on a Büchner funnel. It is then washed with 100 ml. of cold alcohol and air-dried at room temperature. The yield of 2-mercaptopyrimidine hydrochloride is 71–76 g. (60–64%). The product is pure enough for most purposes (Note 4), but it may be recrystallized by dissolving it in 12*N* hydrochloric acid (10 ml. per gram of solid) at about 75°, filtering the hot solution through glass wool or a sintered glass filter, chilling the filtrate in ice, and collecting the golden-yellow crystals on a sintered glass filter. Recovery is 60–65% (Note 5).

B. *2-Mercaptopyrimidine*. Crude 2-mercaptopyrimidine hydrochloride (25 g., 0.17 mole) is suspended in 50 ml. of water in a beaker and stirred rapidly while a 20% aqueous solution of sodium hydroxide (about 27 ml.) is added until the pH of the mixture is 7–8 (Note 6). The precipitated solid is collected on a Büchner funnel and washed on the funnel with 50 ml. of cold water. The damp product is dissolved by heating it in a mixture of 300 ml. of water and 300 ml. of alcohol on the steam bath, and the hot solution is filtered through a fluted paper and allowed to cool slowly to room temperature. The crystals of 2-mercaptopyrimidine are collected, washed with about 50 ml. of the aqueous alcohol, and dried either at room temperature overnight or for several hours in an oven at 110°. The yield is 15–16 g. (80–85%) of yellow needles, m.p. 218–219° (sealed tube).

2. Notes

1. Either commercial absolute alcohol or the 95% grade may be used.
2. 1,1,3,3-Tetraethoxypropane is available from Kay-Fries Chemicals, Inc., New York 16, New York, or from Distillation Products Industries, Rochester 3, New York, and may be used without further purification.
3. Longer boiling does not affect the yield but causes the product to be somewhat dark-colored. A

shorter heating period or lack of mechanical stirring decreases the yield.
4. Electrometric titration shows the purity to be at least 95%. The product does not melt below 300°.
5. If concentrated sulfuric acid is substituted for the hydrochloric acid in the procedure, 2-mercaptopyrimidine bisulfate is obtained in about 50% yield. Recrystallization from aqueous acetic acid provides the bisulfate as yellow needles, m.p. 186–186.5°. (*Anal.* Calcd. for $C_4H_6N_2O_4S_2$: C, 22.9; H, 2.9. Found: C, 23.1; H, 2.9.)
6. pH indicator paper may be used, or the solution may be made weakly basic to litmus. Excess base dissolves the product and should be avoided.

3. Discussion

The synthesis of 2-substituted pyrimidines from 1,3-dicarbonyl compounds and urea derivatives was first described by Evans[2] and was later improved by Hunt, McOmie, and Sayer[3] for the preparation of 2-mercapto-4,6-dimethylpyrimidine. Burness[4] employed 3-ketobutyraldehyde acetal in this procedure to give 2-mercapto-4-methylpyrimidine. 2-Mercaptopyrimidine has been prepared from 1,1,3,3-tetraethoxypropane and thiourea by variations of this basic method[3,5,6] as well as by the reaction of 2-chloropyrimidine with thiourea[7] or sodium hydrosulfide.[8]

4. Merits of the Preparation

This preparation describes a convenient and general method of synthesis of substituted pyrimidines from compounds containing a β-dicarbonyl group, either intact or as the corresponding ketal. The usefulness of the 2-mercaptopyrimidines is enhanced by the ease of removal of the mercapto group by desulfurization[9] or oxidation[10] and its replacement by other functional groups.[10]

References and Notes

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

1,1,3,3-tetraethoxypropane

2-mercaptopyrimidines

ethyl alcohol,
alcohol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

sodium hydroxide (1310-73-2)

urea (57-13-6)

thiourea (62-56-6)

sodium hydrosulfide

2-Chloropyrimidine (1722-12-9)

2-Mercaptopyrimidine,
2-Pyrimidinethiol (1450-85-7)

2-mercaptopyrimidine hydrochloride

1,1,3,3-Tetraethoxypropane (122-31-6)

2-mercaptopyrimidine bisulfate

2-mercapto-4,6-dimethylpyrimidine (22325-27-5)

3-ketobutyraldehyde acetal

2-mercapto-4-methylpyrimidine