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An extremely simple, convenient and mild one-pot reduction of carboxylic acids to alcohols using 3,4,5-trifluorophenylboronic acid and sodium borohydride

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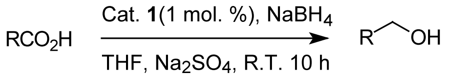
Abstract—Acyloxyboron intermediates formed in situ from carboxylic acids and 3,4,5-trifluorophenylboronic acids react with sodium borohydride in THF to give alcohols in good to high yields. © 2003 Elsevier Science Ltd. All rights reserved.

The reduction of carboxylic acids to alcohols is a key synthetic transformation in organic chemistry.[1] There are several ways to bring about this transformation.[2] These include lithium aluminium hydride, borane and modified sodium borohydride. These methods, however suffer from the limitations such as the need for anhydrous solvents, hazards in handling the reagents, and incompatibility with other functionalities in the substrate. There have also been some reports on the use of sodium borohydride in combination with chlorotrimethylsilane,[3] nickel chloride-diglyme,[4] iodine,[5] and catechol,[6] for the direct conversion of carboxylic acids to the corresponding alcohols.

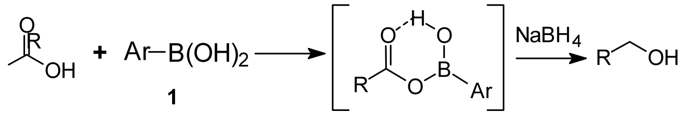
In order to achieve functional group compatibility, an alternative approach is to transform the carboxylic acid into an activated derivative such as mixed anhydrides[7–10] (carboxylic carbonic anhydrides), carboxyl methyl eniminium chlorides,[11] hydroxybenzotriazolyl (HOBt) esters[12] and cyanurates,[13] which can then be reduced with a mild reducing agent like sodium borohydride. Although these procedures often result in good yields of product, they can involve the use of hazardous and expensive reagents.



Scheme 1.

In view of the great utility of the transformation of carboxylic acids into alcohols,[1] an alternative route to bring about this transformation is desirable. In continuation of our interest in the catalytic applications of arylboronic acids, in particular 3,4,5-trifluorophenylboronic acid **1** for organic transformations,[14] we describe here another remarkable catalytic activity of boronic acid **1**, in this case, for the one-pot reduction of carboxylic acids to alcohols using sodium borohydride (Scheme 1).

The reaction is thought to proceed via a six-membered cyclic acyloxyboron intermediate (Scheme 2).



Scheme 2. Ar = 3,4,5-trifluorophenyl.

Keywords: carboxylic acid; 3,4,5-trifluorophenylboronic acid; acyloxyboron intermediates; reduction.

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Table 1. Reduction of carboxylic acids with $NaBH_4$ and boronic acid **1**

Entry	Carboxylic acids	Yield of alcohol[a,b] (%)
1	$R=CH_3(CH_2)_7$-	90
2	$R=Br(CH_2)_3$-	80
3	$R=PhCH_2$-	90
4	R=Ph-	89
5	$R=N_3(CH_2)_4$-	85
6	$R=p$-ClC_6H_4-	87
7	$R=p$-NCC_6H_4-	89
8	$R=p$-HOC_6H_4-	85
9	$R=p$-$O_2NC_6H_4$-	78
10	$R=3,4,5$-$(MeO)_3C_6H_2$-	94
11	$R=2,4$-$(MeO)_2C_6H_3$-	99
12	R=Cbz-Pro-OH	82

[a] Yields refer to the pure isolated product.

[b] Products were characterized by their physical constants, spectroscopic data (IR, ^1H NMR) and elemental microanalyses.

The treatment of various structurally diverse carboxylic acids with sodium borohydride in the presence of a catalytic amount of boronic acid **1** in THF at room temperature resulted in the formation of the corresponding alcohols in good to high yields. The results are summarized in Table 1. As shown in Table 1, carboxylic acids bearing functionalities such as halogeno, cyano, hydroxy, nitro, and even azido, elsewhere in the molecule, underwent smooth reduction by this method. Interestingly, an *N*-protected amino acid (entry 12) was successfully transformed into the corresponding *N*-protected amino alcohol under the reaction conditions, in 82% isolated yield. Therefore this procedure is expected to be suitable for other protected amino acids.

It is important to note that boronic acids $RB(OH)_2$, are usually crystalline solids, stable to air and moisture. Such evidence as exists indicates that they are of relatively low toxicity[15] and environmental impact. Furthermore, a very small amount of boronic acid **1** was found to be an effective catalyst for the reduction of carboxylic acids to alcohols. Thus it is evident that this method is quite safe and inexpensive, in contrast to other reported methods such as those involving the expensive BOP reagent[12] and the hazardous cyanuric chloride.[13]

In conclusion, we have developed a mild, simple, general and relatively benign protocol for the one-pot reduction of carboxylic acids to the corresponding alcohols.

General procedure:

To a solution of carboxylic acid (2 mmol) and sodium borohydride (95 mg, 2.5 mmol) in THF (10 ml) was added Na_2SO_4 (1 g) and boronic acid **1** (1 mol%) and the mixture was stirred at room temperature for 10 h (evolution of gas was observed). After completion of the reaction (TLC), the mixture was filtered, the solvent was evaporated and the residue was taken up in diethyl ether (50 ml), washed with saturated $NaHCO_3$ (3×10 ml) and brine (10 ml). After drying over anhydrous Na_2SO_4, the ether was evaporated to give the product. The product was purified by column chromatography (silica gel, ethyl acetate: petroleum ether, 1:9).

Acknowledgements

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