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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 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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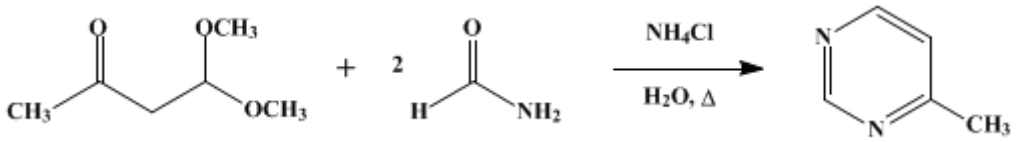
4-METHYLPYRIMIDINE

[Pyrimidine, 4-methyl-]



Submitted by H. Bredereck[1]
Checked by Max Tishler, G. A. Stein, W. F. Jankowski, and J. ten Broeke.

1. Procedure

A 2-l. three-necked flask is equipped with a stirrer, a thermometer, an addition funnel, and a wide-bore reflux condenser (Note 1). A second condenser set downward for distillation is connected to the top of the reflux condenser by means of a head provided with a thermometer well. The thermometer well should be positioned in the connecting head in such a manner that the thermometer gives the temperature at the head of the reflux condenser. *Caution! The flask should be in a hood so that the carbon monoxide evolved cannot be a hazard.*

The three-necked flask is charged with 750 ml. of formamide, 25 ml. of water, and 50 g. of ammonium chloride (Note 2). The mixture is heated to 180–190° in an oil bath, and 400 g. (3.02 moles) of 4,4-dimethoxy-2-butanone (Note 3) is added dropwise with stirring over the course of 6 hours (Note 4). The flow of cooling water in the reflux condenser should be adjusted to a rate such that the methanol and methyl formate formed during the reaction distil out (Note 5). After all the acetal has been added, heating is continued for 1 hour (Note 6). The mixture is allowed to cool and is poured into 1 l. of 1*N* sodium hydroxide. The resultant solution is extracted with chloroform in a liquid-liquid extractor for 24 hours. The chloroform is separated, dried over sodium sulfate, and removed by distillation through a short column on a steam bath.

The residue is distilled under reduced pressure, and all the distillate boiling at 60–80°/15 mm. is collected (Note 7) and (Note 8). Pure 4-methylpyrimidine is obtained by redistillation through a short column at atmospheric pressure; b.p. 140–142°; n_D^{25} 1.4936; weight 153–180 g. (54–63%).

2. Notes

1. A wide-bore condenser is employed to prevent clogging of the tube by ammonium salts that may sublime from the reaction mixture (Note 5). A Liebig condenser is most suitable because it can be cleaned from the top with a rod or wire during the reaction.
2. An acidic salt must be present so that the acetal bonds will be hydrolyzed. Other salts, such as ammonium formate, may be substituted for ammonium chloride.
3. 4,4-Dimethoxy-2-butanone from Chemische Werke Huls, Huls, Germany, was used by the submitter. The checkers used 4,4-dimethoxy-2-butanone (practical grade) from Eastman Organic Chemicals Co., Rochester, New York; it was 95% pure by vapor-phase chromatography.
4. The checkers found that, during the course of the addition, the internal temperature fell from 190° to 140°.
5. The checkers found that, if the temperature at the head of the reflux condenser is kept at 50–55°, no ammonium salts collect in the condenser and, therefore, there is no problem of clogging.
6. The checkers found that the temperature of the reaction mixture remains at 140° during the additional hour of heating.
7. It is advisable to carry out a vacuum distillation prior to the final distillation because the tarry residues obtained by distillation at atmospheric pressure retain a considerable amount of product.
8. The checkers collected their product at 50–70°/30 mm.

3. Discussion

4-Methylpyrimidine has been obtained by the present method[2] and by a three-step method that begins with the condensation of acetoacetic ester with urea to give 2,6-dihydroxy-4-methylpyrimidine; the latter is treated with phosphorus oxychloride to give 2,6-dichloro-4-methylpyrimidine, which is reduced by zinc dust and water[3] or by catalytic hydrogenolysis.[4]

4. Merits of the Preparation

The present one-step procedure for making 4-methylpyrimidine is simpler and easier than the three-step method used in the past. The present procedure and modifications of it have been used to make a variety of 4- and 4,6-substituted pyrimidines.[2,5]

References and Notes

1. Institue für Organische Chemie, Technische Hochschule, Stuttgart, Germany.
2. H. Bredereck, R. Gompper, and G. Morlock, *Ber.*, **90**, 942 (1957).
3. S. Gabriel and J. Colman, *Ber.*, **32**, 1534 (1899).
4. W. Pfleiderer and H. Mosthaf, *Ber.*, **90**, 733 (1957).
5. H. Bredereck, R. Gompper, and G. Morlock, *Ber.*, **91**, 2830 (1958); H. Bredereck, R. Gompper, and H. Herlinger, *Ber.*, **91**, 2832 (1958).

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

methanol (67-56-1)

ammonium chloride (12125-02-9)

formamide (75-12-7)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

Phosphorus Oxychloride (21295-50-1)

zinc (7440-66-6)

urea (57-13-6)

methyl formate (107-31-3)

ammonium formate (540-69-2)

4,4-dimethoxy-2-butanone (5436-21-5)

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

4-Methylpyrimidine,
Pyrimidine, 4-methyl- (3438-46-8)

2,6-dihydroxy-4-methylpyrimidine