Clean and Simple Chemoselective Reduction of Imines to Amines Using Boric Acid-Activated Sodium Borohydride under Solvent-Free Conditions

Byung Tae Cho,* Sang Kyu Kang

Department of Chemistry, Hallym University, Chuncheon, Kangwondo 200-702, Republic of Korea
Fax +82(33)2518491; E-mail: bcho@hallym.ac.kr

Received 26 March 2004

Abstract: The first clean and highly effective solvent-free chemoselective reduction of functionalized aldimines and ketimines bearing easily reducible functional groups, such as ketone, carboxylic acid, ester, nitrite, amide, nitro, furyl and alkylidene groups, to the corresponding amines using boric acid-activated sodium borohydride is described.

Key words: imines, reductions, chemoselectivity, sodium borohydride, solvent-free reaction

The reduction of aldimines and ketimines to the corresponding amines is a very useful transformation in organic synthesis because of their versatile utility as intermediates for synthesis of pharmaceuticals and agrochemicals. As effective reducing methods for these conversions, catalytic hydrogenation, metal hydride reductions using NaBH₄CN, LiBH₄CN, (n-Bu)₃Sn(OCOR)₃, NaBH₄CN–ZnCl₂, NaBH₄CN–Ti(O-i-Pr)₄, NaBH₄CN–Mg(ClO₄)₂, NaBH₄, NaBH₄–NiCl₂, NaBH₄–ZnCl₂ (nickel boride), NaBH₄–ZrCl₄, Ti(O-i-Pr)₄–NaBH₄, NaBH₄–H₂SO₄, NaBH₄–water clay-microwave, borohydride exchange resin, Zn(BH₄)₂, Zn(BH₄)₂–ZnCl₂, Zn(BH₄)₂–SiO₂, pyridine–borane, diborane–MeOH, decaborane, Zn–AcOH, polymethylhydrosiloxane (PMHS–Ti(O-i-Pr)₄), PMHS–ZnCl₂, PMHS–n-BuSn(OCOR)₃, Et₃SiH–CF₃CO₂H, PhMe₃SiH–(C₆F₅)₃Cl, SiH₄–DMF, PMAPA, n-Bu₂SnH–SiO₂, n-Bu₂SnH or n-Bu₂SnCl₄ have been reported. However, most of these reagents have one drawback or another. For example, catalytic hydrogenation is incompatible with compounds containing a carbon-carbon double or triple bond and other reducible functional groups such as nitro, cyano and furyl groups. Cyanoborohydride and tin hydride reagents are highly toxic and generate toxic by-products such as HCN, NaCN or organotin compounds upon workup and may result in the contamination of the product with the toxic compounds. Other hydrides such as zinc borohydride, nickel boride and PMHS–Ti(O-i-Pr)₄ may not be suitable for use in the chemoselective reduction of imines having ketone, ester, amide and nitro groups, since these reagents can reduce those functional groups. Although reductive amination, which involves the initial formation of an imine from the reaction of a carbonyl compound with an amine and its subsequent reduction to an alkylated amine, is an alternative method used for amine synthesis, this process is commonly required for excess amounts of amines to obtain high yields by suppressing undesirable reduction of the starting carbonyls, because metal hydride reagents usually reduce a carbonyl group more rapidly than an imino group due to the lower electrophilicity of an imino group. This requires additional purification to remove excess of amines used from the products and causes lower yields. Chemoselective reduction of an imino group in imine compounds containing various reducible functional groups is one of the most important techniques in obtaining amines bearing these functional groups. However, only limited successful reports for such reductions have been published. Recently, considerable efforts have been paid to solvent-free reactions. These reactions are not only of interest from ecological point of view, but in many cases, also offer considerable synthetic advantages in terms of yield, selectivity and simplicity of the reaction procedure. Sodium borohydride is an inexpensive, safe to handle and environmental friendly reducing agent, which can reduce aldehydes, ketones and acid chlorides. However, there is no report for reduction of imines using this reagent under solvent-free conditions. We report here the first solvent-free chemoselective reduction of imines to amines using boric acid-activated sodium borohydride.

To study chemoselective reduction of imines possessing different kinds of reducible functional groups, we initially chose an aldimine bearing a ketone group, 4-acetylbenezaldehyde-N-phenylimine (1a) and compared its chemoselective reduction with metal hydrides, such as NaBH₄CN, NaBH₄(OAc)₃, Zn(BH₄)₂, pyridine–borane and PMHS–Ti(O-i-Pr)₄. The reductions were carried out under the same reaction conditions adopted for the imine reductions using those metal hydrides with a ratio of hydride to starting carbonyls, because metal hydride reagents usually reduce a carbonyl group more rapidly than an imino group.

SYNLETT 2004, No. 9, pp 1484–1488

Advanced online publication: 01.07.2004
© Georg Thieme Verlag Stuttgart · New York
PMHS–Ti(Oi-Pr)₄ preferentially reduced the ketone group to give 3a (28%) and 4a (7%) (entry 7). In contrast, the reduction of 1a with sodium borohydride in the presence of boric acid under solvent-free conditions provided only 2a in a quantitative yield (entry 1). ¹H NMR analysis of 2a obtained showed it to be chemically pure. The reduction did not afford any undesirable reduction products, such as 3a and 4a. The reduction and work-up procedures were quite simple. A mixture of the 1:1:1 molar ratio of 1a, sodium borohydride and boric acid was intermittently ground over 30 minutes at room temperature using an agate mortar and pestle in air until TLC showed complete disappearance of the starting material. The mixture was quenched with saturated aqueous solution of NaHCO₃, followed by filtration of the resultant suspension to give 2a with no need of solvent extraction. When 1a was ground with sodium borohydride alone in the absence of boric acid under the identical conditions, the reduction proceeded more slowly to give 2a in 11% yield even after 2 hours with recovery of unreacted imine 1a in 84% yield (entry 2). Based on these results, we carried out the solvent-free chemoselective reduction for various aldimines and ketimines 1a–p bearing other reducible functional groups, such as carboxylic acid, ester, nitrile, amide, nitro, furyl and alkenyl groups using boric acid-activated sodium borohydride. As shown in Table 2, all the reductions examined were complete within 1 hour and provided functionalized amine products 2a–p in 97–99% yields. In this reduction, other functional groups included were not reduced at all, showing that a clean chemoselective reduction of an imino group occurred. To the best of our knowledge, this is the first example for solvent-free and highly effective chemoselective reduction of imines to functionalized amines. When the products were obtained as liquid from the reaction, they were isolated by extraction with CH₂Cl₂ or Et₂O after quenching with saturated aqueous solution of NaHCO₃ (entries 2, 8–10, 12, 14 and 15). Influence of substituents on the nitrogen of imines for the reduction was not observed (entries 4, 5 and 6–9). The order of mixing of the reactants had no discernable effect on the rate of reduction, yield and purity of the product. The presence of moisture in air is not critical for the reduction. In this reduction, it is possible that the substrates, imines were activated by boric acid to form iminium salts, which were selectively reduced to the amines. However, it was found that the reduction of imine derivatives with reducing system generated from grinding a 1:1 mixture of sodium borohydride and boric acid was highly chemoselective as well. The results suggest that the reduction also occurs selectively in the condition of little chance of the formation of iminium salts by boric acid. The IR spectrum of this hydride species formed showed at 2381 cm⁻¹ a medium peak and a ¹H decoupled ¹¹B NMR spectrum of its THF suspension exhibited at −1.91 ppm, which were different spectra from those of sodium borohydride. This hydride species was stable in air at least for few hours with no loss of hydride activity. Although the structure of this reducing species and the mechanism of this reduction are unclear so far, it appears that a eutectic temperature with melting point lower than the ambient temperature exists in

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reducing agents</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Product (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>1a</th>
<th>2a</th>
<th>3a</th>
<th>4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄/H₃BO₃ (1:1&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>none</td>
<td>0.5</td>
<td>100 (98)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>NaBH₄&lt;sup&gt;d&lt;/sup&gt;</td>
<td>none</td>
<td>2</td>
<td>87 (84)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>13 (11)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>NaBH₄CN&lt;sup&gt;g&lt;/sup&gt;</td>
<td>MeOH</td>
<td>16</td>
<td>97 (94)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>NaBH(OAc)&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;h&lt;/sup&gt;</td>
<td>DCE&lt;sup&gt;l&lt;/sup&gt;</td>
<td>19</td>
<td>94</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Zn(BH₄)₂&lt;sup&gt;l&lt;/sup&gt;</td>
<td>DME&lt;sup&gt;i&lt;/sup&gt;</td>
<td>38</td>
<td>89</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>BH₃-Pyridine&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Pet. Ether</td>
<td>15</td>
<td>80</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>PMHS/Ti(Oi-Pr)₄&lt;sup&gt;k,l&lt;/sup&gt;</td>
<td>THF</td>
<td>39</td>
<td>65</td>
<td>0</td>
<td>28</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> [Hydride/imine] = 1.0, unless otherwise indicated.
<sup>b</sup> Determined by ¹H NMR analysis.
<sup>c</sup> This study.
<sup>d</sup> DCE = 1,2-dichloroethane.
<sup>e</sup> [Hydride/imine] = 1.5.
<sup>f</sup> DME = 2-dimethoxyethane.
<sup>g</sup> The figures in parentheses indicate isolated yield.

Synlett 2004, No. 9, 1484–1488 © Thieme Stuttgart · New York
In each case, the reaction mixture became oily or sticky during grinding the mixtures even though they are powder states before grinding. Further studies on the reduction for other functional groups using this procedure are in progress.

In summary, we established the first solvent-free chemoselective reduction using boric acid-activated sodium borohydride for aldimines and ketimines in the presence of other reducible functional groups, such as ketone, carboxylic acid, ester, nitrile, amide, nitro, furyl and alkenyl groups. This method proves to be a clean, rapid and very simple procedure in preparing functionalized amine compounds in nearly quantitative yields by simply grinding a 1:1:1 mixture of imine, sodium borohydride and boric acid with an agate mortar and pestle at room temperature.

Acknowledgment

This work was supported by the Research Grant from Hallym University, Korea.

References

LETTER
Clean and Simple Chemoselective Reduction of Imines to Amines


118.5, 130.6, 132.9, 139.4. Anal. Calcd for C8H10N2O2: C, 73.56; H, 5.70; N, 11.66. Found: C, 73.55; H, 5.69; N, 11.68.

N-Phenyl-4-acetamidobenzylamine (2j): Yield: 97%; oil. IR (neat): 3426, 3301, 3193, 3050, 2931, 2840, 1662, 1601, 1511, 1315, 745, 689 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 4.09 (br s, 1 H), 4.43 (s, 2 H), 6.54 (d, J = 8.53 Hz, 2 H), 6.68 (t, J = 7.30 Hz, 1 H), 7.13 (t, J = 7.00 Hz, 2 H), 7.47 (d, J = 8.25 Hz, 2 H), 8.12 (d, J = 8.44 Hz, 2 H). 13C NMR (75 MHz, CDCl₃): δ = 131.5, 113.1, 117.8, 120.6, 128.2, 129.5, 135.6, 137.1, 148.2. Anal. Calcd for C₁₃H₁₂N₂O₂: C, 73.56; H, 5.70; N, 11.66. Found: C, 73.55; H, 5.69; N, 11.68.

N-Phenyl-4-nitosobenzylamine (2k): Yield: 97%; oil. IR (neat): 3409, 3052, 2971, 2927, 2869, 1614, 1588, 1450, 1501, 1013, 744, 702 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 1.28 (d, J = 6.72 Hz, 3 H), 4.09 (br s, 1 H), 4.57 (q, J = 6.67 Hz, 1 H), 6.44 (d, J = 7.63 Hz, 2 H), 6.68 (t, J = 7.33 Hz, 1 H), 7.10 (t, J = 7.94 Hz, 2 H), 7.55 (d, J = 8.85 Hz, 2 H), 8.18 (d, J = 8.85 Hz, 2 H). 13C NMR (50 MHz, CDCl₃): δ = 25.6, 54.0, 114.0, 118.7, 124.8, 127.4, 129.9, 147.2, 147.8, 153.9. Anal. Calcd for C₁₃H₁₅N: C, 79.61; H, 8.52; N, 11.56. Found: C, 79.63; H, 8.52; N, 11.55.

N-Phenyl-2-(1'-cyclohexenyl)(ethyl)aminobenzylamine (2p): Yield: 97%; oil. IR (neat): 3410, 3050, 2925, 2855, 1602, 1504, 1319, 749, 691 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 1.28 (d, J = 6.88 Hz, 3 H), 1.48–1.64 (m, 4 H), 1.94–1.99 (m, 4 H), 3.75 (q, J = 6.60 Hz, 1 H), 3.76 (m, 1 H), 5.66 (s, 1 H), 6.54 (d, J = 7.43 Hz, 2 H), 6.63 (t, J = 7.29 Hz, 1 H), 7.11 (d, J = 7.15, 8.53 Hz, 2 H). 13C NMR (75 MHz, CDCl₃): δ = 21.7, 23.1, 23.2, 24.7, 25.4, 55.1, 113.3, 117.0, 121.8, 129.2, 139.6, 147.9. Anal. Calcd for C₁₅H₂₂N₂O: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.52; H, 9.54; N, 6.98.