SYNTHESIS 2009, No. 4, pp 0660–0664
Advanced online publication: 02.02.2009
DOI: 10.1055/s-0028-1083353; Art ID: T12508SS
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Cobalt(II) Chloride Hexahydrate–Diisopropylamine Catalyzed Mild and Chemoselective Reduction of Carboxylic Esters with Sodium Borohydride

Arun R. Jagdale, Abhimanyu S. Paraskar, Arumugam Sudalai*

Chemical Engineering and Process Development Division, National Chemical Laboratory, Pashan Road, Pune 411 008, India
Fax +91(20)25902676; E-mail: a.sudalai@ncl.res.in

Received 28 July 2008; revised 13 October 2008

Abstract: The cobalt-catalyzed reduction of unsaturated α-cyano carboxylic esters using sodium borohydride (NaBH₄) leads to the corresponding saturated cyano alcohols in high yields. In particular, the new catalytic system cobalt(II) chloride–diisopropylamine in combination with NaBH₄ showed excellent activity in the chemoselective reduction of a variety of carboxylic esters to their corresponding alcohols in good to excellent yields under mild conditions.

Key words: reductions, amines, catalysis, esters, alcohols

Sodium borohydride (NaBH₄) is a mild, inexpensive yet powerful reducing agent capable of reducing a wide range of functional groups, such as aldehydes, ketones, and imines. Despite its low reactivity towards carboxylic esters, studies have indicated that the reactivity of NaBH₄ and its derivatives towards these compounds and carboxylic acids can be enhanced by the addition of certain additives, resulting in the use of reagents such as NaBH₄–MX (MX = LiCl, ZnCl₂, AlCl₃, LiBr, MgBr₂, MgCl₂, CaCl₂), KBH₄–MX (MX = ZnCl₂, AlCl₃, MgCl₂), NaBH₄–trifluoroacetic acid, NaBH₄–sulfuric acid, NaBH₄–iodine, and borane–dimethyl sulfide complex. However, some of the major disadvantages of the reported procedures on ester reduction include the lack of generality and the use of harsh reaction conditions, and higher equivalents of NaBH₄ and additives. The reduction of esters with hydroxy, amino, and cyano substituents at the α-position and that of carbon–carbon double bonds in α,β-unsaturated esters using NaBH₄ have also been reported.

In this paper, we report a simple procedure in which cobalt(II) chloride hexahydrate (CoCl₂·6H₂O) in combination with diisopropylamine catalyzes the chemoselective reduction of carboxylic esters to saturated alcohols using NaBH₄ at ambient conditions. In continuation of our work on the cobalt-catalyzed reduction of carbon–carbon double bonds and phenyl esters using NaBH₄, we became interested in subjecting (E)-ethyl 2-cyano-3-phenylacrylate (1a) to CoCl₂-catalyzed reduction conditions. Surprisingly, we found that ethyl acrylate 1a underwent reduction using NaBH₄ at the carbon–carbon double bond as well as at the ester carbonyl functionality to provide 2-(hydroxymethyl)-3-phenylpropanoic acid (2a) in 95% yield (Scheme 1 and Table 1, entry 2). However, when the reaction was carried out without CoCl₂·6H₂O in ethanol at 25 °C, only the reduction of the carbon–carbon double bond was observed to give ethyl 2-cyano-3-phenylpropanoate (Table 1, entry 1).

Scheme 1 Cobalt(II) chloride hexahydrate catalyzed reduction of α-cyano-α,β-unsaturated esters using sodium borohydride

Table 1 Cobalt(II) Chloride Hexahydrate Catalyzed Reduction of α-Cyano-α,β-unsaturated Esters Using Sodium Borohydride

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>2a</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>4-CIC₆H₄</td>
<td>2b</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>4-MeOCH₂H₄</td>
<td>2c</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>4-Tol</td>
<td>2d</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>3-FCC₆H₄</td>
<td>2e</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>3-O₂NC₆H₄</td>
<td>2f</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>3,4-(MeO)₂C₆H₃</td>
<td>2g</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>3,4-(OCH₂O)₂C₆H₃</td>
<td>2h</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>n-C₆H₁₁</td>
<td>2i</td>
<td>70</td>
</tr>
</tbody>
</table>

α Reaction conditions: cyano ester (10 mmol), NaBH₄ (40 mmol), CoCl₂·6H₂O (1 mol%), EtOH (5 mL), 25 °C, 6 h.
β Isolated yield after chromatographic purification.
γ Ethyl 2-cyano-3-phenylpropanoate was isolated when the reaction was carried out in the absence of CoCl₂·6H₂O.

The results of the reduction of several α-cyano-α,β-unsaturated esters are presented in Table 1; those groups in the ester substrates capable of being reduced, such as nitro and cyano groups, were found to be unaffected under the reduction conditions. The high yields obtained, coupled with the use of ethanol as solvent over diglyme, makes this procedure straightforward and highly economical. It may be that the strong electron-withdrawing nature of the cyano group as well as that of the ester functionality results in the β-positions of the α-cyano esters being more...
electrophilic for carbon–carbon double bond reduction to occur.

This catalytic procedure provides 3-aryl-2-(hydroxymethyl)propanenitriles 2a–h and 3-n-octyl derivative 2i in high yields; such compounds are potential intermediates in the synthesis of aminooxazolines. We noticed that the reduction of α-cyano esters is more facile compared with that of alkyl carboxylic esters with an α-cyano group. To make the ester reduction procedure more general and practical, we became interested in enhancing the reactivity of NaBH₄ by the addition of additives. Thus, the addition of various amines (i.e., Et₃N, DMAP, Me₂NPh, or i-Pr₂NH) in catalytic amounts was shown to enhance the rate of reduction of carboxylic esters at 50 °C, for example the reduction of ethyl cinnamate (Scheme 2 and Table 2, entries 1–6). After careful study, we found that the combination of CoCl₂·6H₂O–i-Pr₂NH in catalytic amounts is an effective catalytic system in the reduction of a variety of esters, including α,β-unsaturated, aliphatic, and aromatic ones and lactones, giving the corresponding saturated alcohols 4 in high yields.

The simultaneous reduction of the carbon–carbon double bond along with the carboxylic ester functionality was also observed in the case of (E)-ethyl 3-arylacrylates (Table 2, entries 7–9). In addition, diethyl 2-benzylidenedmaleate smoothly underwent reduction to provide 2-benzylpropane-1,3-diol (4e) in 94% yield (entry 10). Aromatic esters were reduced to the corresponding benzyl alcohols (entries 11 and 12). More interestingly, aliphatic esters and lactones were reduced to the corresponding alcohols in good yields under mild conditions (entries 13

Table 2 Cobalt(II) Chloride Hexahydrate–Diisopropylamine Catalyzed Chemoselective Reduction of Esters Using Sodium Borohydride: The Role of Diisopropylamine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ester</th>
<th>Additive</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-[OEt]CO₂Et</td>
<td>no catalyst</td>
<td>5a</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Ph-[Cl]CO₂Et</td>
<td>no amine</td>
<td>5a</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>Ph-[MeO]CO₂Et</td>
<td>i-Pr₂NH</td>
<td>4a</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>Ph-[MeO]CO₂Et</td>
<td>DMAP</td>
<td>4a</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Ph-[MeO]CO₂Et</td>
<td>Et₃N</td>
<td>4a</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>Ph-[MeO]CO₂Et</td>
<td>Me₂NPh</td>
<td>4a</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>Ph-[Cl]CO₂Et</td>
<td>i-Pr₂NH</td>
<td>4b</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>Ph-[Cl]CO₂Et</td>
<td>i-Pr₂NH</td>
<td>4c</td>
<td>82</td>
</tr>
<tr>
<td>9</td>
<td>Ph-[Cl]CO₂Et</td>
<td>i-Pr₂NH</td>
<td>4d</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>Ph-[Cl]CO₂Et</td>
<td>i-Pr₂NH</td>
<td>4e</td>
<td>94</td>
</tr>
<tr>
<td>11</td>
<td>PhCO₂Et</td>
<td>i-Pr₂NH</td>
<td>4f</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>4-BrC₆H₄CO₂Et</td>
<td>i-Pr₂NH</td>
<td>4g</td>
<td>82</td>
</tr>
<tr>
<td>13</td>
<td>4-BrC₆H₄CO₂Et</td>
<td>i-Pr₂NH</td>
<td>4h</td>
<td>79</td>
</tr>
<tr>
<td>14</td>
<td>PhCO₂Et</td>
<td>i-Pr₂NH</td>
<td>4i</td>
<td>81</td>
</tr>
</tbody>
</table>

* Reaction conditions: carboxylic ester (2 mmol), NaBH₄ (4 mmol), CoCl₂·6H₂O (10 mol%), i-Pr₂NH (20 mol%), EtOH (12 mL), 50 °C, 24 h.
* Isolated yield after chromatographic purification.

Scheme 2 Cobalt-catalyzed reduction of ethyl cinnamate with sodium borohydride
and 14, respectively). The results of the CoCl$_2$·6H$_2$O–i-Pr$_2$NH/NaBH$_4$ reduction clearly showed that esters can be reduced under mild conditions even when they contain various reducible groups, such as nitro and halo groups; such reactions are quite difficult with other strong reducing agents, e.g. lithium aluminum hydride. Mechanistically, the role of diisopropylamine is probably to enhance the nucleophilicity of the borohydride reagent by way of coordination.

In conclusion, we have demonstrated a simple catalytic combination comprising CoCl$_2$·6H$_2$O–i-Pr$_2$NH with stoichiometric NaBH$_4$ that reduces both the carbon–carbon double bond and ester carbonyl functionality in unsaturated carboxylic esters containing other reducible groups, such as halo, cyano, and nitro groups. Mild reaction conditions, easy-to-handle reagents, and good chemoselectivity are distinct features of this methodology; this procedure is a promising alternative to those involving expensive and difficult-to-handle lithium aluminum hydride.

The IR spectra were collected on a Shimadzu FTIR-8400 spectrometer. The NMR spectroscopy was performed on Bruker AV-200 and AV-400 NMR spectrometers with TMS as an internal standard. Quantitative analyses were determined using a Carlo Erba CHNS-O apparatus. Melting points are uncorrected. Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80 °C was used.

2-(Hydroxymethyl)-3-phenylpropanenitrile (2a): Typical Procedure

To cyano ester 1a (2.01 g, 10 mmol) in a 10-mL round-bottomed flask was added a solution of CoCl$_2$·6H$_2$O (0.024 g, 0.11 mmol) in EtOH (10 mL) under a nitrogen atmosphere. Then, NaBH$_4$ (1.51 g, 40 mmol) was added, and the mixture was stirred at 25 °C for 6 h. After completion of the reaction (monitored by TLC), the mixture was transferred to a separating funnel containing EtOAc–H$_2$O (3:1). The product was purified by column chromatography (EtOAc–petroleum ether, 3:1) to afford 2-(hydroxymethyl)-3-phenylpropanenitrile (2a) as a colorless solid. Yield: 93% (1.2 g); colorless solid; mp 80–82 °C.

1H NMR (200 MHz, CDCl$_3$): $\delta = 2.94 (s, 3 H), 3.10 (s, 3 H), 3.71 (m, 1 H), 7.14 (m, 4 H).

13C NMR (200 MHz, CDCl$_3$): 20.7, 33.7, 36.5, 61.1, 120.5, 129.2, 131.1, 132.4, 137.4.

Anal. Calcd for C$_{12}$H$_{14}$NO: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.32; H, 7.35; N, 8.00.

2-(Hydroxymethyl)-3-3-(3,4-Dimethoxyphenyl)-2-(hydroxymethyl)propanenitrile (2b)

Yield: 98% (1.43 g); yellowish solid; mp 182–184 °C (EtOH–CHCl$_3$).

1H NMR (200 MHz, CDCl$_3$): $\delta = 3.11 (s, 3 H), 3.48 (br s, 1 H), 3.71 (m, 2 H), 7.14 (m, 4 H).

13C NMR (200 MHz, CDCl$_3$): 20.7, 33.7, 36.5, 61.1, 120.5, 129.2, 131.1, 132.4, 137.4.

Anal. Calcd for C$_{15}$H$_{17}$NO$_2$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.22; H, 4.85; N, 13.60.

3-(3,4-Dimethoxyphenyl)-2-(hydroxymethyl)propanenitrile (2g)

Yield: 96% (1.61 g); brown solid; mp 170–171 °C (CHCl$_3$).

IR (CHCl$_3$): 765, 812, 858, 1026, 1072, 1141, 1157, 1238, 1263, 1336, 1421, 1465, 1515, 1591, 1724, 2243, 2837, 2937, 3494 cm$^{-1}$.

1H NMR (200 MHz, CDCl$_3$): $\delta = 3.11 (s, 3 H), 3.48 (br s, 1 H), 3.71 (m, 2 H), 3.81 (s, 1 H), 6.58–6.72 (m, 3 H).

13C NMR (200 MHz, CDCl$_3$): $\delta = 33.7, 36.3, 56.3, 61.1, 114.7, 115.7, 132.2, 132.6, 138.2, 144.5, 147.1.

Anal. Calcd for C$_{15}$H$_{17}$NO$_2$: C, 61.54; H, 6.83; N, 6.33. Found: C, 65.11; H, 6.80; N, 6.35.
IR (CHCl₃): 771, 813, 864, 927, 1039, 1091, 1193, 1247, 1365, 1444, 1510, 1608, 1728, 1843, 2245, 2781, 2893, 3452 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 2.97 (s, 3 H), 3.44 (br s, 1 H), 3.62 (m, 2 H), 5.87 (s, 2 H), 6.53–6.62 (m, 3 H).

13C NMR (200 MHz, CDCl₃): δ = 34.1, 35.3, 61.1, 91.1, 115.3, 115.9, 132.3, 132.8, 138.4, 145.1, 146.5.


IR (CHCl₃): 754, 968, 1029, 1606, 1728, 2893, 3452 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 1.76 (br s, 1 H), 1.78–1.92 (m, 2 H), 2.67 (t, J = 7.3 Hz, 2 H), 3.61 (t, J = 7.3 Hz, 2 H), 7.12 (d, J = 8.5 Hz, 2 H), 7.24 (d, J = 8.5 Hz, 2 H).

13C NMR (50 MHz, CDCl₃): δ = 31.1, 33.7, 61.3, 128.1, 129.5, 131.2, 140.0.

Anal. Calcd for C₉H₁₄O₂: C, 63.35; H, 6.50. Found: C, 63.32; H, 6.52.

3-(3,4-Dimethoxyphenyl)propan-1-ol (4c)

Yield: 82% (320 mg); gum.

IR (CHCl₃): 745, 857, 968, 1029, 1060, 1460, 1495, 3498 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 1.64 (br s, 1 H), 1.61–1.95 (m, 2 H), 2.67 (t, J = 8.1 Hz, 2 H), 3.68 (t, J = 8.1 Hz, 2 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 6.72–6.86 (m, 3 H).

13C NMR (50 MHz, CDCl₃): δ = 31.5, 34.2, 55.7, 55.8, 62.1, 111.2, 111.6, 120.1, 134.3, 147.0, 147.7.


3-(2-Nitrophenyl)propan-1-ol (4d)

Yield: 87% (326 mg); gum.

IR (CHCl₃): 857, 968, 1029, 1060, 1245, 1440, 1507, 3430 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 1.67 (br s, 1 H), 1.87–2.01 (m, 2 H), 1.99 (t, J = 7.6 Hz, 2 H), 3.72 (t, J = 6.2 Hz, 2 H), 7.31–7.60 (m, 3 H), 7.92 (dd, J = 1.2, 8.1 Hz, 1 H).

13C NMR (50 MHz, CDCl₃): δ = 29.1, 33.2, 61.6, 124.4, 126.8, 131.8, 132.8, 136.7, 149.1.


2-Benzylpropane-1,3-diol (4e)

Yield: 94% (342 mg); gum.

IR (CHCl₃): 745, 857, 968, 1029, 1060, 1454, 1498, 3400 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 1.99–2.27 (m, 1 H, and br s, 2 H), 2.62 (d, J = 7.6 Hz, 2 H), 3.63–3.85 (m, 4 H), 7.17–7.36 (m, 5 H).

13C NMR (50 MHz, CDCl₃): δ = 34.1, 43.7, 64.9, 126.0, 128.9, 139.8.

Anal. Calcd for C₁₅H₁₈O₃: C, 72.26; H, 8.49. Found: C, 72.23; H, 8.44.

Phenylnemethanol (4f)

Yield: 86% (382 mg); gum.

IR (CHCl₃): 771, 813, 864, 927, 1039, 1091, 1193, 1247, 1365, 1444, 1510, 1608, 1728, 1843, 2245, 2781, 2893, 3452 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 1.25 (t, J = 7.3 Hz, 3 H), 2.65–2.72 (m, 2 H), 2.81–2.91 (m, 2 H), 4.15 (q, J = 7.3 Hz, 2 H), 7.15–7.33 (m, 5 H).

13C NMR (50 MHz, CDCl₃): δ = 13.9, 30.6, 35.3, 59.8, 125.9, 127.9, 128.1, 140.3, 172.6.


3-(4-Chlorophenyl)propan-1-ol (4b)

Yield: 87% (358 mg); gum.

IR (CHCl₃): 754, 968, 1029, 1060, 1454, 1495, 3325 cm⁻¹.
IR (CHCl₃): 857, 1063, 1245, 1498, 3450 cm⁻¹.

¹H NMR (200 MHz, CDCl₃); δ = 1.42–1.48 (m, 4 H), 1.70 (br s, 1 H), 1.94 (br s, 2 H), 3.91 (m, 2 H), 7.40 (d, J = 8.7 Hz, 2 H), 8.15 (d, J = 8.7 Hz, 2 H).

¹³C NMR (50 MHz, CDCl₃); δ = 28.1, 64.3.


Butane-1,4-diol (4i)

Yield: 85% (312 mg); gum.

IR (CHCl₃): 837, 938, 1291, 3098, cm⁻¹.

References

Acknowledgment

A.R.J. and A.S.P. thank CSIR (Council of Scientific and Industrial Research), New Delhi, for the award of research fellowships. The authors are also thankful to Dr. B. D. Kulkarni, Head, CEPD (Chemical Engineering and Process Development), for his constant support and encouragement.

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