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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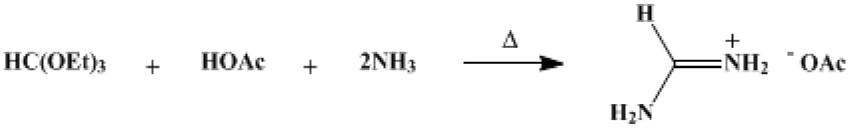
FORMAMIDINE ACETATE



Submitted by Edward C. Taylor, Wendell A. Ehrhart, and M. Kawanisi[1].
Checked by John J. Miller and William D. Emmons.

1. Procedure

In a 500-ml. three-necked flask equipped with a reflux condenser, a gas-inlet tube (Note 1) reaching to the bottom of the flask, a thermometer, and a magnetic stirrer is placed a mixture of 90.0 g. of triethyl orthoformate (Note 2) and 49.2 g. of glacial acetic acid. The flask is immersed in an oil bath maintained at 125–130° (Note 3). When the internal temperature of the mixture reaches 115°, a moderate stream of ammonia is introduced. As the temperature decreases gradually, vigorous refluxing is observed (Note 4). Formamidine acetate starts to crystallize from the boiling mixture after 20–30 minutes. The ammonia flow is continued until no further decrease in temperature is observed (Note 5). The mixture is cooled to room temperature, the precipitate collected by filtration and washed thoroughly with 50 ml. of absolute ethanol. The yield of colorless formamidine acetate is 53.0–55.8 g. (83.8–88.2%), m.p. 162–164° (Note 6). Evaporation of the mother liquor under reduced pressure followed by chilling gives a small additional amount of product (1.0–2.2 g.) (Note 7).

2. Notes

1. An open-end gas-inlet tube should be used rather than a fritted glass inlet because the latter becomes clogged.
2. Commercial triethyl orthoformate, b.p. 50–52° (20 mm.) (Matheson, Coleman and Bell) is used without further purification. It has been reported that it is essential to this procedure that the triethyl orthoformate be slightly wet. Commercial triethyl orthoformate as available in the USA appears to fulfill this requirement, but the anhydrous reagent fails to react. If anhydrous triethyl orthoformate is used, 3 drops of water should be added to ensure a slightly wet reagent (private communication from P. R. H. Speakman).
3. If the temperature is higher than 140°, the product is colored and the yield is lower.
4. This temperature decrease serves as a useful indication of the progress of the reaction.
5. The final temperature of the reaction mixture is usually 72–73°. Total working time is 60–70 minutes.
6. Recrystallization from ethanol does not change the melting point.
7. This material is usually slightly colored and not so pure as the first crop.

3. Discussion

This method is a modification of the procedure described by Taylor and Ehrhart.[2] Formamidine has previously been prepared (as its hydrochloride) from hydrogen cyanide via the formimino ether, which is then treated with ammonia,[3] or by desulfurization of thiourea in the presence of ammonium chloride.[4] The methosulfate salt of formamidine has been reported to be formed by reaction of formamide with dimethyl sulfate.[5]

4. Merits of the Procedure

Because formamidine hydrochloride is extremely deliquescent, considerable care must be exercised in its preparation if satisfactory results are to be achieved. Furthermore, formamidine hydrochloride cannot be used directly in most condensation reactions; it must be treated first with a mole of base to liberate free formamidine. The same restriction applies to the methosulfate salt of formamidine; in addition, complications in synthesis may be anticipated in this latter case because methyl hydrogen sulfate itself is an effective methylating agent.[6]

By contrast, formamidine acetate is not hygroscopic and no particular care need be taken to protect it from atmospheric moisture. Furthermore, formamidine acetate can be used directly without prior treatment with base in syntheses requiring free formamidine.[2,7,8,9,10] Finally, this preparation of formamidine is by far the simplest and most convenient yet reported; it obviates the necessity of using either toxic (hydrogen cyanide) or cumbersome (Raney nickel) reagents, and the method can be adapted to the preparation of N,N'-disubstituted formamidines by substitution of primary amines for ammonia.[11]

References and Notes

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

methosulfate salt of formamidine

ethanol (64-17-5)

acetic acid (64-19-7)

ammonia (7664-41-7)

ammonium chloride (12125-02-9)

formamide (75-12-7)

hydrogen cyanide (74-90-8)

dimethyl sulfate (77-78-1)

Raney nickel (7440-02-0)

methyl hydrogen sulfate (75-93-4)

triethyl orthoformate (122-51-0)

thiourea (62-56-6)

Formamidine acetate (3473-63-0)

Formamidine

formimino ether

formamidine hydrochloride