Facile Reduction of Carboxylic Acids, Esters, Acid Chlorides, Amides and Nitriles to Alcohols or Amines Using NaBH₄/ BF₃·Et₂O

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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. 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. To broaden the utility of NaBH₄, its reactivity has been enhanced with various additives including CeCl₃, CaCl₂, ZnCl₂, CuSO₄, I₂, BH₃·Me₂S, sulfuric acid, catechol, trifluoroacetic acid, sulfur, ZrCl₄, Et₂SeBr₂, methanesulfonic acid, TiCl₄, Al₂O₃, SnCl₂, MnCl₂, SmCpCl₂ (THF)₃, ErCpCl₂ (THF)₃, Amberlyst-15(H⁺), Al₂O₃, (S)-lactic acid derivatives, (L)-tartaric acid, cobalt complex, (-)-N-dodecyl-N-methyl ephedrinium salt, lanthanoid complexes, Cu²⁺-clay/(S)-proline, a chiral surfactant, and 3,4,5-trifuorophenylboronic acid. Nevertheless, research in this field is still very active even now.

In conclusion, NaBH₄/BF₃·Et₂O is an inexpensive and highly versatile reducing system for a wide variety of carboxyls, acid chlorides, carboxylic acids, esters, amides and nitriles.

Experimental Section

General Remarks. TLC was performed on SiO₂ (silica gel 60 F254, Merck). The spots were located by UV light. Column chromatography was carried out on SiO₂ (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 d 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 BF₃·Et₂O (0.0065 mmol) in THF (15 mL) was added slowly to a room temperature solution of NaBH₄ (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

Notes

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, 129.61, 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 (s, 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 C₇H₁₄O: C, 78.65; H, 8.25. Found: C, 78.67; H, 8.22.

**2-Hydroxybenzalcohol (entry 3):** mp. 81-83 °C. IR (KBr): 3450 (-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, 129.70, 129.51, 157.96. Anal. Calcd for C₇H₈O: C, 76.65; H, 8.25. Found: C, 76.73; 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 C₉H₇NO: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.88; H, 4.59; N, 9.12.

**3-Chlorobenzyl alcohol (entry 5):** colorless liquid. IR (KBr): 3364 cm⁻¹. ¹H NMR (CDCl₃): δ = 2.93 (bs, 1H, D₂O exchangeable), 4.55 (s, 2 H), 7.21-7.31 (m, 4 H). ¹³C NMR (CDCl₃): δ = 64.19, 128.21, 128.56, 128.58, 139.13. Anal. Calcd for C₉H₇ClO: 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 C₆H₉NO: 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 C₇H₉NO: 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 (s, 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 C₁₅H₁₄O: C, 71.03; H, 7.95. Found: C, 71.02; H, 7.91.

**Cyclohexymethanol (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-SH-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, 167.55. Anal. Calcd for C₇H₆Cl₂O: C, 31.41; H, 1.32. Found: C, 31.42; H, 1.30.

**(S)-(++)-1,2-Propanediol (entry 11):** colorless liquid. IR
4-Chlorobutanol (entry 12): colorless liquid. IR (KBr): 3370 cm⁻¹ (-NH₂), 3308 cm⁻¹ (-NH₂). Anal. Calcd for C₇H₇F₂O: C, 58.74; H, 4.93; N, 9.79. Found: C, 58.73; H, 4.96; N, 9.83.

2,6-Difluorobenzylamine (entry 15): colorless liquid. IR (KBr): 3269 cm⁻¹ (-NH₂). Anal. Calcd for C₁₇H₁₂F₂N: C, 77.32; H, 5.53; N, 7.82. Found: C, 77.36; H, 5.55; N, 7.84.

4-Chlorobenzylamine (entry 16): colorless liquid. IR (KBr): 3269 cm⁻¹ (-NH₂). Anal. Calcd for C₁₇H₁₂ClN: C, 76.75; H, 5.26; N, 7.18. Found: C, 76.73; H, 5.25; N, 7.16.

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References