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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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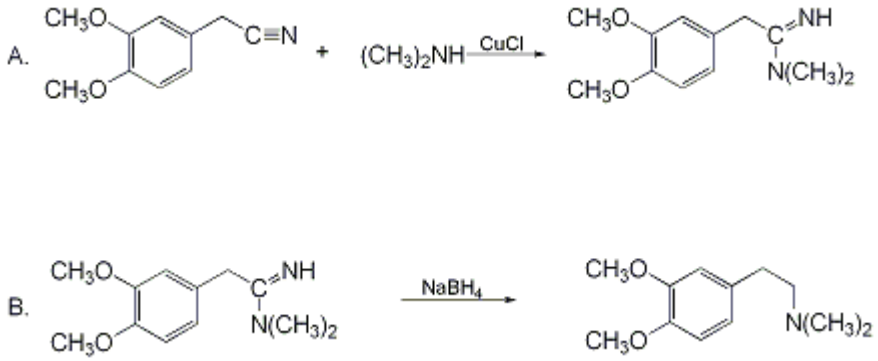
CONVERSION OF NITRILES INTO TERTIARY AMINES: N,N-DIMETHYLHOMOVERATRYLAMINE

[Benzeneethanamine, 3,4-dimethoxy-N,N-dimethyl-]



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Checked by Sam Derrer and Andrew B. Holmes.

1. Procedure

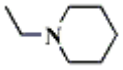
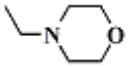
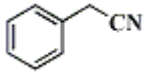
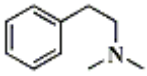
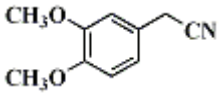
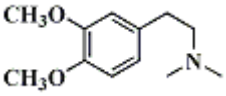
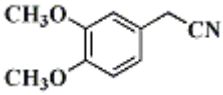
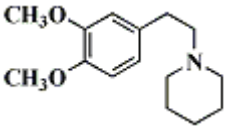
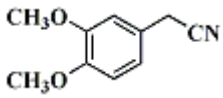
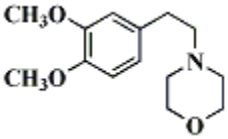
A. 2-(3,4-Dimethoxyphenyl)-N,N-dimethylacetamidine . An oven-dried, 250-mL, single-necked, round-bottomed flask containing a 3-cm magnetic stirring bar is charged with 7.96 g (0.045 mol) of (3,4-dimethoxyphenyl)acetonitrile (Note 1) and 4.95 g (0.050 mol) of copper(I) chloride (Note 2), fitted with a septum, flushed with argon, and maintained under a static pressure of argon using a gas bubbler. Using a 20-mL gas-tight syringe, 45 mL (0.067 mol) of a 1.5 M ethanolic solution of dimethylamine (Note 3) is added successively in three 15-mL portions at room temperature with vigorous stirring. The heterogeneous pale brown mixture is then heated at 70°C for 24 hr, during which time it becomes brown-red. The mixture is cooled to room temperature and poured with vigorous stirring into a 250-mL Erlenmeyer flask containing 70 mL of aqueous 30% sodium hydroxide and 100 mL of diethyl ether (Note 4); the mixture was stirred vigorously for 3 min. The organic layer is separated, and the aqueous layer is extracted with three 75-mL portions of diethyl ether (Note 5). The combined organic extracts are dried over sodium sulfate and filtered through a sintered glass funnel layered with 2 cm of Celite. The solid residue is washed with diethyl ether (20 mL). The combined filtrate and washings are concentrated by rotary evaporation followed by drying under reduced pressure (0.1 mm) for 1.5 hr to provide 9.1-9.4 g (93-96% yield) of a dark brown oil (Note 6),(Note 7). The compound is stored under argon at −18°C until used in step B.

B. N,N-Dimethylhomoveratrylamine . An oven-dried, 100-mL, Erlenmeyer flask is equipped with a magnetic stir bar, and charged with 9.05 g (0.041 mol) of 2-(3,4-dimethoxyphenyl)-N,N-dimethylacetamidine and 37 mL of methanol (Note 8). The solution is cooled to 0°C in an ice bath and 1.87 g (0.049 mol, 1.2 equiv) of sodium borohydride (Note 9) is added with stirring in portions of ca. 0.1 g. The solution is allowed to stand at room temperature for 4 hr, then poured with vigorous stirring into a 250-mL Erlenmeyer flask containing 50 mL of aqueous 30% sodium hydroxide and 100 mL of diethyl ether . The organic layer is separated, and the aqueous layer is extracted with three 75-mL portions of diethyl ether . The combined organic extracts are dried over sodium sulfate and filtered through a sintered glass funnel. The solid residue is washed with 20 mL of diethyl ether . The combined filtrate and washings are concentrated by rotary evaporation followed by drying under reduced pressure (0.3 mm) for 1 hr to provide 7.9-8.1 g (93-95% yield) of N,N-dimethylhomoveratrylamine as a yellow oil. NMR and GC analysis indicate a purity greater than 95% (Note 10).

2. Notes

1. (3,4-Dimethoxyphenyl)acetonitrile was obtained from Aldrich Chemical Company, Inc. , and used without further purification.
2. Copper(I) chloride was obtained as a light green powder from Aldrich Chemical Company, Inc. (ref. Aldrich 21,294-6). The submitters obtained material with the same catalog number as sticks, which were carefully ground immediately before use.
3. The 1.5 M solution of dimethylamine in ethanol was prepared as follows: Aqueous 40% dimethylamine is heated at 65°C under a flow of argon. The gas is passed through potassium hydroxide pellets and blown across a known quantity (100 mL) of absolute ethanol (analytical grade used without purification), then cooled to 0°C in an ice bath, with continuous stirring, for 3 hr. The ethanolic solution is weighed and diluted to 150 mL with absolute alcohol. The ethanolic dimethylamine solution (ca. 1.5 M) is carefully capped and kept under an inert atmosphere at −18°C. The concentration may be measured by pouring a 1-mL aliquot of the ethanolic dimethylamine solution into aqueous 1 N hydrogen chloride . Water and ethanol are removed by rotary evaporation, and the residue is dried over potassium hydroxide pellets under vacuum (0.3 mbar, 2.5 mm) for one night. The weight of residue allows the exact concentration of the ethanolic dimethylamine solution to be measured.
With other less volatile amines (see Table I), the mixture of Cu(I)Cl, nitrile, and amine is simply refluxed in ethanol. In such a case, 1.1 equiv only of amine can be used.

TABLE I
SECONDARY AND TERTIARY AMINE SYNTHESES BY REDUCTIVE N-ALKYLATION OF NITRILE

Nitrile	Starting Amine	Final Amine	Selectivity of Step B	Overall Yield
CH_3CN	hexylamine	$CH_3CH_2NH(CH_2)_5CH_3$	95%	75%
CH_3CN	benzylamine	$CH_3CH_2NHCH_2C_6H_5$	85%	70%
CH_3CN	piperidine		95%	90%
CH_3CN	morpholine		95%	80%
	dimethylamine		> 99%	95%
	dimethylamine		> 99%	95%
	piperidine		> 99%	93%
	morpholine		80%	75%

4. Reagent grade diethyl ether may be used without further purification.
5. The phases were separated with difficulty because of the presence of copper salts. Some product adheres to the flask and separatory funnel.
6. The submitters carried out the drying at 0.3 mbar (2.5 mm) (1 hr) and reported 98% yield. Under these conditions the checkers observed residual ethanol (δ 1.13, t, 3 H J = 7; 3.58, q, 2 H, J = 7) in the ^{1}H NMR spectrum of the product. Most of the ethanol was removed after drying for the longer time at

higher vacuum.
7. The product exhibits the following spectral properties : IR (film) ν cm^{-1}: 3380 (ν_{N-H}), 1590 ($\nu_{C=N}$) ; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.96 (s, 6 H, N-CH_3), 3.59 (s, 2 H), 3.84 (s, 3 H, 4-OCH_3), 3.87 (s, 3 H, 3-OCH_3), 5.50 (br s, 1 H, NH), 6.78-6.87 (m, 3 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.8 (2 × CH_3), 40.9 (CH_2), 55.7 (2 × CH_3), 111.2 (CH), 112.3 (CH), 121.6 (CH), 127.8 (Cq), 147.9 (Cq), 148.9 (Cq), 167.2 (Cq) ; Mass (EI) m/z 222 ($M^{+\bullet}$, 75%), 207 (50%), 177 (45%), 152 (50%), 151 (50%), 71 (100%) . HRMS Calcd. for $C_{12}H_{18}N_2O_2$: 222.136826. Found: 222.136823 . The level of ethanol contamination still remaining was evident from the elemental analysis: Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.8; H, 8.2; N, 12.6. Found: C, 63.75; H, 8.2; N, 12.0 %.
8. Methanol was distilled from magnesium methoxide .
9. Sodium borohydride was obtained from Aldrich Chemical Company, Inc. and used without further purification.
10. The product exhibits the following spectral properties, in agreement with literature data:[3] IR (film) ν cm^{-1}: 2810 (ν_{N-Me}), 2750 (ν_{N-Me}) ; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.28 (s, 6 H, N-CH_3), 2.46-2.58 (m, 2 H, Ar-CH_2), 2.70-2.82 (m, 2 H, N-CH_2), 3.85 (s, 3 H, 4-OCH_3), 3.89 (s, 3 H, 3-OCH_3), 6.72-6.82 (m, 3 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.0 (CH_2), 45.5 (2 × CH_3), 55.8 (CH_3), 55.9 (CH_3), 61.7 (CH_2), 111.3 (CH), 111.9 (CH), 120.5 (CH), 133.0 (Cq), 147.3 (Cq), 148.8 (Cq) ; Mass (EI) m/z 209 ($M^{+\bullet}$, 6%), 151 (8%), 58 (100%) . HRMS. Calcd. for $C_{12}H_{19}NO_2$: 209.1417. Found: 209.1419 . The checkers could not obtain satisfactory elemental analyses. The freshly prepared sample was >95% pure as shown by NMR. Further distillation (through a 5"-Vigreux column or Kugelrohr apparatus) afforded material, bp 96-98°C/0.1 mm, of >98% purity [Hewlett-Packard 5890 series II GC, capillary column SGE 25QC3BP5-0.5, 5% phenylpolysiloxane, temperature gradient 100°C (1 min), 20°C/min, 250°C (5 min)] with 85% mass recovery. After 3 months storage the purity of material dropped to ca. 90%. The hydrochloride has mp 195-196°C (submitters reported 197°C) (from ethanol/diethyl ether) (lit.,[3] 196-197°C).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academic Press; Washington, DC, 1995.

3. Discussion

The procedure described above illustrates a general, two-step method for the preparation of secondary or tertiary amines. It can be considered as a reductive N-alkylation of a nitrile or an N-monoalkylation of a primary or secondary amine. The first step in the procedure involves direct addition of an aliphatic amine to a nitrile promoted by a stoichiometric amount of cuprous chloride, as fully described recently.[4] This method may be used with a large variety of nitriles and primary or secondary aliphatic amines. The nitrile itself may be used as solvent (acetonitrile, benzonitrile). In the case of a primary amine, substrate stoichiometry must be adapted to obtain selectively either the N-monosubstituted amidine [1 eq amine, 1.2 eq Cu(I)Cl in acetonitrile] or the N,N-disubstituted amidine [4 eq amine, 1 eq Cu(I)Cl, 1 eq acetonitrile in alcohol or DMSO].[4]

As summarized in Table I, this strategy is applicable to the synthesis of many secondary or tertiary amines. It must, however, be noted that some arylamines are not sufficiently nucleophilic to be used in this synthesis. For example, anilines do not react under these conditions, although 2-aminopyridine does. The functionality in some amines is incompatible with copper; thus those amines that chelate with copper do not react with nitriles.

The amidine reduction by sodium borohydride is efficient, although longer reaction times (up to 15 hr) may be required depending on the amine used. The mode of decomposition of the intermediate geminal diamine is known to favor preferential expulsion of the less basic amine leaving group.[5] In fact, the alkylated amine was obtained with a selectivity higher than 80% (up to 99%) with all the compounds the submitters tested (see Table I).

The only comparable transformation of nitriles available in the literature is the reduction over palladium with excess dimethylamine in methanol . This reaction requires a large amount of catalyst

(one-quarter or more of the weight of nitrile).[6]

The common synthetic route[3] to N,N-dimethylhomoveratrylamine involves acyl chloride formation from (3,4-dimethoxyphenyl)acetic acid with thionyl chloride (84%),[7] followed by amide formation with dimethylamine (99%),[8] and reduction with lithium aluminum hydride (71%).[9] The procedure provides N,N-dimethylhomoveratrylamine in 59% overall yield, requires three steps and more expensive substrates and reagents.

Another classical alternative is the Eschweiler-Clarke procedure, that involves drastic experimental conditions in which a solution of 88% aqueous formic acid , 35% aqueous formaldehyde and the corresponding primary amine in dimethylformamide is refluxed for 5 hr.[10] Moreover, only methylated amines can be prepared.

Compared with these methods, the reductive N-alkylation of nitriles is much more efficient and practical. The starting materials and reagents are cheaper, and only two steps are involved that proceed in a higher overall yield. Reductive N-alkylation affords, without any chromatographic separation, a product of high purity.

References and Notes

1. Guilhem Rousselet is a graduate student of the "Institut de Formation Supérieure Biomédicale" (IFSBM), Institut Gustave Roussy (Villejuif, France).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N,N-Dimethylhomoveratrylamine:
Benzeneethanamine, 3,4-dimethoxy-N,N-dimethyl-(9); (3490-05-9)

(3,4-Dimethoxyphenyl)acetonitrile:
Acetonitrile, (3,4-dimethoxyphenyl)- (8);
Benzeneacetonitrile, 3,4-dimethoxy- (9); (93-17-4)

Copper(I) chloride:
Copper chloride (8,9); (7758-89-6)

Dimethylamine (8);
Methanamine, N-methyl- (9); (124-40-3)

Sodium borohydride:
Borate (1-), tetrahydro-, sodium- (8,9); (16940-66-2)

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