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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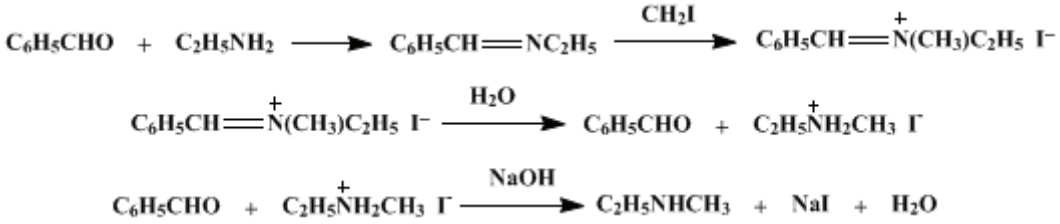
N-METHYLETHYLAMINE

[Ethylamine, N-methyl-]



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Checked by J. K. Williams, H. E. Winberg, C. L. Dickinson, and B. C. McKusick.

1. Procedure

A. *N-Benzylideneethylamine*. Benzaldehyde (466 g., 4.40 moles) is placed in a 2-l. three-necked flask equipped with a mechanical stirrer and a thermometer. The flask is cooled to 5° in an ice bath, and 200 g. (4.44 moles) of anhydrous ethylamine (Note 1) is added to the stirred benzaldehyde at such a rate that the temperature remains below 15°; about 50 minutes is required for the addition. The mixture is stirred for an additional 30 minutes at room temperature and allowed to stand for 1 hour.

The condenser is arranged for downward distillation, and the water is removed from the product by codistillation with 200 ml. of benzene. The residue, N-benzylideneethylamine, is purified by distillation through a 25-cm. Fenske column; b.p. 52–53° (4.5 mm.); n^{23}D 1.5400; weight 470–523 g. (80–89%) (Note 2).

B. *N-Methylethylamine* N-Benzylideneethylamine. (133 g., 1.00 mole) is heated with 156 g. (1.10 moles) of methyl iodide (Note 3) in a 300-ml. pressure bomb at 100° for 24 hours (Note 4). The bomb is cooled to 50° (Note 5), and the dark, viscous oil is poured into a 1-l. beaker containing 200 ml. of water. The bomb is rinsed with three 50-ml. portions of water, and the washings are combined with the main solution. The resulting mixture is heated with manual stirring on a steam bath for 20 minutes and then cooled in an ice bath to room temperature. The resulting mixture is extracted with two 75-ml. portions of ether (Note 6). The ether layer is washed with two 50-ml. portions of water, and the washings are combined with the main aqueous layer, which is then heated at 100° on a steam bath for 20 minutes to remove traces of ether.

For the liberation of N-methylethylamine, a 1-l. Claisen flask is equipped with a 250-ml. separatory funnel and an efficient condenser for distillation. The receiver is cooled with a mixture of acetone and dry ice (Note 7). A solution of 100 g. (2.5 moles) of sodium hydroxide in 100 ml. of water is added to the flask and kept at about 100° by heating on a steam bath. The aqueous solution of N-methylethylamine hydriodide is added to this solution through the separatory funnel in the course of 1.5 hours. After the addition is complete, the final solution is heated for an additional 30 minutes. Crude N-methylethylamine, b.p. 30–70°, collects in the cooled receiver. It is purified by distillation from 25 g. of solid potassium hydroxide in a 250-ml. modified Claisen flask fitted with a 25-cm. Fenske column and a receiver cooled by dry ice and acetone. N-Methylethylamine is collected at 34–35°; weight 49–55 g. (83–93%); n^{25}D 1.3830.

2. Notes

1. The ethylamine is cooled to 5° to prevent loss by evaporation. Addition is made directly from the bottle with intermittent cooling in an ice bath.
2. The aldimine need not be distilled but can be used directly in the next step.
3. Dimethyl sulfate, when substituted for the methyl iodide, reacts vigorously with the aldimine at ice-bath temperatures and gives a 49% yield of N-methylethylamine together with considerable tar.

4. Four times these amounts have been used for N-methylbutylamine with equal success.
5. The pressure bomb is opened while still warm (50°). If the bomb is allowed to cool below this temperature, the product solidifies and removal becomes a problem.
6. The benzaldehyde may be recovered after removal of the ether.
7. Because of the low boiling point of N-methylethylamine, there must be efficient cooling or a portion of the product will be lost.

3. Discussion

This procedure is a modification of the method used for N-methylallylamine.[2]

N-Methylethylamine has been prepared by heating ethylamine with methyl iodide in alcohol at 100°;[3] by the hydrolysis of N-methyl-N-ethylarenesulfonamides,[4,5] *p*-nitroso-N-methyl-N-ethylaniline,[6] or methylethylbenzhydrylidene ammonium iodide;[7] by catalytic hydrogenation of ethyl isocyanate or ethyl isocyanide;[8] and by the reduction of ethyl isocyanate by lithium aluminum hydride,[9] of N-methylacetisoaldoxime by sodium amalgam and acetic acid,[10] or of a nitromethane/ethylmagnesium bromide adduct by zinc and hydrochloric acid.[11]

4. Merits of the Preparation

This preparation illustrates a general method for the synthesis of N-methylalkylamines. The submitters have used it to prepare N-methylbutylamine (Note 4) and N-methylallylamine, and the checkers have used it to prepare N-methylisopropylamine (80%), N-methylisobutylamine (67%), N-methyl-*tert*-butylamine (52%), and N-methyl-2-methoxyethylamine (55%). Secondary amines are useful as starting materials for the synthesis of 1,1-disubstituted hydrazines and asymmetric amine imides.

The method gives better yields, utilizes more readily available starting materials, and is much less laborious than the hydrolysis of N-methyl-N-alkylarenesulfonamides and *p*-nitroso-N, N-dialkylanilines, or the lithium aluminum hydride reduction of alkyl isocyanates. Compared to the closely related procedure of Lucier, Harris, and Korosec,[12] in which the N-benzylidenealkylamine is treated with dialkyl sulfate at atmospheric pressure, the present procedure tends to give higher yields and purer products, but it is less convenient because of the need for a pressure vessel.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 736

References and Notes

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

N-methylacetisoaldoxime

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

dimethyl sulfate (77-78-1)

benzaldehyde (100-52-7)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

zinc (7440-66-6)

sodium (13966-32-0)

Methyl iodide (74-88-4)

lithium aluminum hydride (16853-85-3)

Ethyl isocyanide (624-79-3)

ethylamine (75-04-7)

ethyl isocyanate (109-90-0)

N-Methylbutylamine (110-68-9)

N-Methylethylamine,
Ethylamine, N-methyl- (624-78-2)

N-Benzylideneethylamine (6852-54-6)

N-methylethylamine hydriodide

N-methylallylamine (627-37-2)

methylethylbenzhydrylidene ammonium iodide

N-methylisopropylamine (4747-21-1)

N-methylisobutylamine (625-43-4)

N-methyl-2-methoxyethylamine (38256-93-8)

p-nitroso-N-methyl-N-ethylaniline

N-methyl-tert-butylamine (14610-37-8)