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LETTERS

# Facile and chemoselective reduction of carboxylic acids to alcohols using BOP reagent and sodium borohydride

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## Abstract

Hydroxybenzotriazolyl esters, formed *in situ* from carboxylic acids and BOP reagent, react with sodium borohydride in THF to give alcohols in high yields. This method is convenient, rapid and chemoselective, with such functional groups as nitro, halide, nitrile, azido and ester being unaffected. © 1998 Elsevier Science Ltd. All rights reserved.

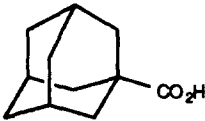
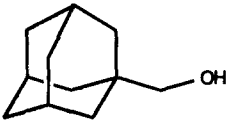
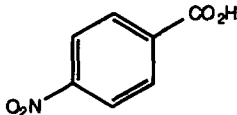
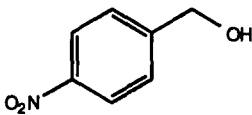
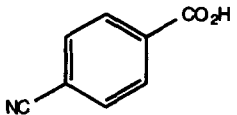
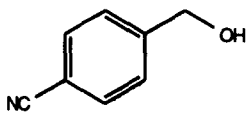
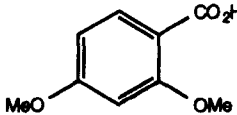
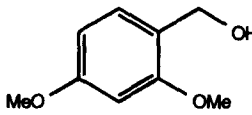


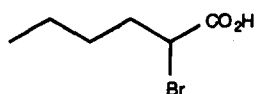
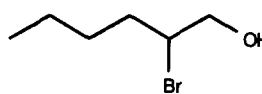


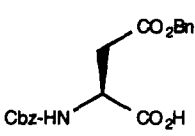
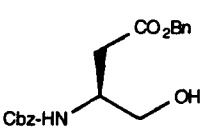


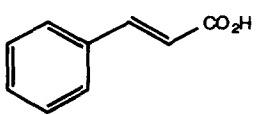
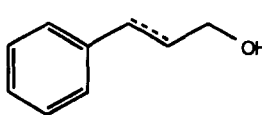
**Keywords:** Alcohols; Carboxylic acids and derivatives; Reduction.

The reduction of carboxylic acids to alcohols is a key synthetic transformation in organic chemistry [1]. Lithium aluminium hydride is commonly used to effect this reaction, but many other functional groups, such as esters, epoxides, nitros, nitriles, amides, halides and azides are also reduced by this reagent. The other reductant routinely used for the direct conversion of a carboxylic acid to the corresponding alcohol is borane, but this reagent is incompatible with several functional groups, most notably olefins, amides, nitriles and epoxides. Sodium borohydride in combination with strong protic or Lewis acids has also been reported to reduce carboxylic acids to alcohols, but the actual reducing species generated in these mixtures is borane, and so these protocols suffer the limitations mentioned above [2].

An alternative approach is to transform the carboxylic acid into an activated derivative, which can then be reduced using a mild reductant such as sodium borohydride. This strategy has been used successfully in the formation of "mixed anhydrides" (mixed carboxylic carbonic anhydrides), formed *in situ* with various chloroformates at low temperature, followed by the reduction of these derivatives to the desired alcohol with sodium borohydride [3–5]. A related approach is to prepare carboxymethyleniminium chlorides, by the reaction of carboxylic acids with *N,N*-dimethylchloromethyleniminium chloride. These unisolated derivatives are also reduced with sodium borohydride to the corresponding alcohols [6]. While these procedures often result in good yields of product, they require anhydrous solvents, inert atmospheres and low temperatures. We now report that hydroxybenzotriazolyl (HOBt) esters of carboxylic acids, formed *in situ* using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) and *N,N*-diisopropylethylamine (DIPEA) in tetrahydrofuran, react rapidly and cleanly with sodium borohydride in a convenient one-pot reaction to give the corresponding alcohols in high yield (Scheme 1).

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Table  
 Yields of alcohols obtained by reduction of carboxylic acids using BOP/NaBH<sub>4</sub>.<sup>a</sup>

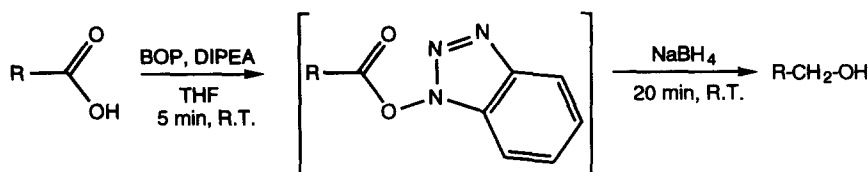
Entry	Carboxylic Acid	Alcohol	Yield (%) <sup>b</sup>
1	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub> CO <sub>2</sub> H	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>17</sub> OH	99
2			91
3			99
4			90
5			96 <sup>c</sup>
6			93
7			87
8			80
9			97
10			93
11			90 <sup>d</sup>

<sup>a</sup> All reactions were performed on a 1.0 mmol scale.

<sup>b</sup> Yields refer to isolated materials which were homogeneous by t.l.c. and n.m.r.

<sup>c</sup> Overnight reaction.

<sup>d</sup> An 82:18 ratio of unsaturated:saturated alcohol was produced.



Scheme 1

The ready formation of HOBt esters of carboxylic acids using BOP reagent and DIPEA in DMF is well known from peptide chemistry, where these reactive intermediates couple rapidly with amines to form peptide bonds with minimal epimerisation [7,8]. We anticipated that these active esters would also react with  $\text{NaBH}_4$  under mild conditions to give alcohols. HOBt esters are relatively stable towards hydrolysis, so we expected that rigorously dried solvents would be unnecessary for these studies. In these experiments, when THF was used as the solvent, formation of the HOBt esters from the carboxylic acids and BOP proceeded within a few minutes, as indicated by the dissolution of the reagents upon addition of base. Subsequent addition of  $\text{NaBH}_4$  to the reaction mixture resulted in the rapid conversion of the HOBt ester to the corresponding alcohol. Evaporation of the solvent and routine aqueous workup gave the alcohol, often without the need for further purification.<sup>2</sup> The major advantage of this procedure is its practical simplicity. The reactions are performed in an open flask at room temperature, without the need for an anhydrous solvent. The reactions are rapid and the workup is simple. Another attractive feature of this protocol is the range of carboxylic acids that undergo this reduction, and the functional groups which are stable to the reaction conditions (Table). Sterically hindered tertiary carboxylic acids (entry 2) react in good yield, as do electron-poor aryl carboxylic acids (entries 3 and 4). In the case of the electron-rich aromatic system 2,4-dimethoxybenzoic acid (entry 5), reduction of the intermediate HOBt ester is slow, and good yields of 2,4-dimethoxybenzyl alcohol were only achieved with an overnight reaction. Functional groups which are incompatible with either  $\text{LiAlH}_4$  or  $\text{BH}_3$  tolerated the reaction conditions described here. For example, nitro, ester and nitrile functional groups were stable to this protocol (entries 3,4 and 9), as were the more sensitive functional groups such as bromide, iodide and even azido (entries 6-8 and 10).

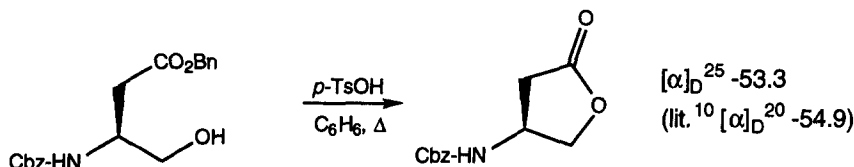
In the case of cinnamic acid (entry 11), the major product was the expected allylic alcohol, but some 3-phenylpropanol was also formed, the product arising from 1,4-conjugate reduction. Previously described [4,6] protocols developed for reducing activated esters with  $\text{NaBH}_4$  are selective for 1,2-reductions of  $\alpha,\beta$ -unsaturated systems, but  $\text{NaBH}_4$  has previously been shown to reduce other cinnamate esters in a 1,4-fashion [9].

A typical procedure is as follows: *N,N*-Diisopropylethylamine (DIPEA) (210  $\mu\text{l}$ , 1.20 mmol) was added to a stirred suspension of 5-azidopentanoic acid (143 mg, 1.00 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) (487 mg, 1.10 mmol) in 5 ml of THF at room temperature. The resulting solution was stirred for 5 min, then  $\text{NaBH}_4$  (38 mg, 1.0 mmol) was added (CAUTION: gas evolution). After stirring for 20 min, the solvent was evaporated and the residue was taken up in diethyl ether (50 ml) and washed with 5% HCl (3x10 ml), saturated  $\text{NaHCO}_3$  (3x10 ml) and brine (10 ml), then dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to a colourless oil. This was dissolved in a little

<sup>2</sup> A by-product of this reaction is the carcinogen hexamethylphosphoramide (HMPA). We expect that pyBOP (benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate) could be used in the place of BOP for these reductions.

diethyl ether and filtered through a plug of silica. Evaporation of the filtrate gave 5-azidopentanol (120 mg, 93%) as a colourless oil.

This procedure can be applied to the reduction of *N*-protected amino acids. For example, Cbz-Asp(OBn)-ol was prepared in high yield from Cbz-Asp(OBn)-OH (entry 9). That this reduction proceeded without epimerisation at the  $\alpha$ -carbon was demonstrated by converting the product to the known Cbz-protected lactone by refluxing in benzene with a catalytic amount of 4-toluenesulfonic acid (Scheme 2). The optical rotation of this material was comparable with that reported by McGarvey *et al.* [10].



Scheme 2

In summary a simple, rapid and high-yielding procedure has been developed for the reduction of a wide range of carboxylic acids to their corresponding alcohols.<sup>3</sup>

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<sup>3</sup> Selected spectral data: **2-Bromohexanol (entry 7)**:  $^1\text{H}$  n.m.r. (300 MHz,  $\text{CDCl}_3$ ) 4.20-4.11, 1H, m, CHBr; 3.82, 1H, dd(*J* 4.1, 12.3),  $\text{CH}_2\text{O}$ ; 3.75, 1H, dd(*J* 7.0, 12.2),  $\text{CH}_2\text{O}$ ; 1.90-1.82, 2H, m,  $\text{CH}_2\text{CHBr}$ ; 1.69, 1H, br s, OH; 1.54-1.26, 4H, m,  $2\times\text{CH}_2$ ; 0.93, 3H, t(*J* 7.2),  $\text{CH}_3$ .  $^{13}\text{C}$  n.m.r. (75 MHz,  $\text{CDCl}_3$ ) 13.9, 22.1, 29.6, 34.6, 60.2, 67.3.

**6-Iodoohexanol (entry 8)**:  $^1\text{H}$  n.m.r. (300 MHz,  $\text{CDCl}_3$ ) 3.61, 2H, t(*J* 6.5),  $\text{CH}_2\text{O}$ ; 3.18, 2H, t(*J* 7.0),  $\text{CH}_2\text{I}$ ; 1.89, 1H, br s, OH; 1.82, 2H, quin(*J* 7.1),  $\text{CH}_2\text{CH}_2\text{I}$ ; 1.55, 2H, quin(*J* 6.8),  $\text{CH}_2\text{CH}_2\text{O}$ ; 1.44-1.32, 4H, m,  $\text{CH}_2\text{CH}_2$ .  $^{13}\text{C}$  n.m.r. (75 MHz,  $\text{CDCl}_3$ ) 7.05, 24.6, 30.2, 32.4, 33.3, 62.6.

**Cbz-Asp(OBn)-ol (entry 9)**: m.p. 74.5-75.9 °C (lit. [3] m.p. 73-75 °C).  $^1\text{H}$  n.m.r. (300 MHz,  $\text{CDCl}_3$ ) 7.30-7.40, 10H, m,  $10\times\text{ArH}$ ; 5.48, 1H, br d(*J* 5.9), NH; 5.12, 2H, s and 5.10, 2H, s,  $2\times\text{PhCH}_2$ ; 4.05-4.15, 1H, m,  $\text{H}_\alpha$ ; 3.73, 2H, d(*J* 4.8),  $\text{CH}_2\text{OH}$ ; 2.70, 2H, d(*J* 6.1),  $\text{CH}_2\text{CO}_2$ ; 2.00, 1H, br s, OH.  $^{13}\text{C}$  n.m.r. (75 MHz,  $\text{CDCl}_3$ ) 35.9, 49.8, 64.3, 66.7, 66.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 135.4, 136.2, 156.2, 171.5.

**5-Azidopentanol (entry 10)**:  $^1\text{H}$  n.m.r. (300 MHz,  $\text{CDCl}_3$ ) 3.63, 2H, t(*J* 6.3),  $\text{CH}_2\text{N}_3$ ; 3.27, 2H, t(*J* 6.8),  $\text{CH}_2\text{O}$ ; 1.83, 1H, br s, OH; 1.67-1.54, 4H, m and 1.49-1.41, 2H, m,  $3\times\text{CH}_2$ .  $^{13}\text{C}$  n.m.r. (75 MHz,  $\text{CDCl}_3$ ) 22.9, 28.6, 32.1, 51.3, 62.4. Infrared (thin film) 3354, 2096  $\text{cm}^{-1}$ .

5-Azidopentanoic acid was prepared in two steps, by the reaction of methyl 5-bromopentanoate with  $\text{NaN}_3$  in DMF (95% yield), followed by hydrolysis of methyl 5-azidopentanoate with LiOH in THF/ $\text{H}_2\text{O}$  (99% yield).  $^1\text{H}$  n.m.r. (300 MHz,  $\text{CDCl}_3$ ) 11.05, 1H, br s, OH; 3.31, 2H, t(*J* 6.3),  $\text{CH}_2\text{N}_3$ ; 2.40, 2H, t(*J* 6.9),  $\text{CH}_2\text{CO}$ ; 1.77-1.62, 4H, m,  $\text{CH}_2\text{CH}_2$ .  $^{13}\text{C}$  n.m.r. (75 MHz,  $\text{CDCl}_3$ ) 21.7, 28.1, 33.3, 51.0, 179.1. Infrared (thin film) 2100, 1709  $\text{cm}^{-1}$ .