

Facile Reduction of Carboxylic Acids, Esters, Acid Chlorides, Amides and Nitriles to Alcohols or Amines Using $\text{NaBH}_4/\text{BF}_3\cdot\text{Et}_2\text{O}$

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The reduction of aldehydes, ketones and carboxylic acid derivatives to the corresponding alcohols or amines is an important transformation in synthetic organic chemistry. Lithium aluminum hydride and boranes are amongst the most commonly used reagents for this purposes.^{1,12} These highly reactive hydrides, however, have severe limitations such as the need for anhydrous solvents, hazardous handling, incompatibility with other functionality, and incomplete reaction. On the other hand, sodium borohydride is more convenient, less expensive, and safer to use, but does not reduce carboxylic acid derivatives, such as nitriles, esters, lactones and amides.¹³ To broaden the utility of NaBH_4 , its reactivity has been enhanced with various additives^{13,14} including CeCl_3 ,¹⁵ CaCl_2 ,¹⁶ ZnCl_2 ,¹⁷ CuSO_4 ,¹⁸ I_2 ,¹⁹ $\text{BH}_3\cdot\text{Me}_2\text{S}$,²⁰ sulfuric acid,²¹ catechol,²² trifluoroacetic acid,²² sulfur,²³ ZrCl_4 ,²⁴ Et_2SeBr_2 ,²⁵ methanesulfonic acid,²⁶ TiCl_4 ,²⁶ Me_3SiCl ,²⁷ SnCl_2 ,²⁸ MnCl_2 ,²⁹ $\text{SmCpCl}_2(\text{THF})_3$,³⁰ $\text{ErCpCl}_2(\text{THF})_3$,³⁰ Amberlyst-15(H^+),³¹ Al_2O_3 ,³² (*S*)-lactic acid derivatives,³³ (*L*)-tartaric acid,³⁴ cobalt complex,³⁵ (+)-*N*-dodecyl-*N*-methyl ephedrenium salt,³⁶ lanthanoid complexes,³⁷ Cu^{2+} -clay/(*S*)-proline,³⁸ a chiral surfactant,³⁹ and 3,4,5-trifluorophenylboronic acid.⁴⁰ Nevertheless, research in this field is still very active even now.¹⁴ We report herein that carboxylic acids, esters, acid chlorides, amides and nitriles can be reduced directly to the corresponding alcohols or amines using $\text{NaBH}_4/\text{BF}_3\cdot\text{Et}_2\text{O}$ in THF.

In continuation of our studies on the reactivity of sodium borohydride toward carboxylic acid derivatives, we found that reduction of benzoic acid by $\text{NaBH}_4/\text{BF}_3\cdot\text{Et}_2\text{O}$ in THF afforded benzyl alcohol in excellent yield. According to the literature,³ treatment of sodium borohydride with boron trifluoride etherate afford borane. Although borane is a good reducing agent, it has some drawbacks, such as low boiling points, low spontaneous ignition temperature and toxicity. Thus, $\text{NaBH}_4/\text{BF}_3\cdot\text{Et}_2\text{O}$ system is a useful borane source. Pettit, *et al.*⁴¹ also reported the reduction of *tert*-butyl 5 α -pregnane-20*S*-carboxylate to 20*S*-*tert*-butoxymethylene-5 α -pregnane using this system. Since the reduction of carboxylic acid derivatives, however, by this binary system $\text{NaBH}_4/\text{BF}_3\cdot\text{Et}_2\text{O}$ has not been reported, a systematic examination of its scope as a reducing agent using a variety of carboxylic acid derivatives was deemed warranted. The results are summarized in Table 1.

In a typical procedure, $\text{BF}_3\cdot\text{Et}_2\text{O}$ in THF is added slowly to a THF solution of substrate and NaBH_4 , and then heated to reflux with stirring until the substrate disappears. After cooling to 0 °C, the reaction is carefully quenched with water and the product is isolated by organic solvent extraction. The carboxylic acids (entries 1-9), esters (entries 11 and 12) and an acid chloride (entry 13) all furnished the corresponding alcohols in excellent yields. In contrast, reduction of muchochloric acid (entry 10) gave rise to 2,3-dichloro-5*H*-furan-2-one (87%) accompanied by a minor amount of 2,3-dichlorobuten-1,4-diol (7.4%). Although generally more difficult to reduce, amides (entries 14 and 15) and a nitrile (entry 16) also efficiently evolved the expected amines. The reduction rates for the latter, however, were slower than the rates for carboxylic acids and carboxylate derivatives.






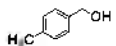






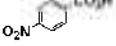
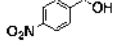














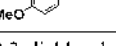
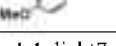


In conclusion, $\text{NaBH}_4/\text{BF}_3\cdot\text{Et}_2\text{O}$ is an inexpensive and highly versatile reducing system for a wide variety of carbonyls, acid chlorides, carboxylic acids, esters, amides and nitriles.

Experimental Section

General Remarks. TLC was performed on SiO_2 (silica gel 60 F254, Merck). The spots were located by UV light. Column chromatography was carried out on SiO_2 (silica gel 60, 70-230 mesh). Melting points were determined with a Thomas-Hoover capillary apparatus and were uncorrected. ¹H and ¹³C NMR spectra were obtained on a Bruker FT NMR-DRX 500 or Varian Inova 500 spectrometer and with chemical shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). IR spectra were obtained on a Hitachi 270-50 or Mattson Genesis Series FT-IR spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C.

General Procedure: Reduction of Carboxylic acids and Carboxylate Derivatives. A solution of $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.0065 mmol) in THF (15 mL) was added slowly to a room temperature solution of NaBH_4 (0.015 mmol) and carboxylic acids or carboxylate derivatives (0.01 mmol) in THF (25 mL) under an inert atmosphere. The mixture was heated to reflux until TLC monitoring showed complete consumption of the substrate. The reaction mixture was cooled to 0 °C, quenched with water (caution: vigorous gas evolution) keeping the

Table 1. NaBH₄/BF₃·Et₂O reductions of carboxylic acids, esters, acid chloride, amides and nitrile

Entry	Substrate	Product	Time (hr)	Yield (%)	Entry	Substrate	Product	Time (hr)	Yield (%)
1			1	97	9			1	97
2			1	95	10			1.5	87 ^a
3			1	93	11			3	94
4			5	94	12			1.5	76
5			1	95	13			1	96
6			0.5	94	14			8	78
7			1.5	98	15			8	89
8			0.5	96	16			5	84

^aBy-product is 2,3-dichlorobut-2-ene-1,4-diol (7.4%).

temperature = 10 °C. After 10 min, the THF was removed under reduced pressure, CH₂Cl₂ (or Et₂O) was added, and the stirring was continued for another 1 h. The organic layer was separated, washed with brine, dried over MgSO₄, and the solvent was removed under reduced pressure. Purification of the residue by SiO₂ chromatography gave pure alcohol in the indicated yield (Table 1).

Benzyl alcohol (entry 1 and 13): colorless liquid. IR (KBr): 3360 (-OH) cm⁻¹. ¹H NMR (CDCl₃): δ = 4.20 (s, 1H, D₂O exchangeable), 4.43 (s, 2H), 7.15-7.25 (m, 5H). ¹³C NMR (CDCl₃): δ = 64.04, 126.57, 126.91, 127.96, 140.55. Anal. Calcd for C₇H₈O: C, 77.75; H, 7.46. Found: C, 77.73; H, 7.41.

4-Methylbenzyl alcohol (entry 2): mp. 60-61 °C. IR (KBr): 3354 (-OH) cm⁻¹. ¹H NMR (CDCl₃): δ = 2.32 (s, 3H), 2.49 (t, 1H, D₂O exchangeable), 4.13 (s, 2H), 7.15-7.25 (m, 5H). ¹³C NMR (CDCl₃): δ = 21.10, 64.96, 127.00, 129.10, 137.15, 137.88. Anal. Calcd for C₈H₁₀O: C, 78.65; H, 8.25. Found: C, 78.67; H, 8.22.

2-Hydroxybenzyl alcohol (entry 3): mp. 81-83 °C. IR (KBr): 3450 (-OH), 3172 (-OH) cm⁻¹. ¹H NMR (CDCl₃): δ = 2.54 (bs, 1H, D₂O exchangeable), 4.83 (s, 2H), 6.82-6.88 (m, 2H), 7.01-7.04 (m, 1H), 7.17-7.25 (m, 1H), 7.35 (bs, 1H, D₂O exchangeable). ¹³C NMR (CDCl₃): δ = 64.52, 116.50, 120.13, 124.71, 127.90, 129.51, 155.97. Anal. Calcd for C₇H₈O₂: C, 67.73; H, 6.50. Found: C, 67.73; H, 6.48.

4-Nitrobenzyl alcohol (entry 4): mp. 92-93 °C. IR (KBr): 3512 (-OH) cm⁻¹. ¹H NMR (CDCl₃): δ = 2.72 (bs, 1H, D₂O exchangeable), 4.81 (s, 2H), 7.51 (d, 2H, *J* = 8.70 Hz), 8.16 (d, 2H, *J* = 9.30 Hz). ¹³C NMR (CDCl₃): δ = 63.77, 123.57, 126.89, 147.07, 148.32. Anal. Calcd for C₇H₇NO₃: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.88; H, 4.59; N, 9.12.

4-Chlorobenzyl alcohol (entry 5): colorless liquid. IR (KBr): 3364 cm⁻¹. ¹H NMR (CDCl₃): δ = 2.93 (bs, 1H, D₂O exchangeable), 4.55 (s, 2H), 7.21-7.31 (m, 4H). ¹³C NMR (CDCl₃): δ = 64.19, 128.21, 128.56, 128.58, 139.13. Anal.

Calcd for C₇H₇ClO: C, 58.97; H, 4.95. Found: C, 58.95; H, 4.94.

(Pyridin-3-yl)methanol (entry 6): colorless liquid. IR (KBr): 3280 cm⁻¹. ¹H NMR (CDCl₃): δ = 4.79 (s, 2H), 5.76 (bs, 1H, D₂O exchangeable), 7.31-7.46 (m, 1H), 7.76-7.91 (m, 1H), 8.37-8.41 (m, 1H), 8.52 (s, 1H). ¹³C NMR (CDCl₃): δ = 60.85, 123.06, 124.75, 137.19, 145.41, 146.24. Anal. Calcd for C₆H₇NO: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.01; H, 6.45; N, 12.79.

(5-Nitrofuran-2-yl)methanol (entry 7): colorless liquid. IR (KBr): 3450 (-OH) cm⁻¹. ¹H NMR (CDCl₃): δ = 3.24 (s, 1H, D₂O exchangeable), 4.71 (s, 2H), 6.57 (d, 1H, *J* = 3.60 Hz), 7.30 (d, 1H, *J* = 3.60 Hz). ¹³C NMR (CDCl₃): δ = 57.10, 110.65, 112.65, 153.21, 157.64. Anal. Calcd for C₅H₅NO₄: C, 41.97; H, 3.52; N, 9.79. Found: C, 41.95; H, 3.51; N, 9.75.

4-Methoxyphenethyl alcohol (entry 8): mp. 27-29 °C. IR (KBr): 3456 (-OH) cm⁻¹. ¹H NMR (CDCl₃): δ = 2.71 (bs, 1H, D₂O exchangeable), 2.75 (t, 3H), 3.74 (s, 5H), 6.82 (d, 2H, *J* = 7.80 Hz), 7.10 (d, 2H, *J* = 8.10 Hz). ¹³C NMR (CDCl₃): δ = 37.99, 55.04, 63.46, 113.76, 129.74, 130.43, 157.96. Anal. Calcd for C₉H₁₂O₂: C, 71.03; H, 7.95. Found: C, 71.02; H, 7.91.

Cyclohexylmethanol (entry 9): colorless liquid. IR (KBr): 3320 (-OH) cm⁻¹. ¹H NMR (CDCl₃): δ = 0.84-0.96 (m, 2H), 1.09-1.31 (m, 3H), 1.40-1.50 (m, 1H), 1.65-1.85 (m, 5H), 3.24 (bs, 1H, D₂O exchangeable), 3.36-3.39 (m, 2H). ¹³C NMR (CDCl₃): δ = 25.68, 26.44, 29.45, 40.21, 68.11. Anal. Calcd for C₇H₁₄O: C, 73.63; H, 12.36. Found: C, 73.63; H, 12.33.

3,4-Dichloro-5H-furan-2-one (entry 10): mp. 52-53 °C. IR (KBr): 1786 (C=O) cm⁻¹. ¹H NMR (CDCl₃): δ = 4.91 (s, 1H). ¹³C NMR (CDCl₃): δ = 70.92, 120.82, 149.03, 165.75. Anal. Calcd for C₄H₂Cl₂O₂: C, 31.41; H, 1.32. Found: C, 31.42; H, 1.30.

(S)-(+)-1,2-Propanediol (entry 11): colorless liquid. IR

(KBr): 3352 cm^{-1} . ^1H NMR (CDCl_3): δ = 1.14 (d, 3H, J = 5.70 Hz), 3.37-3.39 (m, 1H), 3.55-3.62 (m, 1H), 4.38-4.40 (bs, 2H, D_2O exchangeable). ^{13}C NMR (CDCl_3): δ = 18.51, 67.65, 68.07. Anal. Calcd for $\text{C}_3\text{H}_5\text{O}_2$: C, 47.35; H, 10.60. Found: C, 47.33; H, 10.58.

4-Chlorobutanol (entry 12): colorless liquid. IR (KBr): 3346 cm^{-1} . ^1H NMR (CDCl_3): δ = 1.80 (m, 2H), 3.51-3.60 (m, 2H), 3.76 (bs, 5H, D_2O exchangeable), 3.97-4.04 (m, 4H). ^{13}C NMR (CDCl_3): δ = 33.63, 47.46, 57.66, 67.90. Anal. Calcd for $\text{C}_4\text{H}_9\text{ClO}$: C, 44.25; H, 8.36. Found: C, 44.22; H, 8.35.

General Procedure: Reduction of Amides and Nitriles. A solution of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.0065 mmol) in THF (15 mL) was added slowly to a room temperature solution of NaBH_4 (0.015 mmol) and amide or nitrile (0.01 mmol) in THF (25 mL) under an inert atmosphere. The mixture was heated to reflux until TLC monitoring showed complete consumption of the substrate. The reaction mixture was cooled to 0 $^\circ\text{C}$, quenched with water (caution: vigorous gas evolution) keeping the temperature ≤ 10 $^\circ\text{C}$. After 10 min. the THF was removed under reduced pressure. CH_2Cl_2 (or Et_2O) was added, and the stirring was continued for another 1 h. The organic layer was separated, washed with brine, dried over MgSO_4 , and the solvent was removed under reduced pressure. Purification of the residue by SiO_2 chromatography provided the amine as a borane complex. This was dissolved in water (30 mL) to which a 30% aqueous solution of NaOH (5 mL) was added. After stirring for 10 minutes, H_2O_2 (30%, 5 mL) was added and the stirring was continued for another 2 h at room temperature. The reaction mixture was extracted with EtOAc and the combined organic extracts were dried over MgSO_4 and the solvent was removed under reduced pressure. Purification of the residue by SiO_2 chromatography gave pure amine in the indicated yield (Table 1).

Benzyl amine (entry 14): colorless liquid. IR (KBr): 3372 ($-\text{NH}_2$), 3312 ($-\text{NH}_2$) cm^{-1} . ^1H NMR (CDCl_3): δ = 1.31 (s, 2H, D_2O exchangeable), 4.82 (s, 2H), 7.18-7.33 (m, 5H). ^{13}C NMR (CDCl_3): δ = 46.42, 126.63, 126.79, 128.31, 143.22. Anal. Calcd for $\text{C}_7\text{H}_9\text{N}$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.43; H, 8.45; N, 13.03.

2,6-Difluorobenzylamine (entry 15): colorless liquid. IR (KBr): 3370 ($-\text{NH}_2$), 3308 ($-\text{NH}_2$) cm^{-1} . ^1H NMR (CDCl_3): δ = 1.43 (s, 2H, D_2O exchangeable), 4.90 (s, 2H), 6.80-7.21 (m, 3H). ^{13}C NMR (CDCl_3): δ = 52.74, 52.81, 52.85, 111.03, 111.10, 111.37, 111.42, 116.00, 116.32, 116.50, 129.55, 129.74, 129.88, 159.84, 159.94, 163.12, 163.22. Anal. Calcd for $\text{C}_7\text{H}_7\text{F}_2\text{O}$: C, 58.74; H, 4.93; N, 9.79. Found: C, 58.73; H, 4.98; N, 9.90.

4-Chlorobenzylamine (entry 16): colorless liquid. IR (KBr): 3366 ($-\text{NH}_2$), 3310 ($-\text{NH}_2$) cm^{-1} . ^1H NMR (CDCl_3): δ = 1.41 (s, 2H, D_2O exchangeable), 4.81 (s, 2H), 7.20-7.29 (m, 4H). ^{13}C NMR (CDCl_3): δ = 45.62, 128.32, 128.40, 132.24, 141.47. Anal. Calcd for $\text{C}_7\text{H}_8\text{ClN}$: C, 59.38; H, 5.69; N, 9.89. Found: C, 59.37; H, 5.66; N, 9.86.

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