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.

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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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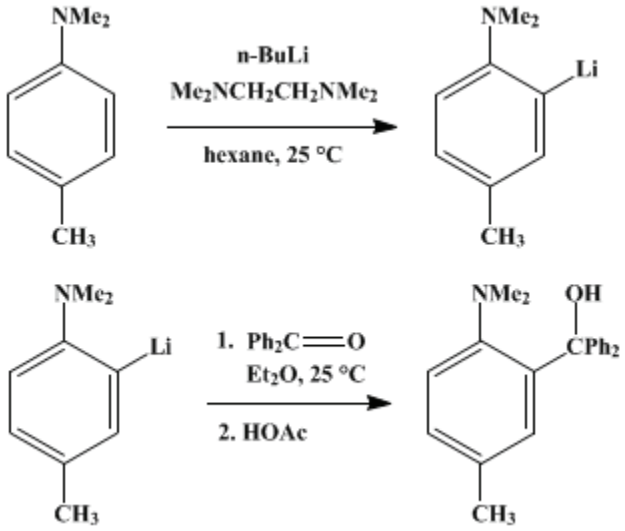
DIRECTED LITHIATION OF AROMATIC COMPOUNDS: (2-DIMETHYLAMINO-5-METHYLPHENYL)DIPHENYLCARBINOL

[Benzenemethanol, 2-(dimethylamino)-5-methyl-α,α-diphenyl-]



Submitted by J. V. Hay and T. M. Harris[1].
Checked by Robert A. Auerbach and Herbert O. House.

1. Procedure

A dry, 500-ml., two-necked flask containing 6.75 g. (0.0500 mole) of *N,N*-dimethyl-*p*-toluidine (Note 1) and 175 ml. of anhydrous hexane (Note 2) is fitted with a Teflon-coated magnetic stirring bar, a pressure-equalizing dropping funnel capped with a rubber septum, and a nitrogen inlet tube. The reaction vessel is flushed with nitrogen, and a static nitrogen atmosphere is maintained within the apparatus for the remainder of the reaction sequence. A solution of 8.8 g. (0.076 mole of *N,N,N′,N′*-tetramethylethylenediamine (Note 3) in 40 ml. of anhydrous hexane is added to the dropping funnel, followed by a hexane solution containing 0.076 mole of *n*-butyllithium (Note 4). The resulting solution, which becomes warm as the organolithium-diamine complex forms, is allowed to stand for 15 minutes, then added to the reaction mixture, dropwise and with stirring over 15–20 minutes. The resulting bright yellow, turbid reaction mixture is stirred at room temperature for 4 hours longer before a solution of 13.8 g. (0.0758 mole) of benzophenone (Note 5) in 40 ml. of anhydrous diethyl ether is added to the reaction mixture, dropwise and with stirring over 20 minutes. The resulting, deep-green solution is stirred for an additional 20 minutes, then poured into a vigorously stirred solution of 12 g. (0.20 mole) of acetic acid in 30 ml. of ether (Note 6). After the reaction solution has been successively extracted with 50 ml. of water and four 50-ml. portions of 5% hydrochloric acid, the aqueous extracts are combined (Note 7) and made basic with aqueous 10% sodium hydroxide. The alkaline mixture is heated to boiling and maintained at this temperature until the escaping vapor is no longer basic to moistened pHydrion paper (Note 8). The mixture is then cooled, and the white solid product which separates is collected on a Büchner funnel and washed with three 20-ml. portions of water. The crude product (m.p. 142–168°) is recrystallized from 250 ml. of 3 : 1 (v/v) hexane-ethyl acetate, giving 6.6–8.2 g. of the amino alcohol product as colorless prisms, m.p. 168–171°. Concentration of the mother liquors gives an additional 0.8–1.2 g. of product, m.p. 167–169°, for a total yield of 7.8–9.0 g. (49–57%). Although the product is sufficiently pure for most purposes, a second recrystallization from hexane-ethyl acetate raises the melting point to 169.5–172° (Note 9).

2. Notes

1. Commercial *N,N*-dimethyl-*p*-toluidine, obtained from Aldrich Chemical Company, Inc., was used without purification.
2. An A.C.S. grade of hexane, obtained from Fisher Scientific Company, was used without further purification.
3. *N,N,N′,N′*-Tetramethylethylenediamine, purchased from Aldrich Chemical Company, Inc., was distilled from calcium hydride immediately before use; b.p. 120–122°.
4. Hexane solutions of *n*-butyllithium, purchased from either Alfa Inorganics, Inc., or Foote Mineral Company, were standardized by the titration procedure of Watson and Eastham.[2] A detailed procedure for this titration is provided in *Org. Synth.*, **Coll. Vol. 6**, 121 (1988).
5. Benzophenone, purchased from Fisher Scientific Company, was used without purification.
6. Reversal of this hydrolysis procedure, the addition of acetic acid to the reaction mixture, had an adverse effect on the yield of product.
7. Some of the aqueous extracts may contain small amounts of suspended particulate matter.
8. This simple steam distillation removes the unchanged *N,N*-dimethyl-*p*-toluidine present in the crude product.
9. The purified product has the following spectral properties: IR (CCl_4) 3050 $cm.^{-1}$ (associated OH); UV (95% C_2H_5OH) max (ε) 251 (905), 258 (823), 264 (720), and 275 nm (432); NMR ($CDCl_3$), δ 2.19 (s, 3H, C-C*H*$_3$), 2.38 [s, 6H, N(C*H*$_3$)$_2$] 6.55 (s, 1H, O*H*), and 7.00–7.50 (m, 13H, aromatic C*H*); *m/e* (rel. int.), 317(M^+, 100), 240(84), 225(28), 224(91), 222(43), 150(25), 134(41), 120(32), 105(41), 91(51), and 77(42).

3. Discussion

This procedure is an adaptation of one described by Hauser and co-workers.[3] The product has also been prepared from 2-bromo-*N,N*-dimethyl-*p*-toluidine by halogen-metal interchange with *n*-butyllithium followed by condensation with benzophenone,[3] a procedure less convenient than that presently described.

Tertiary amines such as *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) and 1,4-diazabicyclo [2.2.2]octane (DABCO) strongly catalyze metallations by alkyllithium reagents. Uncatalyzed lithiation of toluene is very poor,[4] whereas a yield of 90% has been obtained when TMEDA is employed as a catalyst.[5]

It is noteworthy that metallation of *N,N*-dimethyl-*p*-toluidine takes place at a position *ortho* to the dimethylamino group rather than on or *ortho* to the aryl methyl group. Apparently, coordination of lithium by the amino group plays a dominant role in directing metallation even in the presence of TMEDA. Other cases have been reported in which the site of metallation is altered by addition of TMEDA.[6,7]

References and Notes

1. Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235.
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4. H. Gilman and B. J. Gaj, *J. Org. Chem.*, **28**, 1725 (1963).
5. A. W. Langer, Jr., *Trans. N.Y. Acad. Sci.*, **27**, 741 (1965).
6. D. A. Shirley and C. F. Cheng, *J. Organomet. Chem.*, **20**, 251 (1969).
7. D. W. Slocum, G. Book, and C. A. Jennings, *Tetrahedron Lett.*, 3443 (1970).

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

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

toluene (108-88-3)

Benzophenone (119-61-9)

Benzenemethanol (100-51-6)

lithium (7439-93-2)

n-butyllithium (109-72-8)

hexane (110-54-3)

calcium hydride (7789-78-8)

1,4-diazabicyclo[2.2.2]octane (280-57-9)

(2-Dimethylamino-5-methylphenyl)diphenylcarbinol (23667-05-2)

tetramethylethylenediamine (20485-44-3)

N,N,N',N'-tetramethylethylenediamine (110-18-9)

N,N-dimethyl-p-toluidine (99-97-8)

2-bromo-N,N-dimethyl-p-toluidine