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# A convenient method to reduce hydroxyl-substituted aromatic carboxylic acid with $NaBH_4/Me_2SO_4/B(OMe)_3$

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**Abstract**

The reduction of hydroxyl-substituted aromatic carboxylic acid with $NaBH_4/Me_2SO_4/B(OMe)_3$ is described. Borane is generated by the reaction of $NaBH_4$ with $Me_2SO_4$ in THF, which is as efficient as the commercial one. $B(OMe)_3$ has been successfully applied to increase the reactivity and selectivity of this reaction. The optimum ratio of borane/$B(OMe)_3$/acid is studied, and a variety of hydroxyl-substituted aromatic acids are reduced in good yields.


*Keywords:* Reductions; Aromatic carboxylic acids; Borane; Sodium borohydride; Trimethyl borate

Borane is a versatile reducing agent that has shown great utilities in organic synthesis,[1] such as hydroboration of unsaturated C–C bond,[2] reduction of carbonyl compounds,[3] oximes,[4] and imines.[5] However, borane itself is a very harmful and unstable gas. Although its stability is improved by complexing with THF or $SMe_2$, the storage of borane still needs an inert environment such as dry nitrogen or argon atmosphere and at low temperature.[6] Thus, the use of borane on large scale is limited. Alternatively, many $NaBH_4$/additive systems have been developed to replace borane in organic synthesis,[7] in which the additives included chlorotrimethylsilane,[8] iodine,[9] catechol,[10] phenylboronic acid,[11] Lewis acids,[12] and so on. Nevertheless, most of $NaBH_4$/additive reagents are not satisfying for either the low selectivity or high cost of the additives.

One of the most important applications of borane is reducing carboxylic acid to the corresponding alcohol with high selectivity at ambient temperature. The hydroxyl-substituted benzyl alcohol is an important intermediate in the synthesis of many pharmaceuticals.[13] However, while the hydroxyl-substituted carboxylic acid is reduced with borane, poor yield is obtained except much more borane is used because of the effect of hydroxyl group. Usually, the hydroxyl group needs protection before the carboxylic group is reduced, and deprotection after the reduction. The additional protection and deprotection reactions increase the cost and lower the overall yield. The convenient method to reduce hydroxyl-substituted carboxylic acid at ambient temperature is desirable. Herein, we report a novel combination of reagents $NaBH_4/Me_2SO_4/B(OMe)_3$ that reduces hydroxyl-substituted carboxylic acid with high yield in one-pot. BTHF ($BH_3$/THF complex) was generated in situ by the reaction of $NaBH_4$ with $Me_2SO_4$ in THF, while $B(OMe)_3$ was applied to increase the reactivity and selectivity without the protection of hydroxyl group.[14]

The preparation of BTHF was performed by stirring the suspension of $NaBH_4$ in THF together with 1.0 equiv of $Me_2SO_4$ for 1 h at 0 °C and further about 4 h at room temperature until the evolution of methane ceased. For comparison, BTHF prepared in situ with $NaBH_4$ and $Me_2SO_4$ was used in parallel with commercial BTHF (1 M, from Aldrich) to reduce 4-hydroxybenzoic acid. The yield is 92% (8.5 h) and 96% (4 h), respectively (Table 1, entries 8 and 9). Although the results show slight

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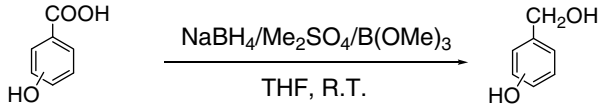
Table 1
The effect of reactant ratio to the reaction




| Entry | Substrate | Product | Equiv $BH_3$[a]/$B(OMe)_3$/acid | $T$ (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 4-HOPhCOOH | 4-HOPh$CH_2OH$ (**1**) | 2/0/1 | 4.5 | 52 |
| 2 | 4-HOPhCOOH | 4-HOPh$CH_2OH$ | 2/1/1 | 4.5 | 84 |
| 3 | 4-HOPhCOOH | 4-HOPh$CH_2OH$ | 2/1.5/1 | 4.5 | 93 |
| 4 | 4-HOPhCOOH | 4-HOPh$CH_2OH$ | 2/2/1 | 4.5 | 96 |
| 5 | 4-HOPhCOOH | 4-HOPh$CH_2OH$ | 2/3/1 | 4.5 | 96 |
| 6 | 4-HOPhCOOH | 4-HOPh$CH_2OH$ | 1.2/2/1 | 4.5 | 27 |
| 7 | 4-HOPhCOOH | 4-HOPh$CH_2OH$ | 1.2/3/1 | 4.5 | 23 |
| 8 | 4-HOPhCOOH | 4-HOPh$CH_2OH$ | 1.5/2/1 | 8.5 | 92 |
| 9 | 4-HOPhCOOH | 4-HOPh$CH_2OH$ | 1.5/2/1 | 4 | 96[c] |
| 10 | 4-HOPhCOOH | 4-HOPh$CH_2OH$ | 1.2/2/1 | 18 | 24[d] |
| 11 | 2-HOPhCOOH | 2-HOPh$CH_2OH$ (**2**) | 2/2/1 | 4 | 97 |
| 12 | 2-HOPhCOOH | 2-HOPh$CH_2OH$ | 2/1.1/1 | 4.5 | 98 |
| 13 | 2-HOPhCOOH | 2-HOPh$CH_2OH$ | 1.5/1.1/1 | 4.5 | 77 |
| 14 | 2-HOPhCOOH | 2-HOPh$CH_2OH$ | 1.2/1.1/1 | 28 | 97[d] |

[a] Borane was in situ prepared with $NaBH_4$ and $Me_2SO_4$ in THF.
[b] Determined by HPLC.
[c] BTHF (1.0 M) from Aldrich.
[d] The solvent was removed in vacuum after the acid reacted with $B(OMe)_3$ for 2 h, and the solid was dissolved in THF for reduction.

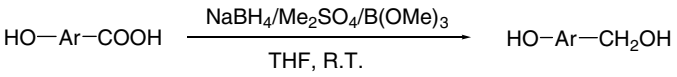
difference, BTHF prepared in situ is as efficient as the commercial one. We also considered to replace $Me_2SO_4$ with $Me_2CO_3$ in view of its toxicity, but it does not work. It is attributable to the lower activity of $Me_2CO_3$ compared with $Me_2SO_4$.

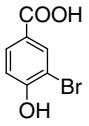
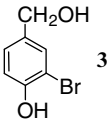
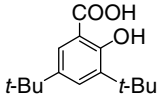
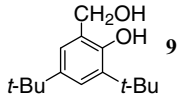
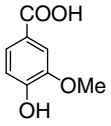
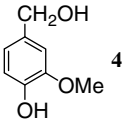
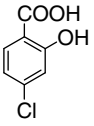
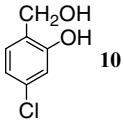
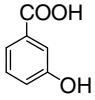
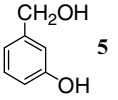
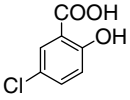
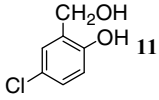
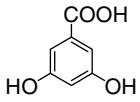
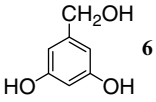
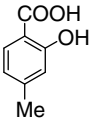
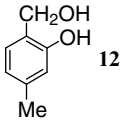
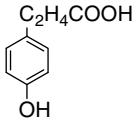
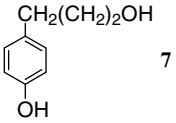
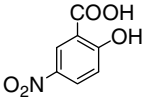
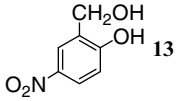
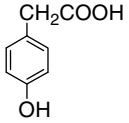
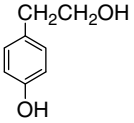
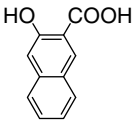
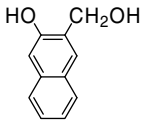
To optimize the reaction condition, 4-hydroxybenzoic acid was employed as the model substrate (Table 1). In the absence of $B(OMe)_3$, the yield was poor, and many side reactions occurred with 2.0 equiv of borane (entry 1). The yield increased with the addition of $B(OMe)_3$, and the best was obtained when 2.0 equiv of $B(OMe)_3$ was used (entries 2–4). Further increasing the amount of $B(OMe)_3$ to 3 equiv did not make significant improvement (entries 4 and 5). Efforts to minimize the amount of borane was unsuccessful. A little amount of acid was reduced when less than 1.5 equiv of $BH_3$/THF was used (entries 6 and 7). So the optimum ratio is borane/$B(OMe)_3$/acid = 2:2:1 for the reduction of 4-hydroxybenzoic acid. In the case of salicylic acid, 1 equiv of $B(OMe)_3$ was enough as the hydroxyl is on the *ortho* position to the carboxylic group (entries 11–13). This indicates $B(OMe)_3$ may have some interaction with the substrates. Considering MeOH may be generated when salicylic acid reacts with $B(OMe)_3$, and would consume 1 equiv of borane. If MeOH was removed, the amount of borane may fall. In order to decrease the amount of borane, salicylic acid was first reacted with $B(OMe)_3$ for about 2 h in THF, then THF and MeOH were removed in vacuum. The white solid obtained was dissolved in THF again, and then reduced by 1.2 equiv of borane. The product was obtained in 97% yield for 28 h (entry 14). But under the same condition, 4-hydroxybenzoic acid did not give the same result (24% yield for 18 h) (entry 10).

Having established the optimum condition, we applied this method to a number of hydroxyl-substituted aromatic acids (Table 2).[15] Good to excellent yields were obtained. Compared with 4-hydroxybenzoic acid, the reduction of 3-methoxy-4-hydroxybenzoic acid gave the product in 98% yield in 1.5 h. This may be due to the effect of electron-donating methoxy group *ortho* to the hydroxy group (entry 2). Dihydroxy substituted acid was successfully reduced to the corresponding alcohol when 2.5 equiv of borane and 3 equiv of $B(OMe)_3$ were applied (entry 4). Aliphatic acids are well known to be more easily reduced to the corresponding alcohols, so both of 4-hydroxy benzenepropanoic acid and 4-hydroxy benzeneacetic acid were reduced to give products in 98% yield in 1.5 h (entries 5 and 6). As for a series of salicylic acids, the substituted functional groups show slight effect on the reactivity. 3,5-Di-tetrabutyl-2-hydroxybenzoic acid was reduced more slowly (only 52% yield in 1.5 h, 6 h needed to complete the reaction) (entry 7) probably because of steric hindrance. The reduction of 4-methylsalicylic acid gave relatively low yield, which is ascribed to instability of the product.

In conclusion, we have developed a convenient and useful method to convert hydroxyl-substituted aromatic carboxyl acid to alcohol using the combination of $NaBH_4$, $Me_2SO_4$, and $B(OMe)_3$. The reagents $NaBH_4/Me_2SO_4$ can be used as a cheap large-scale resource of borane in the laboratory and in industry. The ease of work-up, and the excellent yields of the isolated products indicate that this is a useful and convenient method to prepare hydroxyl-substituted benzyl alcohols.

Table 2
Reduction of hydroxyl-substituted aromatic acids with $NaBH_4/Me_2SO_4/B(OMe)_3$[a]




| Entry | Substrate | Product | Yield[b] (%) | Entry | Substrate | Product | Yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 |  |  **3** | 93 | 7 |  |  **9** | 93[d,f] |
| 2 |  |  **4** | 98[e] | 8 |  |  **10** | 97[d] |
| 3 |  |  **5** | 97 | 9 |  |  **11** | 96[d] |
| 4 |  |  **6** | 81[c] | 10 |  |  **12** | 74[d] |
| 5 |  |  **7** | 98[e] | 11 |  |  **13** | 90[d] |
| 6 |  |  **8** | 98[e] | 12 |  |  **14** | 94[d] |

[a] Borane was in situ prepared with $NaBH_4$ and $Me_2SO_4$ in THF, $BH_3/B(OMe)_3$/acid = 2/2/1, reaction time 4.5 h.
[b] Isolated yield.
[c] $BH_3/B(OMe)_3$/acid = 2.5/3/1.
[d] $BH_3/B(OMe)_3$/acid = 2/1.1/1.
[e] Reaction time 1.5 h.
[f] Reaction time 6 h.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.078.

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14. *General procedure for the reduction of acids to alcohols*: Under a $N_2$ atmosphere, 0.79 g (20 mmol) of $NaBH_4$ (purity: 96%) and 20 mL of anhydrous tetrahydrofuran were introduced into a 50 mL three-neck flask equipped with pressure-equalizing addition funnel, a gas inlet pipe, a thermometer and magnetic stirring bar. The mixture was added dropwise with 2.55 g of $Me_2SO_4$ (20 mmol) at 0 °C over 3 min and stirred for 1 h in an ice-bath and further 4 h at room temperature until no gas generation was observed. A solution of 10 mmol of acid and 2.12 g of $B(OMe)_3$ in anhydrous tetrahydrofuran (10 mL) was added dropwise to the prepared $BH_3$/THF complex solution at room temperature over 30 min. The mixture was stirred at the same temperature for 4.5 h. After the reaction was completed, 10 mL of $H_2O$ was added slowly at 0 °C and the resulting mixture was vigorously stirred for 0.5 h. Then THF was removed on a rotary evaporator. The residue was extracted with ethyl acetate (3 × 50 mL), which was washed with saturated aqueous sodium bicarbonate (3 × 10 mL) and brine (3 × 10 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered, and concentrated to give products.
15. Spectroscopic data for products:
Compound **1**: $^1$H NMR (400 MHz, DMSO): $\delta = 9.25$ (s, 1H, Ph–O*H*), 7.10 (d, $J = 8.4$ Hz, 2H, Ph–*H*), 6.70 (d, $J = 8.4$ Hz, 2H, Ph-*H*), 4.97 (t, $J = 5.6$ Hz, 1H, C–O*H*), 4.36 (d, $J = 5.6$ Hz, 2H, Ph–C$H_2$).
Compound **2**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.35$ (s, 1H, Ph–O*H*), 7.20 (t, $J = 8.0$ Hz, 1H, Ph–*H*), 7.03 (d, $J = 7.6$ Hz, 1H, Ph–*H*), 6.82–6.90 (m, 2H, Ph–*H*), 4.83 (s, 2H, Ph–C$H_2$), 2.53 (s, 1H, $CH_2$–O*H*).
Compound **3**: $^1$H NMR (400 MHz, DMSO): $\delta = 10.05$ (s, 1H, Ph–O*H*), 7.41 (d, $J = 1.6$ Hz, 1H, Ph–*H*), 7.10 (dd, $J = 1.6$, 8.0 Hz, 1H, Ph–*H*), 6.90 (d, $J = 8.0$ Hz, 1H, Ph–*H*), 5.0 (br, 1H, C–O*H*), 4.37 (s, 2H, Ph–C$H_2$).
Compound **4**: $^1$H NMR (400 MHz, DMSO): $\delta = 8.74$ (s, 1H, Ph–O*H*), 6.88 (s, 1H, Ph–*H*), 6.70 (br, 2H, Ph–*H*), 4.97 (t, $J = 6.0$ Hz, 1H, C–O*H*), 4.37 (d, $J = 6.0$ Hz, 2H, Ph–C$H_2$), 3.75 (s, 3H, Ph–OC$H_3$).
Compound **5**: $^1$H NMR (400 MHz, DMSO): $\delta = 9.25$ (s, 1H, Ph–O*H*), 7.09 (d, $J = 8.0$ Hz, 1H, Ph–*H*), 6.74 (br, 1H, Ph–*H*), 6.71 (d, $J = 8.0$ Hz, 1H, Ph–*H*), 6.61 (dd, $J = 1.6$, 8.0 Hz, 1H, Ph–*H*), 4.8 (br, 1H, C–O*H*), 4.41 (s, 2H, Ph–C$H_2$).
Compound **6**: $^1$H NMR (400 MHz, DMSO): $\delta = 9.05$ (s, 2H, Ph–O*H*), 6.17 (s, 2H, Ph–*H*), 6.05 (s, 1H, Ph–*H*), 4.98 (t, $J = 6.0$ Hz, 1H, $CH_2$–O*H*), 4.30 (d, $J = 6.0$ Hz, 2H, Ph–C$H_2$).
Compound **7**: $^1$H NMR (400 MHz, $CDCl_3$ + DMSO): $\delta = 6.99$ (d, $J = 8.4$ Hz, 2H, Ph–*H*), 6.74 (d, $J = 8.4$ Hz, 2H, Ph–*H*), 3.60 (t, $J = 6.8$ Hz, 2H, HO–C$H_2$), 2.58 (t, $J = 8.0$ Hz, 2H, Ph–C$H_2$), 1.81 (m, 2H, Ph–C–C$H_2$).
Compound **8**: $^1$H NMR (400 MHz, DMSO): $\delta = 9.10$ (s, 1H, Ph–O*H*), 6.99 (d, $J = 8.4$ Hz, 2H, Ph–*H*), 6.66 (d, $J = 8.4$ Hz, 2H, Ph–*H*), 4.55 (t, $J = 4.8$ Hz, 1H, C–O*H*), 3.53 (m, 2H, HO–C$H_2$), 2.60 (t, $J = 7.2$ Hz,2H, Ph–C$H_2$).
Compound **9**: $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.54$ (s, 1H, Ph–O*H*), 7.28 (s, 1H, Ph–*H*), 6.89 (s, 1H, Ph–*H*), 4.82 (s, 2H, Ph–C$H_2$), 2.2 (br, 1H, C–O*H*), 1.43 (s, 9H, Ph–$^t$*Bu*), 1.28 (s, 9H, Ph–$^t$*Bu*).
Compound **10**: $^1$H NMR (400 MHz, DMSO): $\delta = 9.83$ (s, 1H, Ph–O*H*), 7.28 (d, $J = 8.0$ Hz, 1H, Ph–*H*), 6.83 (dd, $J = 2.0$, 8.0 Hz, 1H, Ph–*H*), 6.79 (d, $J = 2.0$ Hz, 1H, Ph–*H*), 4.6-5.1 (br, 1H, $CH_2$–O*H*), 4.44 (s, 2H, Ph–C$H_2$).
Compound **11**: $^1$H NMR (400 MHz, DMSO): $\delta = 9.64$ (s, 1H, Ph–O*H*), 7.27 (d, $J = 2.0$ Hz, 1H, Ph–*H*), 7.07 (dd, $J = 2.0$, 8.4 Hz, 1H, Ph–*H*), 6.76 (d, $J = 8.4$ Hz, 1H, Ph–*H*), 5.10 (t, $J = 5.2$ Hz, 1H, C–O*H*), 4.44 (d, $J = 5.2$ Hz, 2H, Ph–C$H_2$).
Compound **12**: $^1$H NMR (400 MHz, DMSO): $\delta = 9.13$ (s, 1H, Ph–O*H*), 7.13 (d, $J = 8.0$ Hz, 1H, Ph–*H*), 6.56–6.59 (m, 2H, Ph–*H*), 4.84 (br, 1H, C–O*H*), 4.43 (s, 2H, Ph–C$H_2$), 2.19 (s, 3H, Ph–C$H_3$).
Compound **13**: $^1$H NMR (400 MHz, DMSO): $\delta = 11.06$ (s, 1H, Ph–O*H*), 8.15 (d, $J = 2.8$ Hz, 1H, Ph–*H*), 7.97 (dd, $J = 2.8$, 8.8 Hz, 1H, Ph–*H*), 6.88 (d, $J = 8.8$ Hz, 1H, Ph–*H*), 5.31 (s, 1H, C–O*H*), 4.45 (s, 2H, Ph–C$H_2$).
Compound **14**: $^1$H NMR (400 MHz, DMSO): $\delta = 9.81$ (s, 1H, Ar-O*H*), 7.82 (s, 1H, Ar-*H*), 7.76 (d, $J = 8.0$ Hz, 1H, Ar-*H*), 7.65 (d, $J = 8.0$ Hz, 1H, Ar-*H*), 7.34 (t, $J = 7.6$ Hz, 1H, Ar-*H*), 7.24 (t, $J = 7.6$ Hz, 1H, Ar-*H*), 7.11 (s, 1H, Ar-*H*), 5.17 (s, 1H, C–O*H*), 4.66 (s, 2H, C$H_2$–OH).