



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.

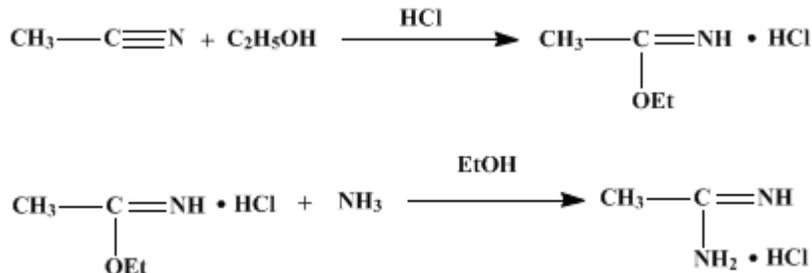
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior 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.

Organic Syntheses, Coll. Vol. 1, p.5 (1941); Vol. 8, p.1 (1928).

ACETAMIDINE HYDROCHLORIDE



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Checked by Frank C. Whitmore

1. Procedure

Dry hydrogen chloride (p. 293) (Note 1) is passed into a solution of 100 g. (2.44 moles) of thoroughly dry acetonitrile (Note 2) in 113 g. (143 cc., 2.5 moles) of absolute ethyl alcohol (Note 1) contained in a 1-l. weighed suction flask (Note 3) surrounded by a freezing mixture of ice and salt, until an increase in weight of 95 g. (2.6 moles) is obtained. This requires about four hours (Note 4) but the time is diminished considerably if proper mechanical stirring is used. The flask is now tightly stoppered, the side arm being attached to a calcium chloride tube, and allowed to stand until the mixture has set to a solid mass of crystals. Usually this requires two or three days.

A solution of dry ammonia gas in absolute ethyl alcohol is prepared and titrated against standard hydrochloric acid, using methyl orange as the indicator. The solution should contain at least 9 per cent of ammonia by weight (Note 5).

The solid crystalline mass of acetimido ethyl ether hydrochloride is broken up and transferred to a dry mortar in which it is ground to a paste with 100 cc. of absolute alcohol and returned to the flask (Note 6). It is then stirred mechanically with an excess of the alcoholic ammonia solution (500 cc. of 9 per cent solution or an equivalent amount of a more concentrated solution). The crystals gradually dissolve and ammonium chloride separates. After stirring for three hours the ammonium chloride is filtered by suction and the filtrate evaporated on the steam bath to a volume of about 200 cc. when a considerable quantity of crystals separates. On cooling, the acetamidine hydrochloride separates in long colorless prisms. These are filtered by suction, washed with 10 cc. of cold alcohol, and dried in a desiccator over sulfuric acid. Concentration of the mother liquor gives a second crop. The product melts at 164–166° and is readily soluble in alcohol and in water. The yield varies from 185 to 210 g. (80–91 per cent of the theoretical amount). The product is somewhat deliquescent and should be kept in a tightly stoppered bottle.

2. Notes

1. Moisture in the reagents affects the yield seriously because of the ease with which the intermediate imido ether is hydrolyzed. The hydrogen chloride must be thoroughly dried by passing it through two wash bottles containing sulfuric acid. If the wash bottles are not effective, a tube containing glass beads mixed with phosphorus pentoxide should be used after the wash bottles. It is well to protect the side arm of the flask by means of a calcium chloride tube. The absolute alcohol used should be at least 99.5 per cent (p. 249).
2. If commercial acetonitrile is used directly, the yields are poor. It should be dried over calcium chloride for at least a week, filtered, and distilled, the fraction boiling at 76–81° being used.
3. If a thinner flask is used, there is danger of its being cracked during the experiment.
4. If a proper safety bottle is placed between the drying train and the flask of acetonitrile, the treatment with hydrogen chloride does not require constant attention during this time.
5. When weaker solutions of ammonia were used, the yields were lower.

6. The grinding of the imido ether hydrochloride is very important, as lumps of this material become coated with [ammonium chloride](#), which prevents the complete action of the [ammonia](#).

7. By a similar procedure [benzamidine hydrochloride](#) can be prepared. Dry [hydrogen chloride](#) is passed into a cooled solution of 51.5 g. (51 cc., 0.5 mole) of [benzonitrile](#) in 25 g. of absolute [ethyl alcohol](#) until 21.3 g. of the gas is absorbed. The reaction mixture is allowed to stand for forty-eight hours, and the solid cake of imido ether hydrochloride is quickly crushed in a dry mortar. The solid is transferred to a liter flask, and an 8 per cent solution of dry [ammonia](#) in absolute [ethyl alcohol](#) containing 12 g. of [ammonia](#) is added slowly in small portions. The reaction mixture is shaken for twenty-four hours, then allowed to stand for forty-eight hours and filtered to remove the [ammonium chloride](#) which has precipitated. (During the shaking the solution may develop a faint pink color. This is probably due to the presence of traces of [glyoxal](#) in the alcohol for this material in basic solution furnishes colored condensation products with [benzamidine](#).) The filtrate is allowed to evaporate to dryness in the open air, and the [benzamidine hydrochloride](#) thus obtained is dissolved in water. The solution is acidified with concentrated [hydrochloric acid](#), decolorized with charcoal, filtered, and the filtrate is evaporated almost to dryness at room temperature. The crystals of [benzamidine hydrochloride dihydrate](#) are filtered and air-dried. The yield is 60–70 g. of material which melts at 70–73°. The filtrate on evaporation to dryness furnishes 15–30 g. of less pure product, melting at 74–82°, which contains a small amount of [ammonium chloride](#) but which can be used satisfactorily in most reactions. The total yield is 80–95 per cent. (A. R. Ronzio and J. B. Ekeley, private communication.)

3. Discussion

The only practical method of preparation is that of Pinner,¹ on which the procedure described is based.

References and Notes

1. Pinner, Ber. **16**, 1654 (1883), **17**, 178 (1884).
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Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

[acetimido ethyl ether hydrochloride](#)

[imido ether](#)

[imido ether hydrochloride](#)

[ethyl alcohol](#),
[alcohol](#) (64-17-5)

[calcium chloride](#) (10043-52-4)

[sulfuric acid](#) (7664-93-9)

[hydrogen chloride](#),
[hydrochloric acid](#) (7647-01-0)

[ammonia](#) (7664-41-7)

ammonium chloride (12125-02-9)

Acetamidine hydrochloride (124-42-5)

acetonitrile (75-05-8)

Benzamidine hydrochloride (1670-14-0)

benzonitrile (100-47-0)

glyoxal (107-22-2)

benzamidine (618-39-3)

benzamidine hydrochloride dihydrate

phosphorus pentoxide (1314-56-3)