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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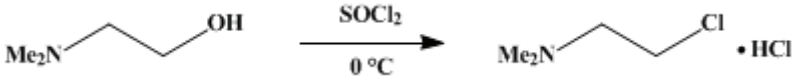
β-DIMETHYLAMINOETHYL CHLORIDE HYDROCHLORIDE

[Ethylamine, 2-chloro-N,N-dimethyl-, hydrochloride]



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Checked by Richard T. Arnold and William Lee.

1. Procedure

Caution! This preparation should be conducted in a good hood.

In a dry 1-l. flask fitted with a sealed mechanical stirrer, an efficient reflux condenser, and a 500-ml. dropping funnel is placed 290 g. (2.44 moles) of thionyl chloride (Note 1). The reaction flask must be cooled in an ice bath throughout the entire period of operation, as the reaction is very exothermic. β-Dimethylaminoethanol (210 g., 2.35 moles) (Note 2) is added dropwise through the funnel to the cooled thionyl chloride (Note 3) over a period of an hour, during which time there is a copious evolution of sulfur dioxide (Note 4). After all the β-dimethylaminoethanol has been added, the ice bath is removed and the reaction mixture is stirred for another hour (Note 5). The temperature of the mixture is 35–50°. At this point the reaction mixture consists of a brown semisolid slush of the desired product together with a slight excess of thionyl chloride.

The entire contents of the reaction flask are transferred to a 2-l. beaker (or wide-mouthed Erlenmeyer flask) containing approximately 1 l. of absolute ethanol (Note 6). The resulting brown solution is heated to boiling on a hot plate, during which time there is a copious evolution of gases (Note 6). The solution is filtered hot, leaving a small amount of insoluble material. Upon cooling of the filtrate in a salt-ice bath, the desired product is obtained as beautiful white crystals which are collected on a Büchner funnel and dried in a vacuum desiccator over phosphorus pentoxide (Note 7). The yield of pure product melting at 201.5–203° is 227–272 g. (67–80%).

Upon evaporation of the last filtrate to one-third of its volume and cooling in a salt-ice bath, an additional 33–69 g. (10–20%) of good-quality product is obtained. The total yield is 296–305 g. (87–90%).

2. Notes

1. Eastman Kodak Company practical grade thionyl chloride is satisfactory.
2. A good commercial grade (Eastman Kodak Company or Union Carbide and Carbon Corporation) of β-dimethylaminoethanol is satisfactory.
3. Continued and efficient cooling of the reaction vessel is needed to prevent too vigorous an evolution of sulfur dioxide and a subsequent loss of thionyl chloride through trapping of this reagent by effluent gases. Cooling also prevents too high a reaction temperature. The reaction proceeds more smoothly if the temperature is kept below 50°.
4. Care should be taken that the dropping funnel inlet does not become clogged with solid product. If the tip of the dropping funnel is in such a position that the drops of β-dimethylaminoethanol fall directly into the thionyl chloride and do not drain down the walls of the flask, mechanical difficulties are reduced markedly. The reaction must be carried out in an efficient hood or with a suitable trap in order to remove the noxious sulfur dioxide formed.
5. The reaction mixture may be stirred for a longer time and allowed to stand overnight without affecting the yield.
6. The ethanol not only converts the excess thionyl chloride to gaseous by-products (sulfur dioxide, hydrogen chloride, and ethyl chloride) but also serves as the recrystallizing solvent for the desired

product. The checkers found that about 80% of this thick product can be poured directly into 800 ml. of ethanol. Two hundred milliliters of warm ethanol should be used to decompose the product remaining in the reaction flask. This is combined with the main portion.
7. The product is somewhat hygroscopic, especially in humid weather. It should be dried in a vacuum desiccator to prevent the formation of hydrated forms.

3. Discussion

β-Dialkylaminoethyl bromide hydrobromides have been known for many years. However, the standard method of preparation requires large volumes of hydrobromic acid.[2] The less expensive analogous chlorides are preferred since their preparation is simpler and their reactivity is sufficient for the synthesis of well-known drugs.[3] Ordinarily β-dialkylaminoalkyl chloride hydrochlorides are prepared in good yield by treatment of β-dialkylaminoalkanols with an excess of thionyl chloride in chloroform or benzene.[4] An article on the German commercial preparation of Atabrine refers to the action of thionyl chloride on β-diethylaminoethanol hydrochloride without solvent.[5] The present method has been published.[6]

References and Notes

1. University of Kansas, Lawrence, Kansas.
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5. Greene, *Am. J. Pharm.*, **120**, 39 (1948).
6. Burckhalter, Stephens, and Hall, *J. Am. Pharm. Assoc.*, **39**, 271 (1950).

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

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

Benzene (71-43-2)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

HYDROBROMIC ACID (10035-10-6)

sulfur dioxide (7446-09-5)

ethyl chloride (75-00-3)

β-Dimethylaminoethyl chloride hydrochloride,
Ethylamine, 2-chloro-N,N-dimethyl-, hydrochloride (4584-46-7)

β-dimethylaminoethanol (108-01-0)

β-diethylaminoethanol hydrochloride (4620-71-7)

phosphorus pentoxide (1314-56-3)