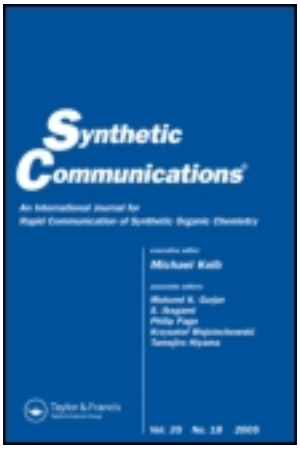


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# Facile and Chemoselective Reduction of Carboxylic Acids into Alcohols via Sodium Borohydride Reduction of N-Acylbenzotriazoles

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# Facile and Chemoselective Reduction of Carboxylic Acids into Alcohols via Sodium Borohydride Reduction of N-Acylbenzotriazoles

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**Abstract:** Carboxylic acids are converted into corresponding alcohols by chemoselective reduction of their benzotriazole amides with sodium borohydride.

**Keywords:** Alcohols, benzotriazole amides, carboxylic acids, reduction

Reduction of carboxylic acids to alcohols is a useful and important transformation in synthetic organic chemistry and is summarized by Larock.[1] Some reagents such as lithium aluminium hydride and borane suffer from limitations such as use of anhydrous solvent, hazards in handling, and incompatibility with other functional or protective groups present in the molecule. Although esters are inert to sodium borohydride,[2] the reducing power can be enhanced by addition of suitable reagents. Alternatively in situ formed mixed anhydrides were reduced with sodium borohydride.[3,4] McGeary reported the reduction of carboxylic acids via hydroxybenzotriazole esters prepared in situ from carboxylic acid and BOP reagents.[5] The chemoselective reduction of carboxylic acids by activation of carbonyl group with cyanuric chloride/fluoride followed by reduction with sodium borohydride has also been reported.[6,7] This article reports the use of benzotriazole for the conversion of carboxylic acids to alcohols. Carboxylic acids were converted into the corresponding N-acylbenzotriazoles **1** in good yields by

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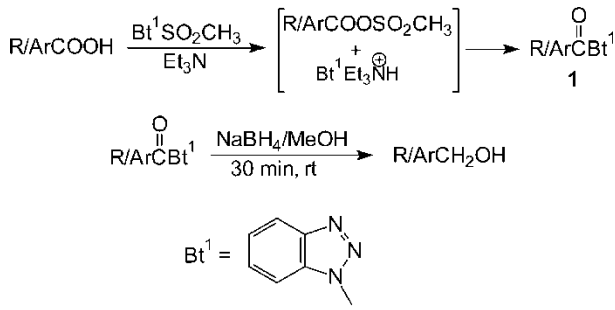


***Scheme 1.***

the known procedure (Scheme 1).[8] The N-acylbenzotriazole derivatives were reduced with 1.0 equiv. of sodium borohydride in methanol to furnish the corresponding alcohols in good yields.

As is evident from Table 1 (entries 10 and 11), this procedure can also be used for the reduction of N-protected amino acids to N-protected amino alcohols in acceptable yields. Moreover, no epimerization at the $\alpha$-carbon was indicated by comparison of the specific rotation value of the product (entry 10) with that reported in literature.[9]

***Table 1.*** Reduction of N-acylbenzotriazoles with sodium borohydride

| Entry | Starting material | Product | Yield (%)[a] |
|---|---|---|---|
| 1 | $C_6H_5COBt^1$ | $C_6H_5CH_2OH$ | 92 |
| 2 | 2-$CH_3C_6H_4$ $COBt^1$ | 2-$CH_3C_6H_4CH_2OH$ | 89 |
| 3 | 4-$CH_3C_6H_4$ $COBt^1$ | 4-$CH_3C_6H_4CH_2OH$ | 78 |
| 4 | 4-$NO_2C_6H_4$ $COBt^1$ | 4-$NO_2C_6H_4CH_2OH$ | 84 |
| 5 | 4-$ClC_6H_4$ $COBt^1$ | 4-$ClC_6H_4CH_2OH$ | 85 |
| 6 | 2-pyridyl $COBt^1$ | 2-pyridyl$CH_2OH$ | 72 |
| 7 | 4-Pyridyl $COBt^1$ | 4-pyridyl$CH_2OH$ | 79 |
| 8 | $PhCH_2$ $COBt^1$ | $PhCH_2CH_2OH$ | 86 |
| 9 | $PhCH=CHCOBt^1$ | $PhCH=CHCH_2OH$<br>$PhCH_2CH_2CH_2OH$ | 84[b] |
| 10 | $PhCH_2\underset{\displaystyle NHBOC}{\underset{\vert}{C}}HCOBt^1$ | $PhCH_2\underset{\displaystyle NHBOC}{\underset{\vert}{C}}HCH_2OH$ | 76[c] |
| 11 | $(CH_3)_2CHCH_2\underset{\displaystyle NHTs}{\underset{\vert}{C}}HCOBt^1$ | $(CH_3)_2CHCH_2\underset{\displaystyle NHTs}{\underset{\vert}{C}}HCH_2OH$ | 86[d] |

[a]Yields refer to purified isolated products characterized by relevant spectroscopic data.

[b]Ratio of unsaturated to saturated alcohol was estimated to be 70:14 from $^1$H NMR spectrum of the crude product.

[c]Mp 92–93°C (lit.[9] Mp 94.5°C); $[\alpha]_D^{25}$ −23.9° (*c* 0.56, $CHCl_3$) [lit.[9] $[\alpha]_D^{25}$ −24.6° (*c* 1, $CHCl_3$)].

[d]$[\alpha]_D^{25}$ −21.27° (*c* 0.33, $CHCl_3$).

## TYPICAL PROCEDURE FOR REDUCTION OF N-[1-(BENZOTRIAZOLE-1-CARBONYL)-3-METHYL-BUTYL]-4-METHYL-BENZENESULFONAMIDE (ENTRY 11)

Sodium borohydride (0.076 g, 2.0 mmol) was added portionwise to a stirred solution of N-[1-(benzotriazole-1-carbonyl)-3-methyl-butyl]-4-methyl-benzenesulfonamide (0.772 g, 2.0 mmol) in methanol (25 mL) at 0°C. After 30 min the ice bath was removed and stirring was continued for 30 min at room temperature. The solvent was removed on a rotary evaporator, and water (20 mL) was added. It was extracted with chloroform (3 × 10 mL), and the combined organic extract was washed with water and brine and dried over anhydrous $Na_2SO_4$. The solvent was evaporated, and the residue was crystallized from hexane/dichloromethane to furnish N-(1-hydroxymethyl-3-methyl-butyl)-4-methyl-benzenesulfonamide as a white solid (0.435 g, 86%), mp 103–105°C, $[\alpha]_D^{25} = -21.3^\circ$ (*c* 0.33, $CHCl_3$). IR (Nujol) $\nu$: 3491, 3173 $cm^{-1}$.

## DATA

$^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 0.55–0.57 (d, 3H, C$\underline{H}_3$), 0.62–0.65 (d, 3H, C$\underline{H}_3$), 1.17–1.31 [m, 2H, $(CH_3)_2CHC\underline{H}_2$], 1.39–1.52 [m, 1H, $(CH_3)_2C\underline{H}$], 2.34 (br s, 1H, O$\underline{H}$), 2.43 (s, 3H, ArC$\underline{H}_3$), 3.24–3.34 (m, 1H, $CH_2C\underline{H}CH_2OH$), 3.42–3.47 (m, 1H, C$\underline{H}$H-OH), 3.55–3.60 (m, 1H, CH$\underline{H}$OH), 4.95–4.98 (d, 1H, N$\underline{H}$), 7.26–7.32 (d, 2H, Ar$\underline{H}$), 7.77–7.80 (d, 2H, Ar$\underline{H}$). $^{13}$C NMR ($CDCl_3$, 300 MHz): $\delta$ 21.48, 21.83, 22.66, 24.27, 40.91, 53.79, 65.13, 127.13, 129.64, 137.56, 143.49. Anal. calcd. for $C_{13}H_{21}NSO_3$: C, 57.56; H, 7.74; N, 5.16. Found: C, 57.68; H, 7.80; N, 5.12.

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