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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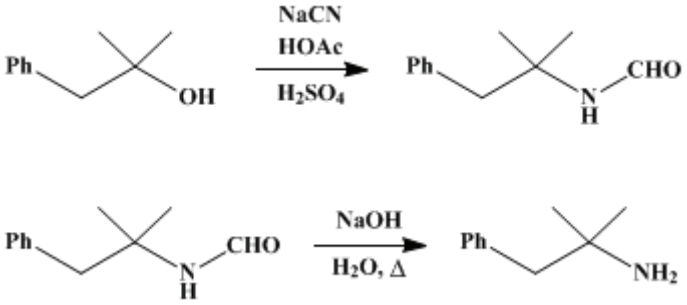
α,α-DIMETHYL-β-PHENETHYLAMINE

[Phenethylamine, α,α-dimethyl]



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Checked by William G. Dauben and Alan Krubiner.

1. Procedure

Caution! This preparation should be conducted in a hood because poisonous hydrogen cyanide may be evolved.

A. *N-Formyl-α,α-dimethyl-β-phenethylamine*. To a 2-l., three-necked, round-bottomed flask fitted with a sealed stirrer carrying a crescent-shaped blade, a thermometer, an addition funnel, and a reflux condenser connected to a trap containing 20% sodium hydroxide solution is added 500 ml. of glacial acetic acid (Note 1). The contents of the flask are cooled to 20° by means of an ice bath, the addition funnel is temporarily replaced by a stopper, and to the stirred acetic acid is added 110 g. (2 moles) of 95% sodium cyanide in small portions. The temperature of the mixture is maintained around 20°, and the addition requires about 20 minutes (Note 2). The addition funnel is replaced, and a previously prepared and cooled solution of 500 g. (272 ml., 4.9 moles) of concentrated sulfuric acid in 250 ml. of glacial acetic acid is added slowly, with stirring, the temperature of the mixture being kept at about 20° by means of an ice bath (Note 3). The ice bath is removed, and 300 g. (2 moles) of α,α-dimethyl-β-phenethyl alcohol (Note 4) is added over a 20-minute period during which the temperature of the mixture rises slowly to 35–45°. The reaction mixture is stirred for an additional 90 minutes (Note 5) and allowed to stand overnight. The amber-colored mixture containing some solid sodium sulfate is aerated with nitrogen for 2 hours *(Caution! In a hood)*, poured into 3 l. of ice water, and the supernatant oil separated. The aqueous phase is neutralized with sodium carbonate and extracted with 600 ml. of ether. The ethereal extract is combined with the original oily supernatant, neutralized with sodium carbonate, and dried over anhydrous sodium sulfate. The solvent is removed under reduced pressure, and the residue is distilled to yield 230–248 g. (65–70%) of product, b.p. 137–141° (2 mm.). Redistillation of the ether-containing fore-run yields up to an additional 14 g. of material.

B. *α,α-Dimethyl-β-phenethylamine*. In a 3-l., three-necked, round-bottomed flask equipped with a reflux condenser and a sealed stirrer are placed 246 g. (1.39 moles) of N-formyl-α,α-dimethyl-β-phenethylamine and 2.1 l. of 20% sodium hydroxide solution. The mixture is heated under reflux with vigorous stirring for 2.5 hours or until a test portion of the oily layer dissolves completely in cold 5% hydrochloric acid. The reaction mixture is cooled, 750 ml. of benzene is added, the mixture is stirred, and the benzene layer is separated. The benzene solution is shaken with a saturated sodium chloride solution, the benzene removed by distillation at atmospheric pressure, and the product distilled at reduced pressure to yield 155–165 g. (75–80%) of α,α-dimethyl-β-phenethylamine, b.p. 80–82° (10 mm.).

2. Notes

1. The reaction may be conducted in other solvents (e.g., dibutyl ether) or in the absence of solvent with some alteration in the order of mixing the reagents. The submitters find for this and a large number of similar preparations that acetic acid generally is most convenient.
2. Most of the sodium cyanide does not dissolve.
3. Care must be taken during the first part of the addition because the reaction is very exothermic.
4. Methallylbenzene or isobutenylbenzene may be used in place of the carbinol with practically identical results.
5. The temperature may continue to rise during the initial portion of this period, but it is controlled by means of an ice bath to limit the temperature of the mixture to 45–50°.

3. Discussion

α,α-Dimethyl-β-phenethylamine has been prepared from benzaldehyde and 2-nitropropane[3] and from isobutyrophenone by a series of steps involving alkylation with benzyl bromide, alkali cleavage, and Hofmann bromamide degradation.[4]

4. Merits of the Preparation

The present method is shorter and less laborious than previously described methods, and it gives better yields of material. The method, now known as the Ritter reaction, is one of considerable scope,[5] having been used with fair to excellent success with many tertiary alcohols or the corresponding alkenes, with benzyl alcohol, and with some secondary alcohols. It has also been used with alkanes, alkadienes, alicyclic and spiro alcohols, alkyl chlorides, glycols, aldehydes, chlorohydrins, N-methylolamides, ethers, carboxylic acids, esters, ketones, and ketoximes. The Ritter reaction has been reviewed.[5] Another example of this reaction is given elsewhere in this volume.[6]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 73

References and Notes

1. Evans Research and Development Corporation, 250 East 43 Street, New York, New York.
2. Drug and Cosmetic Industry, 101 West 31 Street, New York, New York.
3. R. S. Shelton and M. C. Van Campen, Jr., U.S. Patent 2,408,345 (Sept. 1946) [*C.A.*, **41**, 567 (1947)]; B. L. Zenitz, E. B. Macks, and M. L. Moore, *J. Am. Chem. Soc.*, **70**, 955 (1948).
4. L. L. Abell, W. F. Bruce, and J. Seifter, U.S. Patent 2,590,079 (March 1952) [*C.A.*, **46**, 10200 (1952)].
5. L. I. Krinsen and D. J. Cota, *Org. Reactions*, 17, 213 (1969).
6. C. L. Parris, this volume, p. 73.

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

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

hydrogen cyanide (74-90-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

Benzyl alcohol (100-51-6)

dibutyl ether (142-96-1)

benzyl bromide (100-39-0)

2-nitropropane (79-46-9)

Phenethylamine, α,α-dimethyl,
α,α-Dimethyl-β-phenethylamine (122-09-8)

Methallylbenzene (3290-53-7)

isobutenylbenzene (768-49-0)

isobutyrophenone (611-70-1)

α,α-dimethyl-β-phenethyl alcohol (100-86-7)

N-Formyl-α,α-dimethyl-β-phenethylamine (52117-13-2)