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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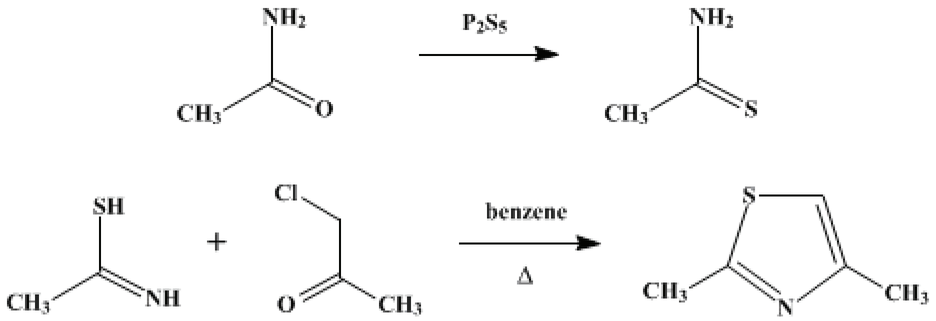
2,4-DIMETHYLTHIAZOLE

[Thiazole, 2,4-dimethyl-]



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1. Procedure

In a 2-l. round-bottomed flask provided with a reflux condenser is placed 200 ml. of dry benzene (Note 1). A mixture of 300 g. (5.08 moles) of finely divided acetamide and 200 g. (0.9 mole) of powdered phosphorus pentasulfide is prepared quickly and transferred immediately to the flask. To this is added 20 ml. of a mixture of 400 ml. (4.97 moles) of chloroacetone (Note 2) and 150 ml. of dry benzene. The exothermic reaction is started by careful heating in a water bath. The water bath is removed, and the remainder of the chloroacetonebenzene mixture is introduced gradually through the reflux condenser (Note 3) and (Note 4). When all the chloroacetone has been added and reaction is no longer apparent, the mixture is refluxed on the water bath for 30 minutes.

About 750 ml. of water is added to the mixture with shaking. After 30 minutes the mixture is poured into a separatory funnel, and the reddish upper layer containing the benzene with some impurities is discarded. The lower layer is made alkaline (Note 5) by the addition of 5 *N* sodium hydroxide or potassium hydroxide, and the crude thiazole, which separates as a black upper layer, is removed with ether, and the aqueous lower layer is extracted with five 120-ml. portions of ether. The combined ethereal extracts are dried over anhydrous sodium sulfate and filtered through glass wool. The ether is removed by distillation from a steam bath (Note 6), and the residual oil is fractionated at atmospheric pressure; the fraction boiling at 140–150° is collected and redistilled. The yield of 2,4-dimethylthiazole boiling at 143–145° (Note 7) is 210–230 g. (41–45% based on the phosphorus pentasulfide).

2. Notes

1. Commercial benzene is satisfactory after being dried over calcium chloride and distilled.
2. Commercial chloroacetone is distilled, and the fraction boiling at 116–122° is used.
3. The progress of the reaction is controlled by the portions of chloroacetone added. If too much is added at once the reaction may become too vigorous. Portions of 20 ml. are safe. Toward the end of the reaction, larger portions may be added.
4. As soon as the reaction has begun, the mixture becomes a gray-black oily liquid.
5. The alkalinity of the deeply colored solution can be tested with phenolphthalein paper. The edges of the wetted paper become visibly red. One should be sure to test the aqueous solution and not the separated thiazole floating on top of the liquid.
6. The thiazole is hygroscopic and should be protected from moisture.
7. Reported boiling points are 144–145.5°/719 mm.[1] and 143°.[1] No 2,4-dimethyloxazole (b.p. 108°) was obtained during the distillation.

3. Discussion

2,4-Dimethylthiazole has been prepared from chloroacetone and thioacetamide,[2] but forming the required thioacetamide in the reaction mixture is to be preferred since no additional manipulation is involved. The method here described is substantially that of E. Merck.[1] Other substituted thiazoles can be prepared by practically the same method.[1] 2,4-Dimethylthiazole has been obtained by dry distillation of 2-methylthiazyl-4-acetic acid,[3] and also by heating 2,4-dimethylthiazole-5-carboxylic acid with calcium oxide.[4]

References and Notes

1. E. Merck, Ger. pat. 670,131 [*C. A.*, **33**, 2909 (1939)].
2. Hantzsch, *Ann.*, **250**, 265 (1889).
3. Steude, *Ann.*, **261**, 41 (1891).
4. Rubleff, *Ann.*, **259**, 266 (1890).

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

chloroacetonebenzene

2-methylthiazyl-4-acetic acid

calcium chloride (10043-52-4)

Acetamide (60-35-5)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

calcium oxide

phenolphthalein (77-09-8)

chloroacetone (78-95-5)

phosphorus pentasulfide

thiazole (288-47-1)

2,4-Dimethylthiazole,
Thiazole, 2,4-dimethyl- (541-58-2)

2,4-dimethyloxazole (7208-05-1)

thioacetamide (62-55-5)

2,4-dimethylthiazole-5-carboxylic acid