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Reduction of pentafluorophenyl esters to the corresponding primary alcohols using sodium borohydride

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Abstract—Primary alcohols and chiral N-protected 2-amino alcohols can be obtained in high yields from the reaction of pentafluorophenyl esters of the corresponding carboxylic acids with sodium borohydride in THF under mild conditions. This reductive method is rapid and compatible with various functional groups as well as with the most common N-protective groups Z, Boc and Fmoc.

Reduction of carboxylic acids to alcohols is an important transformation in synthetic organic chemistry. The available methods have been summarized by Larock.[1] There have also been reports on the use of sodium borohydride in combination with iodine,[2] cathechol–TFA,[3] aluminium hydride and triethylamine,[4] $ZnBH_4$ and trifluoroacetic anhydride,[5] sodium borohydride in the presence of either the SmI_2–$Sm(OTf)_3$–MeOH system[6] or 3,4,5-trifluorophenyl boronic acid.[7]

Primary alcohols can also be obtained by converting carboxylic acids into a variety of derivatives, which are subsequently reduced under mild conditions. Esters can be reduced with $ZnBH_4$ under sonication,[8] or with $Ti(O\textit{i}\text{-}Pr)_4$ and $(EtO)_3SiH$,[9] or by electroreduction.[10]

The sodium borohydride reduction of mixed anhydrides,[11–14] carboxyl methyl eniminium chlorides,[15] 1-succinimidyl esters,[16] 1-hydroxybenzotriazolyl (HOBt) esters,[17] fluorides,[18] chlorides,[19] and aromatic carboxylic acids via methyl esters[20] has also been reported.

N-Acyl amino acids and free amino acids,[21] as well as pentachlorophenyl esters of *N*-Boc-protected amino acids[22] can also be reduced with the $NaBH_4$–I_2 system in THF. In general, several methods have been reported for the enhancement of reactivity and selectivity of sodium borohydride in organic synthesis which have been reviewed by Periasamy and Thirumalaikumar.[23]

N-Protected 2-amino alcohols are valuable starting materials for the synthesis of optically active intermediates, such as α-amino aldehydes,[24] diamines[25] and triamines[26] as well as for the synthesis of enzyme inhibitors,[27] anti-inflammatory[28] and cytotoxic agents.[29]

We present here a convenient method for the preparation of primary alcohols and optically pure N-protected 2-amino alcohols by the sodium borohydride reduction of pentafluorophenyl esters of the corresponding carboxylic acid or N-protected-L-amino acids, respectively, within 15 min–4.0 h, at room temperature (Scheme 1).

The increased reactivity of such esters might be regarded as an additional exemplification of organofluorine chemistry in which functional groups placed in a different electronic environment strongly modify the reactivity in comparison with the corresponding hydrogenated molecules.

We prepared a variety of carboxylic acid and N-protected amino acid pentafluorophenyl esters[30] in almost quantitative yields. The active esters were converted into alcohols in dry THF with $NaBH_4$ at room temperature, as described below.

Keywords: Reduction; Pentafluorophenyl esters; Alcohols; Amino alcohols.
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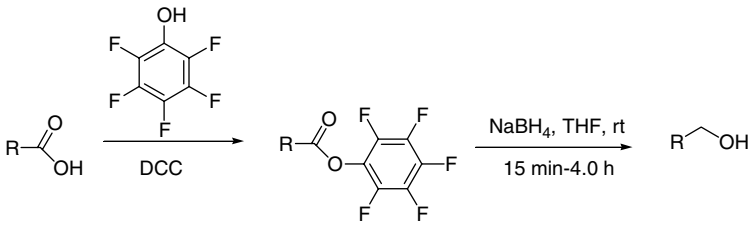


Scheme 1.

Table 1. Reaction time and yields of alcohols obtained by reduction of pentafluorophenyl esters (RCOOPfp) using $NaBH_4$ in THF

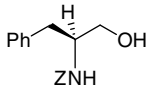
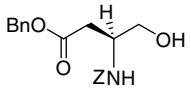
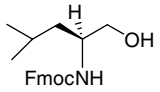
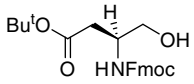
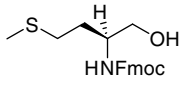
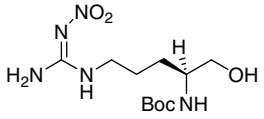
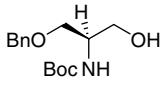
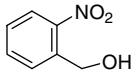
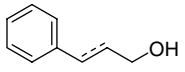
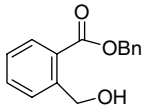
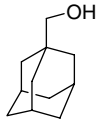
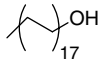
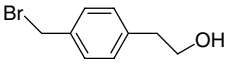
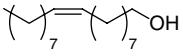
Entry	Alcohol	Yield[a] (%)	Time
1		95	15 min
2		90	15 min
3		95	15 min
4		92[b]	30 min
5		85	20 min
6		95	15 min
7		90[b]	15 min
8		95	2.5 h
9		80[b,c]	3.5 h
10		90[d]	3.5 h
11		85	3.5 h
12		80	3.5 h

Table 1 (*continued*)

Entry	Alcohol	Yield[a] (%)	Time
13		85	3.5 h
14		68[e]	4 h

[a] Yields refer to isolated and purified products.
[b] Purified by column chromatography using petroleum ether–ethyl acetate 1:1.
[c] A 75:25 ratio of unsaturated:saturated alcohols was produced.
[d] Purified by column chromatography using petroleum ether–ethyl acetate 7:3.
[e] Purified by preparative TLC using chloroform–methanol 9:1.

The reductions were complete within 15–30 min in the case of the amino acids, but took longer (2.5–4.0 h) in other cases (Table 1).

All the products were characterized by ^1H NMR, ^{13}C NMR, IR, melting points and measurement of the specific rotation and were found to be in accordance with those in the literature.

The choice of $NaBH_4$ as a reducing agent was especially advantageous when compared with the $NaBH_4$–I_2 system that has been used in similar cases. It is a simpler reagent and led to faster reactions and higher yields in all the cases studied. For example, in the case of *N*-Cbz–phenylalaninol (entry 1) the $NaBH_4$–I_2 system gave an 80% yield after 1.5 h and with 4-(bromomethyl)-benzeneethanol (entry 13), the reaction was left overnight to afford the product in 60% yield.

Our method is also compatible with other functional groups such as halide, nitro, ester (OBn, OBu^t), the benzyl ether of serine and thioether of methionine. Moreover, the most common N-protecting groups (Z, Boc, Fmoc) of amino acids remained intact.

In the case of cinnamic acid (entry 9), the major product was the expected allylic alcohol, but some 3-phenylpropanol, arising from 1,4-conjugate reduction, was also observed. Such reduction of cinnamate esters in a 1,4-fashion had been previously described.[17,31]

In conclusion, the simplicity of the reduction procedure applied on very easily prepared or commercially available pentafluorophenyl esters, the high yields of the

obtained products in very short times, combined with high optical purity in the case of 2-amino alcohols from L-amino acids, are prominent features of the present method.

General procedure: To a suspension of $NaBH_4$ (1.2–1.5 mmol)[32] in dry THF (2–3 mL), pentafluorophenyl ester (1 mmol) was added and the mixture was stirred at room temperature. The reaction was followed by TLC and upon completion, the mixture was cooled to 0 °C, acidified with 1 N HCl and evaporated under vacuum. The residue was diluted with ethyl acetate and washed with water and brine. After drying over Na_2SO_4 and evaporation of the solvent, the product was isolated and purified by recrystallization, column chromatography or preparative TLC.

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32. Excess $NaBH_4$ (50%) was used for the reactions in entries 8, 11 and 13.