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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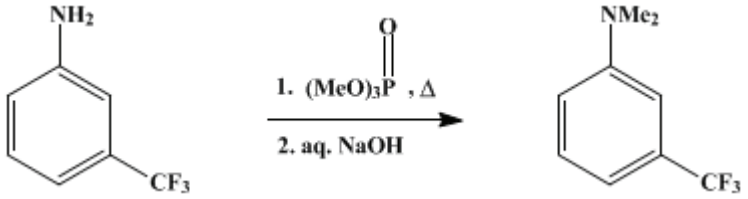
m-TRIFLUOROMETHYL-N,N-DIMETHYLANILINE

[*m*-Toluidine, α,α,α-trifluoro-N,N-dimethyl-]



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1. Procedure

A solution of 16.1 g. (0.100 mole) of *m*-trifluoromethylaniline (Note 1) and 14.3 g. (0.102 mole) of trimethyl phosphate (Note 2) is added to a 300-ml. round-bottomed flask with a side arm. The flask is equipped with a thermometer, magnetic stirrer, and air condenser topped by a water condenser under a nitrogen atmosphere. The stirred reaction mixture is gradually heated by an oil bath to approximately 150° over 30–60 minutes; at this point there is a mild exothermic reaction such that the temperature of the reaction reaches 160–170° and reflux starts (Note 3). After 2 hours at reflux (reaction temperature 145–150°) with oil-bath temperature maintained at 180–200°, the reaction mixture is cooled to room temperature.

A solution of 15 g. of sodium hydroxide in 100 ml. of water is added, and the mixture is stirred vigorously for 1.5 hours to hydrolyze the phosphate ester. The hydrolysis is initially mildly exothermic, and the reaction temperature increases to 50–70°. An additional 200 ml. of water is added. The product, which separates as an oil, is extracted with two 150-ml. portions of ether (Note 4). The combined ether extracts are dried for at least several hours over a mixture of anhydrous magnesium sulfate and sodium hydroxide pellets, filtered, and concentrated by distillation of the ether through a Vigreux column. The residue is distilled at reduced pressure. *m*-Trifluoromethyl-N,N-dimethylaniline is collected at 66–67° (4.5 mm.) and weighs 10.4–11.0 g. (55–58%); n^{24}D 1.4834–1.4828 (Note 5), (Note 6).

2. Notes

1. *m*-Trifluoromethylaniline (under the name *m*-aminobenzotrifluoride) obtained from Columbia Organic Chemicals Co., Inc., Columbia, South Carolina, was employed. The aniline is also available from Eastman Kodak under the name α,α,α-trifluoro-*m*-toluidine.
2. Trimethyl phosphate obtained from Columbia Organic Chemicals was employed. Although the phosphate ester is reported to be nontoxic under normal handling conditions,[2] use of a hood is recommended.
3. Separation of the reaction mixture into two phases can be observed if the stirrer is stopped for a short period at this point and is also noted on cooling after completion of reflux.
4. The phosphate salts sometimes precipitate before or during the extraction and should be removed by suction filtration to facilitate the extraction. Precipitation may be avoided by addition of larger volumes of water before extraction.
5. A very small forecut is discarded, and only a small amount of tarry residue remains in the pot after the distillation is complete. A spinning-band distillation column was employed by the submitter, but a simple Claisen head is considered adequate because of lack of by-products.
6. The product is free from secondary aniline product on the basis of infrared and n.m.r. proton analysis. If equimolar amounts of aniline and phosphate are employed, the product is obtained in a higher yield (12.3 g., 65%), but it contains a trace of *m*-trifluoromethyl-N-methylaniline as detected by infrared analysis. This secondary aniline is readily removed by heating the product to reflux with 1 ml. of acetic anhydride followed by redistillation. Use of a larger molar excess of trimethyl phosphate does not affect

the purity but does decrease the yield significantly.

3. Discussion

The described method of dialkylation of anilines is essentially that of Billman and co-workers.[3,2] It has not previously been applied to *m*-trifluoromethylaniline. *m*-Trifluoromethyl-N,N-dimethylaniline has been prepared in 29% yield by alkylating *m*-trifluoromethylaniline with methyl iodide.[4]

The use of trialkyl phosphates for dialkylation of anilines has been found applicable to naphthylamines[2] and to a large number of anilines substituted in the ortho, meta, or para position by groups such as chloro, methoxy, and methyl[3] and in the meta position by fluoroalkyl (author's laboratory). The reaction has been used to introduce ethyl and *n*-butyl as well as methyl groups by employing the appropriate phosphate esters. The reported yields range from 50% to 95%.

This method has two major advantages over other alkylation procedures: much less manipulation and higher yields; and no troublesome by-products, such as monoalkylated or quaternary products. The Eschweiler-Clarke procedure[5] for alkylation of amines (formaldehyde-formic acid) also has these synthetic advantages for the aliphatic series but gives high molecular weight condensation products with anilines (anilines highly substituted in the ortho-para position may be employed successfully, but *m*-trifluoromethylaniline gives only a resin).

The phosphate method has not been synthetically useful for alkylation of anilines of low basicity such as *p*-nitro-[2] or *p*-trifluoroaniline. Only monoalkylation occurs in introducing branched-chain alkyl groups such as isopropyl.[2] Use of this method for alkylation of aliphatic amines has not been reported.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 181

References and Notes

1. Contribution No. 940 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware.
2. J. H. Billman, A. Radike, and B. W. Mundy, *J. Am. Chem. Soc.*, **64**, 2977 (1942).
3. D. G. Thomas, J. H. Billman, and C. E. Davis, *J. Am. Chem. Soc.*, **68**, 895 (1946).
4. J. D. Roberts, R. L. Webb, and E. A. McElhill, *J. Am. Chem. Soc.*, **72**, 408 (1950).
5. M. L. Moore, *Org. Reactions*, **5**, 309 (1949).

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

ether (60-29-7)

acetic anhydride (108-24-7)

aniline (62-53-3)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

Methyl iodide (74-88-4)

formaldehyde-formic acid (298-12-4)

magnesium sulfate (7487-88-9)

trimethyl phosphate (512-56-1)

m-trifluoromethylaniline,
m-aminobenzotrifluoride,
α,α,α-Trifluoro-m-toluidine (98-16-8)

m-Trifluoromethyl-N,N-dimethylaniline,
m-Toluidine, α,α,α-trifluoro-N,N-dimethyl- (329-00-0)

m-trifluoromethyl-N-methylaniline