A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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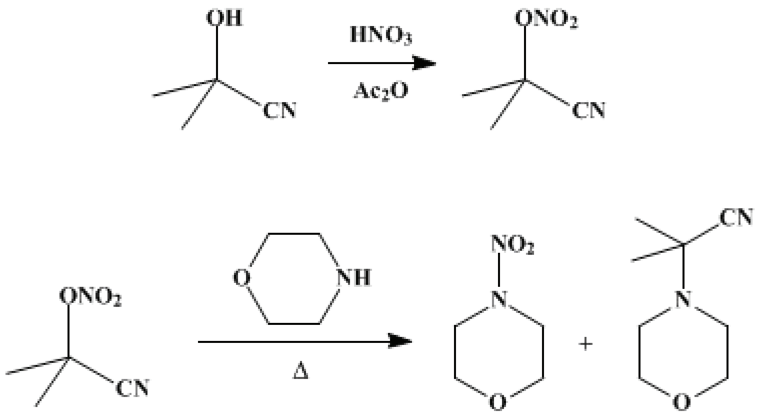
N-NITROMORPHOLINE

[Morpholine, 4-nitro-]



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1. Procedure

Caution! The nitrating mixture consisting of fuming nitric acid and acetic anhydride is an extremely active one, and combinations of it and organic materials are potentially explosive. The nitration should be carried out behind adequate safety shields. Acetone cyanohydrin nitrate is moderately explosive (Note 6) and all operations with it, but particularly its distillation, should be carried out behind safety shields.

A. *Acetone cyanohydrin nitrate*. White fuming nitric acid (106 ml., 158 g., 2.3 moles) (Note 1) is added dropwise to 380 ml. (408 g., 4.00 moles) of acetic anhydride at 3–5° contained in a 2-l. three-necked flask fitted with a stirrer, a thermometer, and a dropping funnel and immersed in an ice bath. After the addition, which requires 45 minutes, the mixture is stirred at 5° for 15 minutes (Note 2). Acetone cyanohydrin (92 ml., 85 g., 1.00 mole (Note 3) is added dropwise to the mixture at 5–10° over a 45-minute period. After the addition, the ice bath is removed and the mixture is allowed to warm to room temperature and is stirred there for 30 minutes. It is then poured into 600 g. of ice and water, and the resulting mixture is stirred for 90 minutes to dissolve the acetic anhydride.

The mixture is extracted with four 100-ml. portions of methylene chloride. The extracts are combined, washed successively with 100 ml. of water and four 100-ml. portions of 5% sodium carbonate solution (Note 4), and dried over anhydrous magnesium sulfate. The methylene chloride is removed by evaporation at 30–40° under the pressure of a water aspirator, and the residue is distilled through a 30-cm. Vigreux column to yield 85–90 g. (65–69%) (Note 5) of acetone cyanohydrin nitrate (Note 6); b.p. 62–65°/10 mm.; n_D^{20} 1.4170–1.4175 (Note 7).

B. *N-Nitromorpholine*. Morpholine (34.8 g., 0.40 mole) and 26 g. (0.20 mole) of acetone cyanohydrin nitrate are mixed in a 50-ml. round-bottomed flask equipped with a thermometer well. A condenser is attached, and the mixture is heated slowly. At about 60° an exotherm ensues that raises the temperature of the mixture to 110°. The mixture is allowed to cool to 80° and maintained there for 1 hour. It is poured into 200 ml. of 10% hydrochloric acid *Caution! Do in a hood! (Note 8))* and extracted with three 100-ml. portions of methylene chloride (Note 9). The extracts are combined, washed successively with two 100-ml. portions of water, 100 ml. of 10% hydrochloric acid, and 100 ml. of water, and dried over anhydrous magnesium sulfate. The solvent is removed by evaporation on a water aspirator at room temperature to yield a pale-yellow oil (Note 10).

The oil is dissolved in 80 ml. of absolute ethanol. The solution is cooled to 0–5°, causing white crystals of N-nitromorpholine to precipitate; weight 15–17 g. (57–64%); m.p. 52–54° (Note 11).

2. Notes

1. This is 90% nitric acid, d. 1.48–1.50. In order to remove dissolved nitrogen oxides from it, 0.5 g. of urea is added and the mixture is air-sparged for 20 minutes. The acid should be colorless before it is added to the acetic anhydride.
2. The nitrating mixture should be colorless at this point. If it is not, 0.5 g. of urea should be added and the mixture air-sparged until colorless.
3. Suitable acetone cyanohydrin can be purchased from the Rohm and Haas Co. and other commercial sources, or it can be prepared as described in *Organic Syntheses*.[2]
4. Washing with the carbonate solution should be continued until the organic layer is free of acid. Traces of acid may cause extensive decomposition during the distillation.
5. Similar yields were observed in preparations on three times this scale.
6. Acetone cyanohydrin nitrate should be regarded as a moderately explosive material and should be handled carefully and distilled behind a safety shield. For purposes of comparison, the drop-weight sensitivities on the Olin-Mathieson drop-weight tester of three materials are: propyl nitrate, 10 kg.-cm.; acetone cyanohydrin nitrate, 40 kg.-cm; nitromethane, 60 kg.-cm.
7. The product obtained from this distillation usually contains small amounts of acetone cyanohydrin acetate, as evidenced by an ester carbonyl band at 1740 cm.$^{-1}$ in its infrared spectrum. This material does not interfere with the nitration reactions of the reagent. It may be removed by fractionation through a more efficient column.
8. This operation should be carried out in a good hood because hydrogen cyanide is evolved at this point.
9. The aqueous solution contains α-morpholinoisobutyronitrile in the form of its hydrochloride. It is formed by condensation of morpholine with the acetone and hydrogen cyanide formed in the nitration reaction. It is because of this side reaction that the excess amine is employed.
10. Occasionally this oil solidifies after removal of the last traces of solvent; in these instances it is necessary to warm the ethanol slightly to effect solution.
11. In nitrating amines other than morpholine, particularly on a larger scale, it may be desirable to carry out the reaction in acetonitrile to control the temperature better.[3]

3. Discussion

N-Nitromorpholine has been prepared by the oxidation of N-nitrosomorpholine with peroxytrifluoroacetic acid,[4] by the chloride ion-catalyzed reaction of nitric acid with morpholine,[5] by the action of nitric acid and acetic anhydride on N-formyl-morpholine,[6] by the reaction of dinitrogen pentoxide with morpholine,[7] and by alkaline nitration of morpholine with acetone cyanohydrin nitrate.[3]

4. Merits of the Preparation

This synthesis of N-nitromorpholine is representative of a rather general reaction for the preparation of both primary and secondary nitramines.[3] It represents the simplest process for obtaining both types of compounds. The reaction is unique in that a nitration is carried out under neutral or alkaline conditions. Acetone cyanohydrin nitrate may also be used for the nitration of many active methylene compounds.[8]

References and Notes

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

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic anhydride (108-24-7)

acetonitrile (75-05-8)

nitric acid (7697-37-2)

hydrogen cyanide (74-90-8)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

acetone (67-64-1)

urea (57-13-6)

Nitromethane (75-52-5)

methylene chloride (75-09-2)

Acetone cyanohydrin (75-86-5)

magnesium sulfate (7487-88-9)

morpholine (110-91-8)

Acetone cyanohydrin nitrate (40561-27-1)

peroxytrifluoroacetic acid

N-Nitromorpholine,
Morpholine, 4-nitro- (4164-32-3)

propyl nitrate (627-13-4)

acetone cyanohydrin acetate

α-morpholinoisobutyronitrile

N-nitrosomorpholine (59-89-2)

N-formyl-morpholine (4394-85-8)