Organic Syntheses

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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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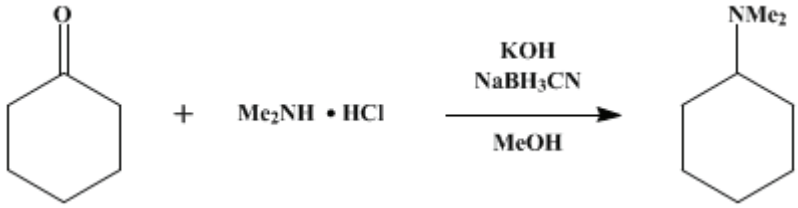
REDUCTIVE AMINATION WITH SODIUM CYANOBOROHYDRIDE: *N,N*-DIMETHYLCYCLOHEXYLAMINE

[Cyclohexanamine, 4,4-dimethyl-]



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Checked by K. Abe and S. Masamune.

1. Procedure

A solution of 21.4 g. (0.262 mole) of dimethylamine hydrochloride in 150 ml. of methanol is prepared in a 500-ml., round-bottomed flask. Potassium hydroxide (4 g.) is added in one portion to the magnetically stirred solution (Note 1). When the pellets are completely dissolved, 19.6 g. (0.200 mole) of cyclohexanone is added in one portion. The resulting suspension is stirred at room temperature for 15 minutes before a solution of 4.75 g. (0.0754 mole) of sodium cyanoborohydride (Note 2) and (Note 3) in 50 ml. of methanol is added dropwise over 30 minutes to the stirred suspension. After the addition is complete, the suspension is stirred for 30 minutes. Potassium hydroxide (15 g.) is then added, and stirring is continued until the pellets are completely dissolved. The reaction mixture is filtered with suction, and the volume of the filtrate is reduced to approximately 50 ml. with a rotary evaporator while the bath temperature is kept below 45° (Note 4) and (Note 5). To this concentrate is added 10 ml. of water and 25 ml. of saturated aqueous sodium chloride, and the layers are separated. The aqueous layer is extracted with two 50-ml. portions of diethyl ether. The organic layer previously separated and the ethereal extracts are combined and extracted with three 20-ml. portions of 6 *M* hydrochloric acid (Note 6). The combined acid layers are saturated with sodium chloride and extracted with four 30-ml. portions of ether (Note 7). The aqueous solution is cooled to 0° in an ice bath and brought to pH > 12 by addition of potassium hydroxide pellets to the stirred solution (Note 8) and (Note 9). The layers are separated, and the aqueous layer is extracted with two 40-ml. portions of ether. The combined organic layers are washed with 10 ml. of saturated aqueous sodium chloride, dried over anhydrous potassium carbonate, and freed of ether with a rotary evaporator (Note 4). This crude product is fractionated through a 15-cm. Vigreux column (Note 10). After 1–3 g. of a forerun, b.p. 144–155° (Note 11) is separated, the fraction boiling at 156–159° is collected, yielding 13.3–13.7 g. (52–54%) of *N,N*-dimethylcyclohexylamine, n_D^{25} 1.4521 (Note 12).

2. Notes

1. Precipitation of potassium chloride begins immediately; the presence of this solid does not interfere with the reaction, and removal by filtration will result in loss of dimethylamine.
2. Sodium cyanoborohydride is available as a pale brown solid from Alfa Inorganics, Inc.
3. The commercially available material can be used without further purification. Use of material purified by the published procedure[2] gives a less colored crude product, but makes no improvement in yield or purity of the final product.
4. Since the product boils at 75° (15 mm.), care should be exercised to prevent loss of material in the evaporation process.
5. It is normal for additional potassium chloride to precipitate as the evaporation continues.
6. *Caution! This addition of hydrochloric acid into a separatory funnel occurs with considerable heat evolution, causing the ether to boil. The initial addition must be carried out with gentle swirling and cooling.*

7. GC analysis shows that the ethereal extract contains solely cyclohexanol (>98%).
8. The aqueous layer in this step is saturated with ether, and the addition of potassium hydroxide must be carried out gradually to prevent the contents of the flask from boiling over.
9. Copious amounts of potassium chloride precipitate during this addition. It is not necessary to remove the salt by filtration before the ether extraction.
10. A still pot with a volume of at least 100-ml. should be used for the distillation, since foaming occurs as the distillation proceeds.
11. On a 2-m. GC column packed with 10% Apiezon L and heated to 100°, the retention times for *N,N*-dimethylcyclohexylamine and cyclohexanol are 15 and 4 minutes, respectively. The composition of this forerun is 80–85% of the amine and 20–15% of the alcohol.
12. GC analysis of the product shows that the product is at least 99.2% pure and is contaminated only with trace amounts of cyclohexanol. The submitter reported a 62–69% yield (15.7–17.5 g.) using the indicated scale.

3. Discussion

N,N-Dimethylcyclohexylamine has been prepared by catalytic reductive alkylation[3,4] and by the Leuckart reaction.[5] The present method is experimentally simple, requires no special apparatus, and is generally applicable to the synthesis of a variety of primary, secondary, and tertiary amines, as illustrated in Table I.

TABLE I
REPRESENTATIVE REDUCTIVE AMINATIONS WITH $NaBH_3CN$[2]

Compound	Amine	Product	Yield, %
Cyclohexanone	NH_3	Cyclohexylamine	45
Cyclohexanone	CH_3NH_2	*N*-Methylcyclohexylamine	41
Cyclohexanone	CH_3NHCH_3	*N,N*-Dimethylcyclohexylamine	53
Acetophenone	NH_3	α-Phenylethylamine	77
Acetophenone	CH_3NH_2	*N*-Methylphenethylamine	78
Isobutyraldehyde	$PhNH_2$	*N*-Isobutylaniline	78
Glutaraldehyde	CH_3NH_2	*N*-Methylpiperidine	43

The submitter has found that use of sodium borohydride instead of sodium cyanoborohydride in the present procedure results in the almost exclusive formation of cyclohexanol with less than 3% of basic material.

References and Notes

1. Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455.
2. R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).
3. J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5030 (1951).
4. W. S. Emerson, *Org. React.*, **4**, 174 (1948).
5. R. D. Bach, *J. Org. Chem.*, **33**, 1647 (1968).

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

NH_3

CH_3NH_2

$PhNH_2$

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

Cyclohexanol (108-93-0)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

Acetophenone (98-86-2)

potassium hydroxide (1310-58-3)

dimethylamine (124-40-3)

dimethylamine hydrochloride (506-59-2)

potassium chloride (7447-40-7)

cyclohexylamine (108-91-8)

isobutyraldehyde (78-84-2)

α-Phenylethylamine (3886-69-9)

N-Methylphenethylamine (589-08-2)

glutaraldehyde (111-30-8)

N-Methylpiperidine (626-67-5)

sodium borohydride (16940-66-2)

sodium cyanoborohydride (25895-60-7)

Cyclohexanamine, 4,4-dimethyl-

N,N-Dimethylcyclohexylamine (98-94-2)

N-Methylcyclohexylamine (100-60-7)

N-Isobutylaniline