Tetrahedron Vol. 48, No. 2, pp. 371-376, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00
Pergamon Press plc

Reduction of Carboxylic Acids into Alcohols Using $NaBH_4$ in the Presence of Catechol and/or CF_3COOH [†]

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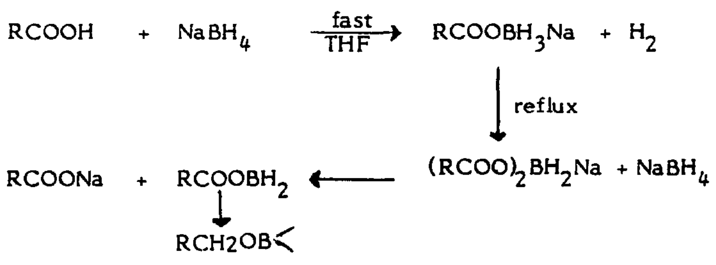
(*Received in UK* 12 *November* 1991)

Abstract: Reaction of aliphatic carboxylic acids (1 eq) using $NaBH_4$ (2 eq) and catechol (2 eq) in THF at 25°C gives the corresponding alcohols in 47-49% yield besides the unreacted carboxylic acids. Reduction of aliphatic carboxylic acids (1 eq) using $NaBH_4$ (2 eq), catechol (2 eq) and CF_3COOH (1 eq) gives the aliphatic alcohols in 87-94% yields. Reductions using aliphatic acids (1 eq), $NaBH_4$ (1 eq) and CF_3COOH (1 eq) also give aliphatic alcohols in 93-95% yields. Under these conditions, the aromatic acids give poor yields. However, capric acid (1 eq) is selectively reduced to 1-decanol in 72% yield in the presence of benzoic acid (1 eq).

Although there are several methods available for the reduction of carboxylic acids into alcohols,[1-3] efforts are still continuing for the development of more convenient methods for selective reductions. For example, benzyl triethylammonium borohydride/$(CH_3)_3SiCl$,[3c] and $NaBH_4/I_2$,[4] systems have been recently reported to reduce carboxylic acids into alcohols. In 1977, Kabalka et al reported that the sodium salt of stearic acid (1 eq) is reduced by catecholborane (2 eq) in THF in 6h at room temperature.[5] The authors rightly pointed out that this facile reduction of the sodium salt of a carboxylic acid by catecholborane is surprising since RCOONa simply coordinates with diborane and does not undergo reduction at room temperature. In continuation of our efforts on the synthetic utilization of $RCOOH/NaBH_4$,[6,7] and catecholborane[8] systems, we have decided to examine these systems further in order to explore the possibility of developing more convenient methods for the reduction of carboxylic acids using $NaBH_4$. We describe here that the carboxylic acids can be reduced to the corresponding alcohols using $NaBH_4$-catechol, $NaBH_4$-catechol-CF_3COOH and $NaBH_4$-CF_3COOH systems with some selectivities.

In 1985, Cho and Yoon reported that acyloxyborohydrides were reduced to the corresponding alcohols under THF reflux conditions.[9] However, the reduction went only to 50%. The authors rationalized these results on the basis of the sequence of reactions shown in Scheme 1.

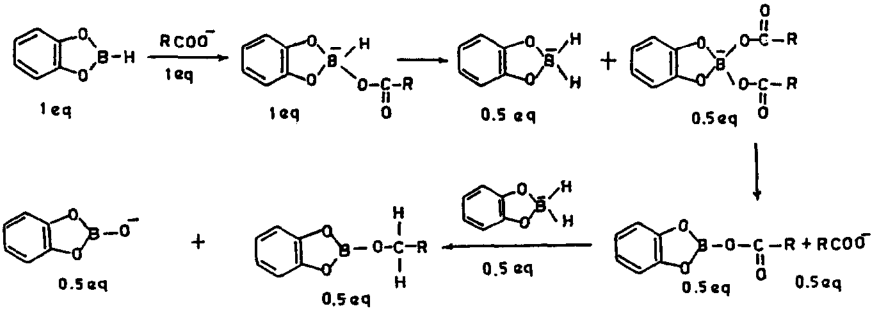
Scheme 1



[†] Dedicated to Professor H.C. Brown on the occasion of his 80th birth-day.

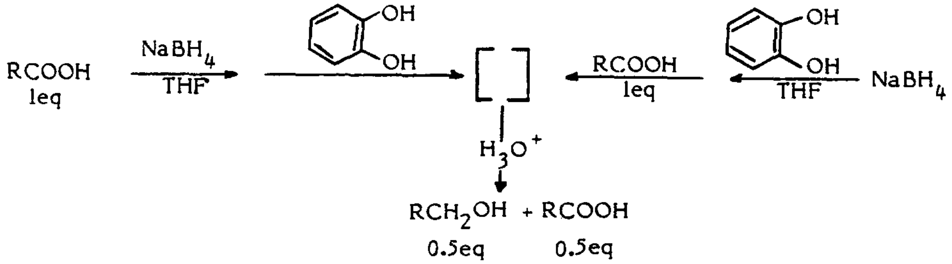
Since 0.5 equivalent of the carboxylic moiety is converted to the unreactive $RCOO^-$ species, the reaction went only to 50%. The facile reduction of carboxylate anion by catecholborane at 25°C must also go through initial formation of the ate complex and the results can be rationalized on the basis of the sequence of reactions shown in Scheme 2.

Scheme 2



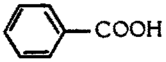
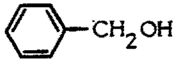
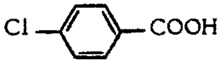
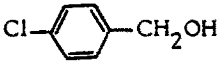
Since Kabalka utilized 2 mole equivalent of catecholborane per mole of the carboxylate anion, the reaction went to completion. It occurred to us that if the above reaction sequences are true, it may be possible to reduce carboxylic acids using catechol and borohydride at room temperature. In order to examine this possibility, we have performed experiments in two ways (Scheme 3) (i) $NaBH_4$ (20 mM) was taken in THF (20 ml) and catechol (20 mM) was added at 25°C followed by capric acid (10 mM) at 0°C and the mixture was stirred for 4h at room temperature. After work up (see experimental section), 1-decanol was isolated in 48% yield besides unreacted acid. (ii) In another run, $NaBH_4$ (20 mM) was taken in THF (20 ml) and capric acid (10 mM) was added at 0°C followed by catechol (20 mM) at 0°C and the mixture was stirred for 4h at 25°C. After work up, 1-decanol was isolated in 47% yield besides the unreacted capric acid. There was no improvement in the percentage of conversion when more amount of $NaBH_4$ or $NaBH_4$ and catechol were used for the same amount of carboxylic acid. Although the conversion is only upto 50%, the yield is high if the recovered acid is taken into account. Also, there was no reduction when phenol (2 eq) was used in the place of catechol.

Scheme 3



This reagent system is useful for the reduction of carboxylic acid group when an olefin or an ester is also present in the molecule. For example, the half ester of sebacic acid [R = $H_3COOC\text{-}(CH_2)_8$] is converted to the corresponding alcohol in 47% yield besides the unreacted starting acid. Also, 10-undecenoic acid is converted to 10-undecenol in 49% yield. Under these conditions, benzoic acid gave very low yields (∠ 10%) of benzyl alcohol.

Table 1: Reduction of Carboxylic Acids Using $NaBH_4$/catechol/CF_3COOH System.

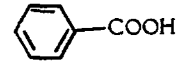
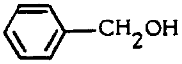
Entry No.	Substrate [RCOOH][a]	Time [h][b]	Product	Yield [%][e]
1	$CH_3(CH_2)_7COOH$	4	$CH_3(CH_2)_7CH_2OH$	87
2	$CH_3(CH_2)_8COOH$	4	$CH_3(CH_2)_8CH_2OH$	88
3	$CH_3(CH_2)_{10}COOH$	4	$CH_3(CH_2)_{10}CH_2OH$	91
4	$CH_3(CH_2)_{12}COOH$	4	$CH_3(CH_2)_{12}CH_2OH$	91
5	$CH_3(CH_2)_{14}COOH$	4	$CH_3(CH_2)_{14}CH_2OH$	92
6	$CH_3(CH_2)_{16}COOH$	4	$CH_3(CH_2)_{16}CH_2OH$	94
7		12		20
8		12		62
9	$HOOC\text{-}(CH_2)_8\text{-}COOH$[c]	12	$HOH_2C\text{-}(CH_2)_8\text{-}CH_2OH$	68
10	$H_3COOC\text{-}(CH_2)_8\text{-}COOH$[d]	12	$H_3COOC\text{-}(CH_2)_8\text{-}CH_2OH$	89

(a) Reactions were carried out using RCOOH (10 mM), $NaBH_4$(20 mM), catechol (20 mM) and CF_3COOH (10 mM) in THF (40 ml) under N_2 atmosphere, (see experimental section). (b) Time taken after adding CF_3COOH (see experimental section). (c) 5 mM of the carboxylic acid was utilized. (d) In this case, CF_3COOH (10 mM) was added 10h after stirring the RCOOH-$NaBH_4$-catechol mixture. (e) Yields are of products isolated by column chromatography on silica gel using hexane/ethylacetate as eluent. The products were identified by spectral data (IR, ^1H NMR, ^{13}C NMR) and comparison with the data of authentic samples.

The results can be tentatively explained as shown in Scheme 2, assuming that the reaction conditions outlined in Scheme 3 would lead to the same intermediate species. However, since there will not be any free catecholborane available under the conditions described in Scheme 3, one half equivalent of $RCOO^-$ will remain unreacted. It occurred to us that if a mixture of two carboxylic acids are used and if one of them could readily dissociate to give $RCOO^-$, then there is a possibility of achieving higher percentage of reduction of the other acid. It appeared that CF_3COOH would be useful for this purpose since the CF_3COO^- species is expected to be relatively stable, good leaving and poorly coordinating group. We have observed that the conversion of carboxylic acid into alcohol is more efficient when 0.5 eq each of RCOOH and CF_3COOH are utilized. The results are summarized in Table 1. The aliphatic acids are reduced into the corresponding alcohols in high yields (87-94%). Benzoic acid gives the alcohol in poor yield (20%). However, the result is better with p-chlorobenzoic acid. The low yield obtained in the case of benzoic acid suggested the possibility of achieving the reduction of aliphatic acid in the presence of benzoic acid. In order to examine this possibility, we carried out an experiment for 4h at 25°C using benzoic acid (5 mM) and capric acid (5 mM) in the place of carboxylic acid (10 mM) as described in Table 1 and isolated 1-decanol in 72% yield. GLC analysis of the crude product revealed the absence of benzyl alcohol.

The dicarboxylic acid (Table 1) gave somewhat poor results. However, it has been reported that dicarboxylic acids form polymeric boron derivatives in reactions with diborane leading to incomplete reductions.[10] Selective reduction of carboxylic acid is achieved when it is present along with the carboxylic ester group (Table 1). However, it was observed that when 10-decenoic acid was utilized, the olefinic group also underwent hydroboration. This is surprising since catecholborane does not hydroborate olefins at room temperature.

Table 2: Reduction of Carboxylic Acids Using $NaBH_4/CF_3COOH$ System.

Entry No.	Substrate (RCOOH)[a]	Time [h][b]	Product	Yield [%][d]
1	$CH_3(CH_2)_7COOH$	4	$CH_3(CH_2)_7CH_2OH$	93
2	$CH_3(CH_2)_8COOH$	4	$CH_3(CH_2)_8CH_2OH$	95
3		12		30
4	$HOOC\text{-}(CH_2)_8\text{-}COOH$[c]	12	$HOH_2C(CH_2)_8CH_2OH$	65
5	$H_3COOC(CH_2)_8COOH$	12	$H_3COOC(CH_2)_8CH_2OH$	78

(a) Reactions were carried out using RCOOH (10 mM), $NaBH_4$ (10 mM) and CF_3COOH (10 mM) in THF (40 ml) under N_2 atmosphere (see experimental section). (b) Time taken after the addition of CF_3COOH. (c) 5 mM of the acid was utilized. (d) Yields are of products isolated by column chromatography on silica gel using hexane/ethyl acetate as eluent. The products were identified by spectral data (IR, ^1H NMR, ^{13}C NMR) and comparison with the data of authentic samples.

As outlined previously, Cho and Yoon have reported that acyloxyborohydride in refluxing THF gave reduction to the extent of 50% (Scheme 1).[9] It was of interest to examine whether use of CF_3COOH (1 eq), RCOOH (1 eq) and $NaBH_4$ (1 eq) would lead to the reduction of RCOOH to more extent, since if this can be achieved then the use of catechol can be avoided and the hydride can be utilized in a more efficient manner. It is indeed the case and results similar to those observed using catechol are obtained. The results are summarised in Table 2. In this case also the benzoic acid gave alcohol in only 30% yield. However, when benzoic acid (5 mM) and capric acid (5 mM) were utilized, 1-decanol was obtained in 72% yield in 4h under the conditions described in Table 2 and GLC analysis of the crude product did not indicate the presence of benzyl alcohol. Similar selective reduction of aliphatic acid over aromatic acid by $NaBH_4$ in THF at reflux temperature was observed by Cho and Yoon.[9]

In conclusion, the reagent systems, catechol-$NaBH_4$, catechol-$NaBH_4$-CF_3COOH and $NaBH_4$-CF_3COOH in THF are useful in reduction of carboxylic acids to the corresponding alcohols with some selectivities.

EXPERIMENTAL SECTION

General: Tetrahydrofuran distilled freshly over benzophenone-sodium was used for all the experiments. Infrared spectra were recorded on a Perkin-Elmer IR Spectrometer 1310 with polystyrene as reference. NMR spectra were recorded on a JEOL-FX-100 spectrometer in deuterated chloroform using tetramethyl silane as internal standard. The chemical shifts(δ) are expressed in ppm downfield from the signal for internal Me_4Si. For t.l.c., plates coated with silica gel were run in hexane/ethyl acetate mixture and spots were developed in iodine chamber. For column chromatographic purification under gravity, column grade silica gel (100-200 mesh size) was employed.

General procedure for the reduction of RCOOH using $NaBH_4$-catechol: Sodium borohydride (0.76 g, 0.02 mole) in dry THF (20 ml) was taken in a two-necked RB flask. To the slurry, pelargonic acid (1.58 g, 0.01 mole) was added slowly under N_2 atmosphere over 15 min at 0°C. After the evolution of H_2 gas ceased, catechol (2.2 g, 0.02 mole) dissoved in THF (20 ml) was added slowly at 0°C. The reaction mixture was stirred for 4h at 25°C and quenched carefully with dil.HCl (5 ml, 3N). The aqueous layer was extracted with ether (3 x 10 ml). The combined organic extract was washed with 1N NaOH solution, water, brine solution and dried over anhydrous $MgSO_4$. Evaporation of solvent afforded 1-nonanol which was purified by column chromatography (n-hexane:ethyl acetate/90:10). Yield: 0.69 g, 48%. I.R.: 3350, 1060 cm^{-1}. ^{13}C NMR ($CDCl_3$): 63.1, 32.8, 31.9, 29.6, 29.5, 29.3, 25.8, 22.7, 14.1.

Reduction of undecenoic acid with catechol/$NaBH_4$ system - Reverse addition: Sodium borohydride (0.76 g, 0.02 mole) in dry THF (20 ml) was taken in a two-necked RB flask. Catechol (2.2 g, 0.02 mole) in dry THF (20 ml) was added to the slurry over 15 min. at 25°C. After completion of H_2 gas evolution, 10-undecenoic acid (1.86 g, 0.01 mole) was added slowly in over 15 min. at 0°C. The mixture was stirred for 4h at 25°C and quenched with dil.HCl (5 ml, 3N) carefully. It was washed with 1N NaOH solution, water, brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 10-undecenol which was purified by column chromatography (n-hexane:ethylacetate/90:10). Yield: 0.84 g, 49%. IR: 3350, 3100, 1640, 1070, 920 cm^{-1}. ^{13}C NMR ($CDCl_3$): 139.1, 114.1, 62.6, 33.6, 32.4, 29.8, 29.4, 29.3, 28.9, 28.8, 25.6.

General procedure for reduction of acids with catechol/NaBH$_4$ system in the presence of CF$_3$COOH: Catechol (2.2 g, 0.02 mole) in dry THF (20 ml) was added over 15 min. at 25°C to a slurry of sodium borohydride (0.76 g, 0.02 mole) in dry THF. After the evolution of gas ceased, sebacic acid (1.01 g, 0.005 mole) in dry THF (20 ml) was added followed by CF_3COOH (1.14 g, 0.01 mole) at 0°C and stirred for 4h at 25°C. The mixture was quenched with dil.HCl (5 ml, 3N) carefully and washed with 1N NaOH solution, water, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated to obtain the corresponding diol which was purified by column chromatography. Yield: 0.59 g, 68%. IR: 3325, 1430, 1060 cm^{-1}. ^{13}C NMR ($CDCl_3$): 62.7, 32.5, 29.2, 25.5.

General procedure for reduction of aliphatic acid over aromatic acid using catechol-NaBH$_4$ system in the presence of CF$_3$COOH: To the catechol borohydride mixture prepared as described above using sodiumborohydride (0.76 g, 0.02 mole) and catechol (2.2 g, 0.02 mole), capric acid (0.86 g, 0.05 mole) and benzoic acid (0.61 g, 0.005 mole) mixture in 20 ml of dry THF was added slowly at 0°C followed by CF_3COOH (1.14 g, 0.01 mole). The reaction mixture was stirred for 4h at 25°C and quenched carefully with HCl (5 ml, 3N) and worked up as outlined before. 1-Decanol was obtained in 72% yield. IR: 3350, 1060 cm^{-1}. ^{13}C NMR ($CDCl_3$): 62.5, 32.5, 31.9, 29.6, 29.3, 25.8, 22.6, 13.9. The ^{1}H NMR and GLC analysis of the crude product revealed the absence of benzyl alcohol.

General procedure for reduction of acids with NaBH$_4$ in the presence of CF$_3$COOH: To a suspension of sodium borohydride (0.76 g, 0.01 mole) in dry THF (20 ml), the half ester acid of sebacic acid (2.16 g, 0.01 mole) in dry THF was added. CF_3COOH (1.14 g, 0.01 mole) was added over 15 min. at 0°C and stirred for 4h at 25°C. The mixture was quenched with dil.HCl (5 ml, 3N), extracted with ether (3 x 10 ml), washed with 1N NaOH solution, water, brine and dried over anhydrous $MgSO_4$. The corresponding alcohol was purified by column chromatography (n-hexane: ethyl acetate/90:10). Yield: 1.57 g, 78%. IR: 3375, 1730, 1060 cm^{-1}. ^{13}C NMR ($CDCl_3$): 171.1, 61.9, 50.9, 33.7, 33.5, 32.1, 28.8, 28.7, 25.3, 24.4

Acknowledgements: We are grateful to the CSIR, New Delhi, for the support of this research work. We also thank the UGC, New Delhi, for Special Assistance and COSIST support.

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