Reductive Amination of Ketones and Aldehydes at the Mercury-Cathode

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Secondary Amines are prepared in good yields by potential-controlled reduction of aldehydes or ketones at a mercury cathode in an aqueous solution containing a primary amine. For cyclic ketones, high diastereoselectivities are obtained in some cases.

Secondary amines can be prepared by reductive amination of carbonyl compounds. In aqueous medium, an aldehyde or ketone and a primary amine equilibrate to the corresponding Schiff base. Because of its lower reduction potential compared with the aldehye or ketone, the Schiff base may be reduced selectively to yield a secondary amine after electron- and proton-transfers. In general, these reductions are carried out using the expensive sodium cyanoborohydride[1] or hydrogen in presence of platinum, palladium or nickel catalysts.[2] The latter method has the disadvantage of being able to hydrogenate other groups such as double bonds or aromatic rings; furthermore, most catalysts cannot be used in the presence of sulphur-containing substrates.[2]

The electrochemical reduction of cyclohexanone in presence of methylamine at a mercury cathode to yield *N*-methylcyclohexylamine has been reported.[3] This single example prompted us to investigate the conversion of a variety of aldehydes and ketones to secondary amines (Table 1).

All reductions were carried out with a 10–15 fold excess of the primary amine, half neutralized with hydrochloric acid to give a buffered solution of pH 10–11. Ethanol was added in some cases to improve the solubility of the aldehyde or ketone. After simple work-up, pure products were obtained in good yields. Only in the reaction of hexanal with ethylamine to form *N*-ethylhexylamine (**1**), was a by-product, 5-(*N*-ethylaminomethyl)-6-undecanol, formed in 10% yield, probably by autocondensation of the aldehyde and amination of the resultant aldol. Double bonds and aromatic rings are not attacked under the applied potential-controlled conditions.

Reductive amination of monosubstituted cyclohexanones and bicyclo[2.2.1]heptan-2-one results in a mixture of *cis/trans*- or *endo/exo*-isomers; their ratios are given in Table 2. It is obvious that there is an increase in diastereoselectivity when the bulkier isopropylamine is used instead of methylamine. Thermodynamically favored *trans*-amines are obtained from cyclohexanones.

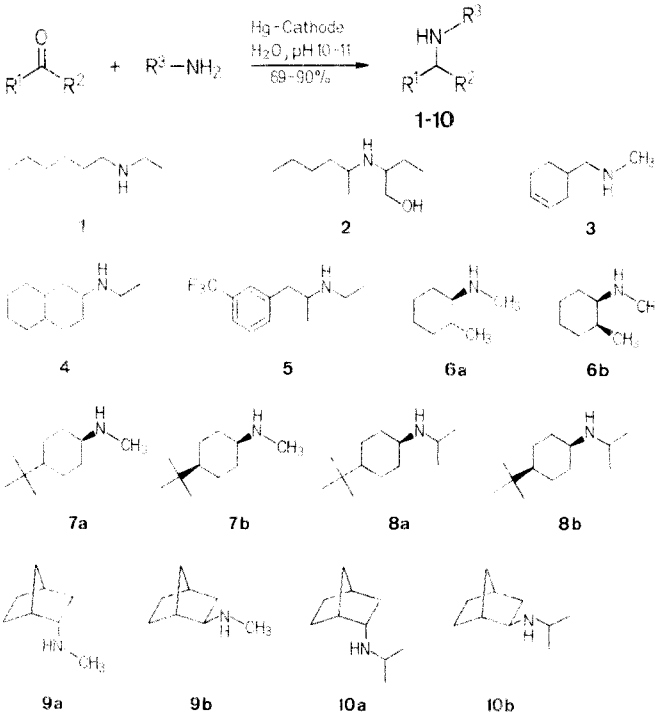

Table 1. Preparation of Secondary Amines by Cathodic Reductive Amination

Aldehyde or Ketone	Amine[a]	Reduction-Potential[b]	Product	Yield[c] (%)
Hexanal	Ethylamine[d]	−1.57 V	**1**	69[e]
2-Hexanone	(*R*)-2-Amino-1-butanol	−1.80 V	**2**	72
3-Cyclohexene-1-carboxaldehyde	Methylamine[d]	−1.55 V	**3**	90
2-Decafone[f]	Ethylamine[d]	−1.65 V	**4**	83
1-[3-(Trifluoromethyl)-phenyl]-2-propanone	Ethylamine[d]	−1.75 V	**5**	87
2-Methylcyclohexanone	Methylamine	−1.72 V	**6**	80
4-*t*-Butylcyclohexanone	Methylamine	−1.65 V	**7**	73
4-*t*-Butylcyclohexanone	i-Propylamine[d]	−1.68 V	**8**	81
Bicyclo[2.2.1]heptan-2-one	Methylamine	−1.66 V	**9**	80
Bicyclo[2.2.1]heptan-2-one	i-Propylamine[d]	−1.90 V	**10**	76

[a] 150 mmol in 100 mL water, half-neutralized with hydrochloric acid.
[b] v.s. SCE.
[c] Yield of isolated product, purity checked by GLC.
[d] 50% aqueous ethanol used instead of water.
[e] Purified by Kugelrohr distillation (75 °C oven temperature, 20 mbar).
[f] Mixture *cis/trans* (4:1).

while bicyclo[2.2.1]heptan-2-one leads to an excess of *endo*-product. A similar selectivity was found for the reduction of ketones with dissolving metals in protic media.[4] Reduction of 2-hexanone in the presence of (*R*)-2-amino-1-butanol gave only poor diastereoselectivity (1.1:1); no further assignment of the isomers was made.

Table 2. Diastereoselectivity of Cathodic Reductive Amination

Isomer *trans/endo*	*cis/exo*	Ratio a : b[a]
6a	**6b**	2 : 1
7a	**7b**	14 : 1
8a	**8b**	> 20 : 1[b]
9a	**9b**	3.5 : 1
10a	**10b**	> 20 : 1[b]

[a] Detected by GLC (4.7 m glass column, ⌀ 2 mm, 10% CW 20M).
[b] No **b** could be detected by GLC and NMR.

The scope of the reported reaction is limited by the solubility of the aldehyde or ketone in the aqueous electrolyte, even though in some cases electrolysis of an emulsion was successful. Furthermore, sterically hindered substrates such as camphor or *tert*-butylamine could not be converted, probably because the concentrations of Schiff base in the equilibrium are too small.

In summary, cathodic reductive amination may be considered as a good alternative to existing methods for the preparation of secondary amines, because of its high chemoselectivity, good yields, simple work-up and low reagent costs.

N-Ethyl-1-methyl-2-(3-trifluoromethylphenyl)ethylamine (5); Typical Procedure:

A solution of 1-(3-trifluoromethylphenyl)-2-propanone (2.02 g, 10 mmol) in an electrolyte consisting of 70% aqueous ethylamine (10 mL, 150 mmol), 2 N HCl (37.5 mL) and EtOH (50 mL) is purged with N_2 and electrolyzed at 10°C with a controlled potential of −1.75 V (vs. SCE) in a divided cell with a mercury pool as working electrode and a platinum anode. The current drops from an initial 50 mA to 2–3 mA when the necessary 1960 As have been consumed. Then the electrolyte is acidified by adding 2 N HCl (to pH 1). After the EtOH is removed under reduced pressure, the aqueous solution is extracted with ether (2 × 50 mL) and NaOH is added (to pH 14). The alkaline solution is extracted with ether (3 × 50 mL), and the combined organic phase is dried ($MgSO_4$). Removal of the solvent under reduced pressure gives **5**; yield: 2.0 g (87%).

N-Ethylhexylamine (**1**): n_D^{20} = 1.4208 (Lit.[5] 1.4206).

MS (70 eV): *m/z* (%) = 129 (M^+, 5); 114 (1); 59 (4); 58 (100); 44 (12); 43 (6); 41 (5).

^{1}H-NMR ($CDCl_3$/TMS, 60 MHz): δ = 0.7–1.7 (m, 14 H); 1.85 (s, 1 H, NH); 2.4–3.9 (m, 4 H, NCH_2).

2-(1-Methylpentylamino)-1-butanol (**2**): n_D^{20} = 1.4495.

$C_{10}H_{23}NO$ (173.3) calc. C 69.31 H 13.38 N 8.08; found 69.45 13.44 8.01

MS (70 eV): *m/z* (%) = 158 (8); 142 (80); 126 (10); 116 (30); 98 (12); 84 (10); 70 (15); 60 (14); 58 (100).

IR (film): ν = 3000–3600, 2970, 2930, 2870, 1460, 1380, 1050 cm^{-1}.

^{1}H-NMR (CD_3OD/TMS, 300 MHz): δ = 0.9 (m, 6 H, CH_3-5', CH_3-4); 1.0 (d, 3 H, J = 6.2 Hz, CH_3-C-1'); 1.4 (m, 8 H, CH_2-3, 2', 3', 4'); 2.0 (br, 1 H, OH); 2.7 (m, 2 H, CH_2-1); 3.2 (m, 1 H, CH-1'); 3.6 (m, 1 H, CH-2).

N-Methyl-(3-cyclohexenylmethyl)amine (**3**): n_D^{20} = 1.4717.

MS (70 eV): *m/z* (%): 125 (M^+, 4); 79 (5); 44 (100).

^{1}H-NMR ($CDCl_3$/TMS, 60 MHz)[6]: δ = 1.4–2.3 (m, 8 H, H_{cyc}, NH); 2.4 (m, 5 H, NCH_3, NCH_2); 5.7 (m, 2 H, C=CH).

N-Ethyl-3-bicyclo[4.4.0]decylamine (**4**): n_D^{20} = 1.4869.

$C_{12}H_{23}N$ (181.3) calc. C 79.49 H 12.79 N 7.72; found 79.35 12.71 7.67

MS (70 eV): *m/z* (%) = 181 (M^+, 8); 110 (22); 84 (100); 71 (14); 56 (14); 41 (13).

IR (film): ν = 3250, 2800–2950, 1460, 1440, 1370, 1300, 1260, 1110–1140, 970, 955, 700–730 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS, 300 MHz): δ = 0.8–2.0 (m, 17 H, H-1, H-2, H-4–H-10, NH); 1.11 (t, 3 H, J = 7.2 Hz, CH_3); 2.47 (m, 0.8 H, H-3_{ax}); 2.68 (q, 2 H, J = 7.2 Hz, NCH_2).

N-Ethyl-1-methyl-2-(3-trifluoromethylphenyl)ethylamine (**5**): n_D^{20} = 1.4540.

MS (70 eV) *m/z* (%) = 230 (2); 216 (3); 159 (9); 119 (2); 109 (4); 73 (6); 72 (100); 56 (4); 44 (34).

^{1}H-NMR ($CDCl_3$/TMS, 300 MHz): δ = 1.1 (m, 6 H, CH_3); 2.5–3.0 (m, 5 H, NCH, N=CH_2, $ArCH_2$); 7.4 (m, 5 H, H_{arom}).

Hydrochloride of **5**: m.p. 168°C (Lit.[7] m.p. 166°C).

trans- and cis-N-Methyl-(2-methylcyclohexyl)amine (**6a** *and* **6b**): n_D^{20} = 1.4565.

MS (70 eV): *m/z* (%) = 128 (3); 127 (M^+, 14); 84 (30); 70 (100); 57 (18); 44 (12); 42 (11).

^{1}H-NMR ($CDCl_3$/TMS, 300 MHz):[8] **6a** δ = 0.94–1.77 (m, 9 H, H-2–H-6); 0.95 (d, 3 H, J = 7.1 Hz, CCH_3); 1.94 (m, 1 H, NH); 2.01 (m, 1 H, CHN); 2.40 (s, 3 H, NCH_3). **6b** δ = 0.89 (d, 3 H, J = 7.1 Hz, CCH_3); 0.94–1.77 (m, 9 H, H-2–H-6); 1.94 (m, 1 H, NH); 2.38 (s, 3 H, NCH_3); 2.47 (m, 1 H, CHN).

^{13}C-NMR (CD_3OD): **6a** δ = 19.5 (2-CH_3); 26.4 (C-5); 27.1 (C-4); 31.6 (C-6); 33.1 (NCH_3); 35.7 (C-3); 38.3 (C-2); 65.6 (C-1). **6b** δ = 13.2 (2-CH_3); 22.5; 25.4; 27.8; 32.6; 33.1 (NCH_3); 33.6 (C-2); 61.8 (C-1).

trans- and cis-N-Methyl-(4-tert-butylcyclohexyl)amine (**7a** *and* **7b**): n_D^{20} = 1.4632.

MS (70 eV): *m/z* (%) = 169 (M^+, 4); 154 (1); 123 (3); 112 (3); 98 (4); 81 (5); 70 (100); 57 (20); 41 (7).

^{1}H-NMR ($CDCl_3$/TMS, 300 MHz):[9] **7a** δ = 0.84 (s, 3 H, $C(CH_3)_3$); 0.92–1.97 (m, 9 H, H-2–H-6); 1.99 (m, 1 H, H-1); 2.23 (m, 1 H, NH); 2.41 (s, 9 H, NCH_3).

^{13}C-NMR (CD_3OD):[10] **7a** δ = 27.2 (C-3); 28.1 ($C(\underline{C}H_3)_3$); 33.1 ($\underline{C}(CH_3)_3$); 33.3 ($N-CH_3$); 33.8 (C-2); 49.3 (C-4); 59.9 (C-1).

trans-N-Isopropyl-(4-tert-butylcyclohexyl)amine (**8a**): n_D^{20} = 1.4570.

MS (70 eV): *m/z* (%) 197 (M^+,2); 182 (10); 126 (4); 98 (100); 74 (34); 59 (46); 45 (48); 44 (44).

^{1}H-NMR ($CDCl_3$/TMS, 300 MHz):[11] δ = 0.84 (s, 9 H, $C(CH_3)_3$); 0.89–1.95 (m, 9 H, H-2–H-6); 1.05 (d, 6 H, J = 6.3 Hz, $C(CH_3)_2$); 1.97 (m, 1 H, H-1); 2.44 (m, 1 H, NH); 2.98 (sept, 1 H, J = 6.3 Hz, $C\underline{H}(CH_3)_2$).

^{13}C-NMR ($CDCl_3$): δ = 23.1 ($C(\underline{C}H_3)$; 25.9 (C-3); 27.2 ($CH(\underline{C}H_3)_2$). 31.9 ($\underline{C}(CH_3)_3$); 34.1 (C-2); 44.4 ($\underline{C}H(CH_3)_2$); 47.5 (C-4); 53.5 (C-1).

endo- and exo-N-Methyl-2-bicyclo[2.2.1]heptylamine (**9a** *and* **9b**): n_D^{20} = 1.4759 ($^{12}n_D^{25}$ = 1.4731).

MS (70 eV): *m/z* (%) = 126 (10); 125 (M^+, 85); 124 (16); 96 (90); 94 (40); 84 (60); 70 (90); 57 (100); 44 (100); 42 (64).

^{1}H-NMR ($CDCl_3$/TMS, 300 MHz): **9a** δ = 0.66 (ddd, 1 H, J = 14.7 Hz, 4.8 Hz, 3.3 Hz),3-H_{endo}; 1.04–1.70 (m, 7 H, NH, H-5, H-6, H-7); 1.89 (dddd, 1 H, J = 14.7 Hz, 12.1 Hz, 5.4 Hz, 3.5 Hz, 3-H_{exo}); 2.16 (m, 1 H, H-4); 2.28 (m, 1 H, H-1); 2.34 (s, 3 H, NCH_3); 2.91 (ddd, 1 H, J = 12.1 Hz, 4.8 Hz, 4.8 Hz, H-2).

^{13}C-NMR ($CDCl_3$): **9a** δ = 20.0 (C-6); 29.5 (C-5); 34.5 (NCH_3); 36.2 (C-4); 37.5 (C-7); 37.6 (C-3); 38.7 (C-1); 60.1 (C-2). **9b** δ = 26.4 (C-6); 28.1 (C-5); 33.9 (NCH_3); 34.3 (C-7); 35.1 (C-4); 39.3 (C-3); 39.8 (C-1); 63.4 (C-2).

Hydrochloride of **9**: m.p. 199°C (Lit.[13] m.p. 199–200°C).

endo-N-Isopropyl-2-bicyclo[2.2.1]heptylamine (**10a**): n_D^{20} = 1.4679.

$C_{10}H_{19}N$ (153.3) calc. C 78.37 H 12.50 N 9.14; found 78.38 12.58 9.28.

MS (70 eV): *m/z* (%) = 153 (M^+, 42); 138 (100); 124 (32); 112 (32); 110 (46); 98 (40); 95 (38); 85 (36); 72 (60); 70 (71); 67 (34); 58 (40); 56 (34); 44 (100); 43 (44); 41 (45).

IR (film): ν = 2950, 2850, 1465, 1445, 1375, 1360, 1340, 1320, 1170, 1120, 1085, 1055, 670–700 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS, 300 MHz): δ = 0.61 (ddd, 1 H, J = 12.5 Hz, 4.6 Hz, 2.7 Hz, H-3_{endo}); 1.04 (2 d, 6 H, J = 6.3 Hz, $CH(CH_3)_2$); 1.1–1.65

(m, 7H, NH, H-5, H-6, H-7); 1.95 (dddd, 1H, J = 12.5 Hz, 10.8 Hz, 4.8 Hz, 2.9 Hz, H-3_{exo}); 2.14 (m, H-4); 2.27 (m, 1H, H-1); 2.77 (m, 1H, C<u>H</u>$(CH_3)_2$); 3.14 (dddd, 1H, J = 10.8 Hz, 4.6 Hz, 4.3 Hz, 1.4 Hz, H-2).

^{13}C-NMR ($CDCl_3$): δ = 20.3 (C-6); 22.0, 23.6 (CH(<u>C</u>$H_3)_2$); 29.9 (C-5); 36.3 (C-4); 37.8 (C-7); 38.4 (C-3); 39.1 (C-1); 46.2 (<u>C</u>H$(CH_3)_2$); 56.3 (C-2).

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