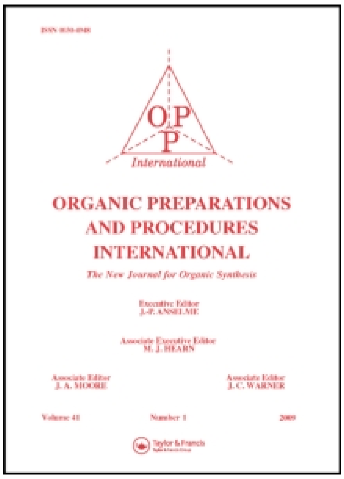

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# A CONVENIENT REDUCTION OF HIGHLY FUNCTIONALIZED AROMATIC CARBOXYLIC ACIDS TO ALCOHOLS WITH BORANE-THF AND BORON TRIFLUORIDE-ETHERATE

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# A CONVENIENT REDUCTION OF HIGHLY FUNCTIONALIZED AROMATIC CARBOXYLIC ACIDS TO ALCOHOLS WITH BORANE-THF AND BORON TRIFLUORIDE-ETHERATE

*Submitted by* (12/04/01)
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The reduction of carboxylic acids to the corresponding alcohols has been performed with a variety of metal hydrides and complex metal hydrides, such as $LiAlH_4$, and its alkoxy derivatives,[1] $NaBH_4$-Lewis acids,[2] boranes[3] and combinations of borane-Lewis acids.[4] The selective reduction of highly functionalized aromatic carboxylic acids with borane complexes is still not very well studied in the literature. During the recent synthesis of an important neurodegeneration inhibitor and its analogs, large quantities of key intermediate 3-hydroxy-4-nitrobenzyl alcohol (**2**) were needed. Compound **2** could be obtained from the reduction 3-hydroxy-4-nitrobenzoic acid (**1**). Most of the known reducing reagents, such as $LiAlH_4$,[5] $BH_3$-THF,[3b] $BH_3$-$Me_2S$,[6] $NaBH_4/I_2$,[7] $ClCO_2$*i*-Bu/$NaBH_4$,[8] and *i*-$Bu_2AlH$,[9] gave incomplete (0–60% conversion) reaction.[10] However, the reduction of compound **1** with the combination of $BH_3$-THF and $BF_3$-$Et_2O$ gave complete conversion and 91% isolated yield of alcohol **2**. A thorough on-line literature search showed no previous examples using this combination for the reduction of functionalized aryl carboxylic acids to the corresponding benzyl alcohols. This encouraged us to further study this reagent in reduction reactions.

The reaction we now report involves the addition of a 1.0 M solution of $BH_3$-THF in THF to a mixture of benzoic acid and $BF_3$-$Et_2O$ in THF at ambient temperature and under an inert atmosphere. Hydrogen gas evolves immediately. The reaction mixture is then stirred at ambient temperature overnight. After quenching with methanol, the crude product is purified by recrystallization or chromatography. The results of the reaction are summarized in Table 2. This reduction tolerates a variety of functional groups on the benzoic acids such as nitro, hydroxy, chloro, bromo, trifluoromethyl, thio, cyano and methyl ester. Very good to excellent yields were obtained from the reduction of these highly functionalized compounds. The reduction of 3-hydroxy-4-methyl-2-nitrobenzoic acid gave both low conversion and yield. This may be due to the electron-withdrawing nitro group *ortho* to the carboxylic acid, as discussed by Brown and coworkers.[3b] Diacids were reduced to the corresponding diols when 4 eq of borane-THF and 2 eq of $BF_3$-$Et_2O$ were applied. Attempted partial reduction of the diacid with one half of the borane-THF complex unfortunately led to a low yield (42%) of the desired reduction product, together with some diol and recovered diacid. A highly halogenated acid (5-bromo-2,3,4-trifluorobenzoic acid) was reduced in 96% yield without the fluorine or bromine functions being affected. A heterocyclic acid also gave a good yield of the reduction product. Aliphatic acids, which are well known to be more easily reduced than their aromatic counterparts, are expected to undergo this transformation under these conditions and an example is provided in the last entry of Table 2, where the keto group was reduced as well. The reduction of 3-hydroxy-4-nitrobenzoic acid (**1**) with $BH_3$-$SMe_2$/$BF_3$-$Et_2O$ using the literature conditions[4] gave alcohol **2** in 66% yield, which is much lower than our result (91%).

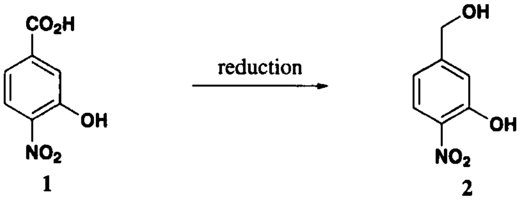


**Table 1**. Reactant Ratio Study for the Reduction of 1 to 2

| Entry | Acid (mmols) | $BH_3$-THF (mmols) | $BF_3$-$Et_2O$ (mmols) | Yield % |
|---|---|---|---|---|
| 1 | 10 | 20 | 5 | 63 |
| 2 | 10 | 20 | 10 | 91 |
| 3 | 10 | 20 | 15 | 90 |
| 4 | 10 | 20 | 20 | 82 |
| 5 | 10 | 5 | 10 | No Reaction |
| 6 | 10 | 10 | 10 | No Reaction |
| 7 | 10 | 15 | 10 | 59 |
| 8 | 10 | 25 | 10 | 77 |

The best ratio of reactants for the reduction of 3-hydroxy-4-nitrobenzoic acid was determined and the results are listed in Table 1. No reaction occurred when less than 1.5 eq. of $BH_3$-THF was used (entries 5, 6). With a fixed amount of $BH_3$-THF (2.0 eq.) and less than 1.0 eq. (entry 1) or more than 1.5 eq. (entry 4) of $BF_3$-$Et_2O$ lower yields were obtained. Similar yields resulted when 1.0 or 1.5 eq. of $BF_3$-$Et_2O$ was used. When the amount of $BF_3$-$Et_2O$ (1.0 eq.) was fixed, the best result was obtained when 2.0 eq. of $BH_3$-THF (entry 8) was applied. We found that the optimum ratio is acid: $BH_3$-THF : $BF_3$-$Et_2O$ = 1 : 2 : 1. We also carried out this reduction in hexane (60% yield), ethyl acetate (61% yield), diethyl ether (70% yield) and methylene chloride (79% yield). THF gave the best result (91% yield), possibly due to the greater solubility of the acid in this solvent.

In conclusion, we have developed a useful method to convert aromatic carboxylic acids to their corresponding benzylic alcohols using the combination of borane-THF and boron trifluoride-etherate complex. A wide variety of functional groups can be tolerated with these mild reaction conditions. The facile reaction experimental conditions, the ease of work-up, and the excellent yields of the isolated products indicate that the reduction of benzoic acids with this methodology is a useful and convenient method for the preparation of highly functionalized benzyl alcohols.

**Table 2.** Reduction of Substituted Benzoic Acids with $BH_3$-THF/$BF_3$-$Et_2O$

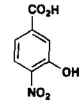
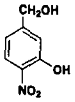
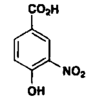
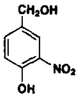
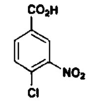
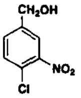
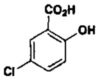
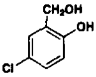
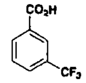
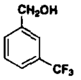
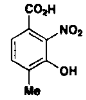
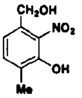
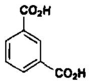
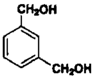
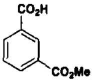
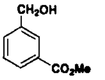
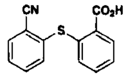
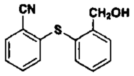
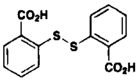
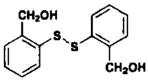
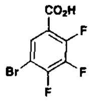
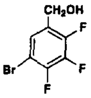
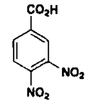
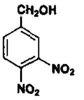
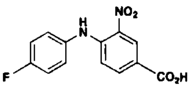
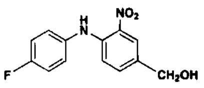
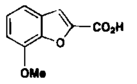
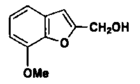
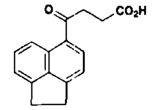
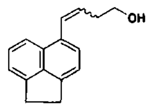
| Entry | Acid | Product[a] | % Yield | mp (°C) | Lit. mp(°C) |
|---|---|---|---|---|---|
| 1 |  |  | 91 | 93-94 | 90-92[11] |
| 2 |  |  | 93 | 92-93 | 97[12] |
| 3 |  |  | 96 | 60-62 | 66[13] |
| 4 |  |  | 85 | 87-89 | 90-91[14] |
| 5 |  |  | 97 | Oil | Oil[15] |
| 6 |  |  | 24[b] | 70-71 | c |
| 7 |  |  | 95 | 56-58 | 57[16] |
| 8 |  |  | 82 | Oil | Oil[17] |
| 9 |  |  | 68 | 76-77 | Ref. [18] |
| 10 |  |  | 75 | 136-137 | 141-142[19] |
| 11 |  |  | 96 | Oil | d |
| 12 |  |  | 89 | 133-135 | 55.5-57[20] |

**Table 2.** Continued...

| Entry | Acid | Product[a] | % Yield | mp (°C) | Lit. mp(°C) |
|---|---|---|---|---|---|
| 13 |  |  | 88 | 154-155 | e |
| 14 |  |  | 86 | Oil | Oil[21] |
| 15 |  |  | 91 | Oil[22] | f |

a) All structures are confirmed by NMR, IR, and MS. Solid products were recrystallized from hexane-EtOAc, and liquid products were purified by flash chromatography (silica gel, hexane-EtOAc). b) Recovered acid: 29%. c) Calcd. For $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.07; H, 4.77; N, 7.55. d) Calcd. For $C_7H_4BrF_3O$: C, 34.89; H, 1.67; F, 23.65; Br, 33.16. Found: C, 35.02; H, 1.61; F, 23.75; Br, 33.38. e) Calcd. For $C_{13}H_{11}FN_2O_3$: C, 59.54; H, 4.23; N, 10.68; F, 7.24. Found: C, 59.26; H, 4.07; N, 10.54; F, 7.12. f) Calcd. For $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.60; H, 7.11.

## EXPERIMENTAL SECTION

The acids, BH3-THF and BF3-Et2O were obtained from Aldrich Chemical Co. and used as received. THF was obtained from Burdick & Jackson and freshly distilled from sodium. Melting points were determined with a Thomas Hoover apparatus and are uncorrected. $^1H$ NMR spectra were recorded on a Varian-Gemini-400 in $CDCl_3$ as both solvent and internal standard.

**General Procedure for the Reduction of Acids to Alcohols.**- To a solution of the substituted aromatic acid (10 mmol) in dry THF (50 mL, 0.2 M), at ambient temperature, under nitrogen atmosphere, was added boron trifluoride diethyl etherate (10 mmol), followed by the addition of borane-tetrahydrofuran complex (1.0 M solution in THF, 20 mmol) over 5 min. The mixture was stirred at ambient temperature for 18 hrs and then quenched by the careful addition of methanol until the gas evolution ceased and then with water (20 mL). The mixture was evaporated *in vacuo* and the residue was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by recrystallization or flash chromatography.

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10. The ratios of unreacted acid (**1**) and alcohol (**2**) in the final reaction mixtures were determined by HPLC and are as follows (**1**:**2**): LAH: 56:44; $BH_3$-THF: 36:64; $BH_3$-$Me_2S$: 37:63; $NaBH_4/I_2$: 100:0; $ClCO_2$*i*-Bu/$NaBH_4$: 100:0; and *i*-$Bu_2AlH$: 84:26.

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22. The keto group was also redued to the alcohol as expected according to: E. Breuer, *Tetrahedron Lett.*, **20**, 1849 (1967). Dehydration took place upon work-up of the reaction to give the conjugated alkene, regardless of the conditions used to quench it (methanol or water). From the $^1$H NMR spectrum, a 1/6.5 *cis/trans* ratio was determined.