Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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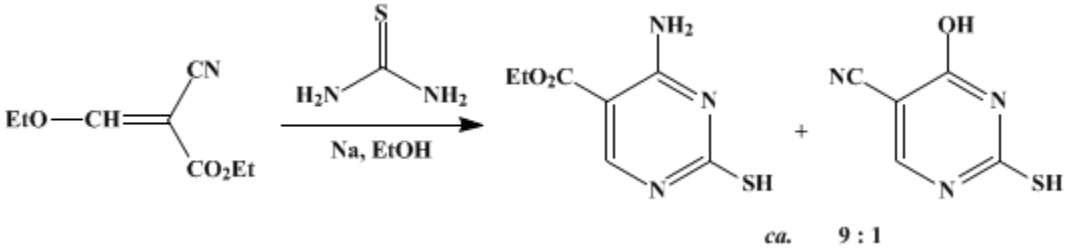
2-MERCAPTO-4-AMINO-5-CARBETHOXYPYRIMIDINE AND 2-MERCAPTO-4-HYDROXY-5-CYANOPYRIMIDINE

[5-Pyrimidinecarboxylic acid, 4-amino-2-mercapto-, ethyl ester]

[5-Pyrimidinecarbonitrile, 4-hydroxy-2-mercapto-]



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Checked by B. C. McKusick and Stephen Proskow.

1. Procedure

A. *2-Mercapto-4-amino-5-carbethoxypyrimidine.* A 5-l. three-necked, round-bottomed flask mounted in a heating mantle is fitted with a 250-ml. dropping funnel, an efficient, sealed, mechanical stirrer, and a reflux condenser connected to a calcium chloride drying tube. Absolute ethanol (625 ml.) is placed in the flask, the stirrer is started, and 23 g. (1 g. atom) of freshly cut sodium is added in portions. After the sodium has dissolved, 76.1 g. (1 mole) of thiourea is added to the warm, stirred solution in one portion. When the bulk of the thiourea has dissolved, 169 g. (1 mole) of liquefied ethyl ethoxymethylenecyanoacetate is added from the dropping funnel to the stirred mixture over a period of 2 hours (Note 1). This rate of addition keeps the reaction mixture warm. The solution is then stirred and gently refluxed for 6 hours. The sodium salt of the carbethoxypyrimidine may precipitate during the course of the reaction.

The reaction mixture is cooled to 50–60°, and 1.75 l. of water is added, followed by 65 ml. of acetic acid to make the mixture distinctly acidic. The resulting suspension is stirred and boiled for 5 minutes in order to effect complete decomposition of the sodium salt.

The mixture is cooled to 25°, and the crystalline 2-mercapto-4-amino-5-carbethoxypyrimidine is collected on a 10-cm. Büchner funnel and washed successively with five 50-ml. portions of water, 50 ml. of acetone, and 50 ml. of ether (Note 2). The carbethoxypyrimidine weighs 152–159 g. (76–80%) and melts with decomposition at 259–260° (Note 3) after being dried for 5 hours at 110° and atmospheric pressure. It is in the form of a cream-colored powder that is sufficiently pure for synthetic purposes. Pure carbethoxypyrimidine can be obtained by recrystallizing the crude product once from 50% acetic acid, using 170 ml. per gram of pyrimidine.

B. *2-Mercapto-4-hydroxy-5-cyanopyrimidine.* The aqueous filtrate from which the crude 2-mercapto-4-amino-5-carbethoxypyrimidine separated is cooled overnight at 0°, and the cyanopyrimidine that precipitates is collected on a suction filter. The crude product is recrystallized from about 200 ml. of 10% acetic acid with 1 g. of decolorizing charcoal added. Two additional recrystallizations done similarly give the pure cyanopyrimidine as faintly yellow crystals, m.p. 265–272° (dec.) (Note 3). The yield is 10–18 g. (7–12%).

2. Notes

1. Ethyl ethoxymethylenecyanoacetate can be prepared in the laboratory from ethyl cyanoacetate and ethyl orthoformate according to the directions of de Bellemont.[2] The submitters and checkers used a

commercial product, m.p. 45–50°, obtained from Kay-Fries, Inc., New York. The liquefied product is weighed and poured into the dropping funnel. An infrared heating lamp is used to keep it liquid during the addition.
2. For complete removal of a yellow impurity, the product should be stirred well with each portion of water before filtration. If the solid is not washed with organic solvents, drying of the caked product will be slow.
3. The decomposition point is greatly dependent on the rate of heating. The checkers found that the carbethoxypyrimidine heated on a Fisher-Johns melting-point block at a rate of 4° per minute decomposed at 280–285°. Under the same conditions, the cyanopyrimidine decomposed at 285–289°. Both products started to darken around 260°. In the infrared, the carbethoxypyrimidine has a strong band at 5.88 μ and no absorption in the 4.4 μ range, whereas the cyanopyrimidine has a strong band at 4.48 μ and no absorption at 5.88 μ.

3. Discussion

The described procedure is based on the methods of Johnson and Ambler[3] and Anderson et al.,[4] as modified by Ulbricht and Price.[5] This procedure is illustrative of a general method of preparing pyrimidines, wherein one condenses thiourea, guanidine, or an amidine with alkoxymethylenemalonic esters, alkoxymethylenecyanoacetic esters, or alkoxymethylenemalononitrile. Kenner and Todd recently reviewed the synthesis of pyrimidines.[6]

2-Mercapto-4-amino-5-carbethoxypyrimidine has been converted to 2-methylmercapto-4-amino-5-hydroxymethylpyrimidine,[5] an antimetabolite possessing antitumor activity,[7] by methylation of the mercapto group followed by reduction of the ester group to a hydroxymethyl group with lithium aluminum hydride.[5]

References and Notes

1. University of Pennsylvania, Philadelphia 4, Pennsylvania; supported in part by U.S.P.H.S. Grant No. CY–2189.
2. de Bellemont, *Bull. soc. chim. France*, [3] **25**, 18 (1901).
3. Johnson and Ambler, *J. Am. Chem. Soc.*, **33**, 978 (1911).
4. Anderson, Halverstadt, Miller, and Roblin, *J. Am. Chem. Soc.*, **67**, 2197 (1945).
5. Ulbricht and Price, *J. Org. Chem.*, **21**, 567 (1956).
6. Kenner and Todd, "Pyrimidine and Its Derivatives" in Elderfield, *Heterocyclic Compounds*, Vol. 6, pp. 234–323, John Wiley & Sons, New York, 1957.
7. Okuda and Price, *J. Org. Chem.*, **23**, 1738 (1958).

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

sodium salt of the carbethoxypyrimidine

decolorizing charcoal

amidine

ethanol (64-17-5)

acetic acid (64-19-7)

ether (60-29-7)

acetone (67-64-1)

sodium (13966-32-0)

Ethyl cyanoacetate (105-56-6)

Ethyl orthoformate

thiourea (62-56-6)

pyrimidine (289-95-2)

guanidine (113-00-8)

lithium aluminum hydride (16853-85-3)

2-Mercapto-4-amino-5-carbethoxypyrimidine,
5-Pyrimidinecarboxylic acid, 4-amino-2-mercapto-, ethyl ester (774-07-2)

2-Mercapto-4-hydroxy-5-cyanopyrimidine,
5-Pyrimidinecarbonitrile, 4-hydroxy-2-mercapto- (23945-49-5)

ethyl ethoxymethylenecyanoacetate

carbethoxypyrimidine (42839-08-7)

cyanopyrimidine (14080-23-0)

2-methylmercapto-4-amino-5-hydroxymethylpyrimidine