

Convenient Procedure for the Reduction of Carboxylic Acids *via* Acyloxyborohydrides

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A new convenient method for the reduction of carboxylic acids to the corresponding alcohols *a via* acyloxyborohydrides was explored. Acyloxyborohydrides, prepared from the reaction of various carboxylic acids and sodium borohydride, underwent reduction to the corresponding alcohols readily by the addition of dimethyl sulfate or Lewis acids, such as boron trifluoride etherate and triphenyl borate, presumably through acyloxyboranes. By utilizing this procedure, aliphatic and aromatic acids are rapidly and quantitatively reduced to the corresponding alcohols in tetrahydrofuran either at room temperature (or at 65°. This procedure provides selective reduction of carboxylic acids in the presence of halogen, nitro, and heterocyclic rings such as furan and thiophene.

Introduction

The reduction of carboxylic acids to the corresponding alcohols may be carried out with a variety of metal hydrides, such as lithium aluminum hydride,^{1,2} lithium trimethoxyaluminumhydride,³ aluminum hydride⁴ and mixed hydride.⁵ However, borane is well known to be a most useful reducing agent for the conversion of carboxylic acids to alcohols, since it has rather mild reducing characteristics, capable of selective reductions in the presence of other functional groups.^{6,7} And acyloxyborane species have proved to be reactive intermediates in this reaction.⁸

On the other hand, it has been reported that the reaction of sodium borohydride and carboxylic acids in the molar ratio of 1:1 evolves 1 equivalent of hydrogen and leads to the formation of sodium monoacyloxyborohydrides, however the reduction does not occur at room temperature.⁹⁻¹¹

Since dimethyl sulfate or Lewis acid could be expected to abstract hydride from acyloxyborohydrides to give acyloxyboranes, reactive intermediates to alcohols, we decided to study a new, convenient procedure for the reduction of carboxylic acids to the corresponding alcohols *via* acyloxyborohydrides.

Experimental

General

All glasswares were thoroughly dried in a drying oven and cooled down under a stream of dry nitrogen just prior to use. Most of the organic compounds utilized in this study were commercial products of the highest purity. They were further purified by distillation or recrystallization when necessary. Sodium borohydride (98% Aldrich Chem. Co) was used without further purification, but dried out in a heating vacuum oven at 120° for 12 h.

All of the solvents used were dried with excess lithium aluminum hydride, distilled under nitrogen, and stored over 4Å molecular sieve in a flask equipped with a rubber septum inlet and a connection to a mercury bubbler. All reduction experiments were carried out under a dry nitrogen atmos-

phere. Hypodermic syringes were used to transfer the solution. Glpc analysis was performed on Hewlett Packard Model 5840A instrument equipped with flame ionization detector. All of the yields of products were determined by utilizing suitable internal standards and authentic mixtures. The following columns were used: 10% carbowax 20 M on chromosorb WHP, 6ft, 0.125 inch, 10% OV-17 on chromosorb WHP, 6 ft, 0.125 inch and 10% OV-1 on chromosorb WHP, 6ft, 0.125 inch. Refractive indexes were measured by the use of Baush and Lomb Abbe-3L refractometer. Infrared spectra were determined by the use of Perkin Elmer Model 735B Infrared spectrophotometer. Melting points were measured with Mettler Model FP-5 melting point apparatus equipped with Mettler Model FP-51 furnace.

Reaction of Sodium Borohydride with Carboxylic Acids in THF at 65°

Reaction of *n*-decanoic acid was representative. A clean 100 ml, oven-dried, flask with a side arm, fitted with a rubber cap, a magnetic stirring bar, and a reflux condenser connected to a gas buret was cooled down to room temperature under a stream of nitrogen. Then sodium borohydride (0.4162 g, 11 mmol) was introduced, followed by THF (20 ml) and diphenyl ether (5 mmol, 10 ml) in THF to serve as an internal standard for glpc analysis. Finally, 10 ml of 1 M solution (10 mmol) of *n*-decanoic acid in THF was added slowly. 10 mmol of hydrogen gas was evolved immediately. The reaction mixture was stirred under reflux in an oil bath. After 6 h, 1 ml of the reaction mixture was withdrawn, hydrolyzed with 1 M sulfuric acid, made alkaline with 3 N sodium hydroxide, extracted with ether, and analyzed by glpc. This revealed the presence of 49% *n*-decanol. The results were summarized in Table 1.

Reaction of Sodium Acyloxyborohydride with Lewis Acid in THF at Room Temperature.

n-Decanoic acid and triphenyl borate were chosen as a representative acid and Lewis acid, respectively. 5.5 ml (10 mmol) of 1.82 M solution of triphenyl borate in THF was added to the mixture (14.5 ml) of 10 mmol of sodium *n*-decanoyloxyborohydride in THF, prepared from the reaction of sodium

borohydride and *n*-decanoic acid, and 5 mmol of diphenyl ether to serve as an internal standard as described in the previous experiment. The reaction mixture was stirred at room temperature. After 3 h, 1 ml of the reaction mixture was withdrawn, hydrolyzed with 1 *M* sulfuric acid (1 ml), made alkaline with 3 *N* sodium hydroxide (2 ml), extracted with ether and analyzed by glpc. The analysis showed the formation of 92% *n*-decanol. The results were summarized in Table 2.

Reaction of Sodium *n*-Decanoyloxyborohydride with Different Molar Ratio of $\text{BF}_3 \cdot \text{OEt}_2$ in THF at Room Temperature.

Reaction of sodium *n*-decanoyloxyborohydride with 0.5 molar equivalent of $\text{BF}_3 \cdot \text{OEt}_2$ was representative. To the mixture (15 ml) of 10 mmol of sodium *n*-decanoyloxyborohydride, prepared from the reaction of sodium borohydride and *n*-decanoic acid, and 5 mmol of diphenyl ether to serve as an internal standard for glpc analysis as described in the previous experiments was added 5 ml (5 mmol) of 1 *M* solution of $\text{BF}_3 \cdot \text{OEt}_2$ in THF. The resulting clear mixture was stirred at room temperature. After appropriate time intervals, 1 ml of the reaction mixture was withdrawn, hydrolyzed with dilute sulfuric acid, made alkaline with dilute sodium hydroxide, extracted with ether and analyzed by glpc. The analysis revealed the formation of *n*-decanol in yields of 48% at 0.5 h, 50% at 1 h, 51% at 3 h, 52% at 6 h, and 55% at 24 h, respectively. Similarly, the reaction with 0.1, 1.0 and 2.0 molar equivalents of $\text{BF}_3 \cdot \text{OEt}_2$ was also carried out under the same condition. The results were summarized in Figure 1.

Reaction of Sodium *n*-Decanoyloxyborohydride with 100% H_2SO_4 in THF at Room Temperature.

To the mixture (15 ml) of sodium *n*-decanoyloxyborohydride (10 mmol) of in THF and diphenyl ether (5 mmol) in in THF to serve as an internal standard as described in the previous experiment, was added 5 ml (5.5 mmol) of 1.1 *M* solution of 100% H_2SO_4 in THF. The reaction mixture was maintained at room temperature. After 3 h, the work-up procedure for analysis of product was performed as described in the previous experiments. This revealed the presence of 82% *n*-decanol. At 6 h, the analysis of the reaction mixture with same work-up procedure showed the formation of 93% *n*-decanol. The results were summarized in Table 2.

Reaction of Sodium Acyloxyborohydrides with Dimethyl Sulfate in THF.

The following experiment will illustrate the technique utilized in cases where the reaction product was subjected to gas chromatographic examination. Reaction of sodium *n*-decanoyloxyborohydride with dimethyl sulfate was representative. Into a 50 ml, pre-dried flask with a side arm, fitted with a silicon rubber cap, a magnetic stirring bar, and a reflux condenser connected to a gas buret was introduced 0.1462 g (11 mmol) of sodium borohydride, followed by 5 ml of THF and 5 ml of 1 *M* solution of diphenyl ether in THF to serve as an internal standard. Finally, 5 ml (10 mmol) of 2 *M* solution of *n*-decanoic acid in THF was added slowly with a rigorous stirring. Hydrogen (10 mmol) gas was evolved immediately. To this reaction mixture, 5 ml (11 mmol) of 2.2 *M*

solution of dimethyl sulfate in THF was added slowly. The reaction mixture was maintained at room temperature. Methane (11 mmol) gas was liberated in approximate 6 h. After 6 h, 1 ml of reaction mixture was withdrawn by a syringe, hydrolyzed with 1 *M* sulfuric acid, made alkaline with 3 *N* sodium hydroxide, extracted with ether and analyzed by glpc. The analysis indicated the formation of 98% *n*-decanol. The same reaction was also carried out at 65°. In such reaction, reaction mixture was refluxed after the addition of dimethyl sulfate. *n*-Decanol was obtained quantitatively in 1 h. The results were summarized in Table 4. Alternatively, the same reaction was carried out in other solvents such as dioxane, diglyme and toluene at room temperature. The results in dioxane and diglyme were similar to those in THF, giving *n*-decanol in yields of 97% and 98% in 6 h, respectively, whereas no product was obtained in toluene. The results were summarized in Table 3.

Reaction of Sodium Acyloxyborohydrides with Dimethyl Sulfate in THF. (Preparative Method).

In order to isolate reduction products, reactions were carried out on a 50 mmol or 100 mmol scale. Two representative examples were illustrated as follows.

n-Hexyl Alcohol. Into a pre-dried 250 ml flask, with a side arm, fitted with a silicon rubber septum, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler, were charged 4.162 g (110 mmol) of sodium borohydride and 58 ml of THF. The flask was immersed in a water bath and the system was flushed with dry nitrogen. Then, 20 ml (100 mmol) of 5 *M* solution of *n*-hexanoic acid in THF was added over a period of 0.5 h under stirring. Hydrogen liberated was vented through the mercury bubbler to a hood. When the evolution of hydrogen had ceased, 22 ml (110 mmol) of 5 *M* solution of dimethyl sulfate was added slowly in 0.5 h. The resulting mixture was heated to reflux for 1 h, cooled down to room temperature and added 30 ml of methanol cautiously for hydrolysis. After stirring for 1 h, the reaction mixture was filtered and the filtrate was concentrated until all the solvent was evaporated on a rotary evaporator. The residue was dissolved in 30 ml of water, made alkaline with 3 *N* sodium hydroxide and extracted with three 50 ml portions of ether. The combined ether extracts were dried over anhydrous potassium carbonate. After removal of the solvent, *n*-hexyl alcohol was obtained by a fractional distillation, yield: 9.4 g (92%), bp 92–94°/60 mmHg (*lit.*¹² 158°/760 mmHg), n_D^{20} 1.4168 (*lit.*¹² n_D^{20} 1.4178).

p-Nitrobenzyl Alcohol. 2.08 g (55 mmol) of sodium borohydride and 8.356 g (50 mmol) of *p*-nitrobenzoic acid were introduced into a clean pre-dried 250 ml flask with a side arm, fitted with a rubber cap, a magnetic stirring bar and a reflux condenser connected to a mercury bubbler. Then, 70 ml of THF was injected into the reaction flask. The reaction mixture was stirred at room temperature until evolution of hydrogen ceased. Finally, 27.5 ml (55 mmol) of 2 *M* solution of dimethyl sulfate in THF was added over a period of 0.5 h. After 1 h, the reaction mixture was heated to reflux in an oil bath. After 3 h, the reaction mixture was hydrolyzed with dilute sulfuric acid, made alkaline with dilute sodium hy-

dioxide and extracted with ether as described in the previous experiment. The combined extracts were dried over anhydrous potassium carbonate. Removal of solvents gave the pale yellow solid. The solid was washed with 20 ml of hot hexane, giving 7.5 g (98%) of *p*-nitrobenzyl alcohol, mp 92–93° (*lit*¹³, mp 93°) with an IR spectrum identical with the authentic material. The results were summarized in Table 4.

Results and Discussion

Reaction of Carboxylic Acids With Sodium Borohydride in THF

n-Decanoic acid and benzoic acid were chosen for the reaction with sodium borohydride in THF. In both cases, the hydrogen gas was evolved immediately and quantitatively. However, the reductions were not observed at room temperature as reported earlier.^{9–11} At 65°, the reductions underwent moderately but only up to 50% as shown in Table 1.¹⁴

Reaction of Acyloxyborohydrides with Dimethyl Sulfate, Lewis Acids and 100% Sulfuric Acid in THF

n-Decanoic Acid was chosen as a representative acid. Sodium mono *n*-decanoyloxyborohydride prepared from the reaction of sodium borohydride and *n*-decanoic acid was reacted with both equimolar dimethyl sulfate and Lewis acids such as boron trifluoride etherate and triphenyl borate, and 0.5 molar equivalent of 100% sulfuric acid in THF. As expected, all the reactions were proceeded smoothly, completing the reduction in 3 h to 6 h at room temperature. (Table 2).

This clearly shows the formation of acyloxyboranes through

TABLE 1: Reaction of Sodium Borohydride with Representative Carboxylic Acids in THF^a

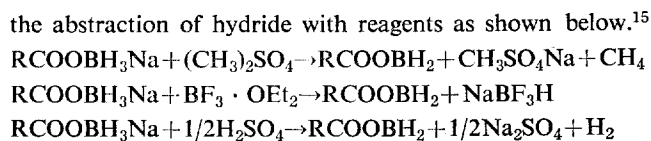
Compounds	Temp. °C	Products ^b		
		3 h	6 h	24 h
<i>n</i> -Decanoic acid	r.t.		0	0
	65	40	49	50
Benzoic acid	r.t.		0	0
	65	28	47	50

^a10 mmol of carboxylic acids to 11 mmol of sodium borohydride in 40 ml of THF, except where otherwise indicated. ^bPercent yields of the corresponding alcohols estimated by glpc analysis.

TABLE 2: Conversion Reaction of Sodium Mono *n*-Decanoyloxyborohydride to *n*-Decanol in THF at Room Temperature^a

Reagents	Product ^c			
	1 h	3 h	6 h	24 h
Dimethyl sulfate	86	92	95	
Boron trifluoride etherate	92	96	98	
Triphenyl borate	88	92	97	
Triethyl borate			0	0
Sulfuric acid ^b (100%)	73	82	93	

^aTo acyloxyborohydride, equimolar reagents were added. ^b0.5 molar equivalent of 100% H₂SO₄ was used. ^cPercent yields of product alcohol estimated by glpc.



In the case of boron trifluoride etherate, in order to find out the stoichiometry of the reaction and/or possible catalytic effect, the reactions were carried out with 0.1, 0.5, 1 and 2 molar equivalents of boron trifluoride etherate. As shown in Figure 1, the results clearly indicated that 1 molar equivalent of boron trifluoride etherate was necessary for the complete reduction.

Next, we have tried this reaction in the additional three other solvents, namely dioxane, diglyme and toluene. As shown in Table 3, the reaction does not occur in toluene, but yields are similar in the three ethereal solvents. Therefore we have chosen dimethyl sulfate (reagent) and tetrahydrofuran (solvent) for the reduction.

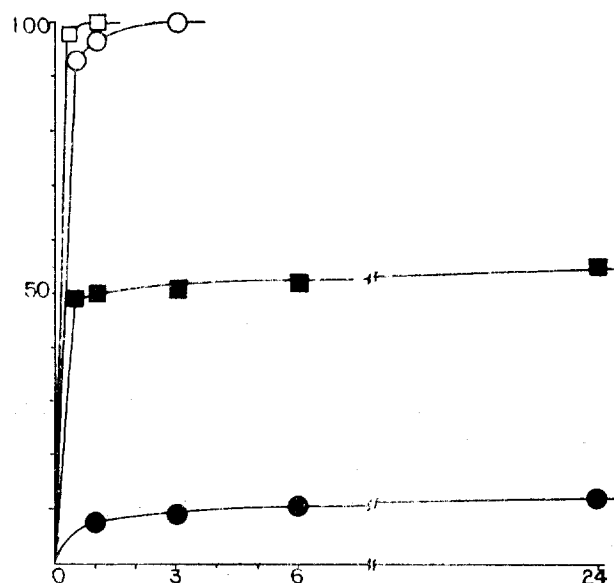


Figure 1. Reduction of Sodium *n*-Decanoyloxyborohydride with Boron Trifluoride Etherate in THF at Room Temperature. *n*-C₉H₁₉COOBH₃Na/BF₃·OEt₂; 1/2 (□), 1/1 (○), 1/0.5 (■), 1/0.1 (●)

TABLE 3: Reaction of Sodium *n*-Decanoyloxyborohydride with Dimethyl Sulfate in Various Solvents at Room Temperature^{a, b}

Solvents	Product ^c		
	1h	3h	6h
Tetrahydrofuran	86	95	98
Dioxane	65	82	97
Diglyme	87	92	98
Toluene	no reaction		

^aTo sodium acyloxyborohydrides prepared from the reaction of 10 mmol of carboxylic acids and 11 mmol of sodium borohydride was added 11 mmol of dimethyl sulfate. ^bThe reaction mixtures were 0.5M for acyloxyborohydrides and dimethyl sulfate in the corresponding solvents. ^cPercent yields of product alcohol estimated by glpc, unless otherwise indicated.

TABLE 4: Reaction of Representative Sodium Acyloxyborohydrides with Dimethyl Sulfate in THF^{a, b}

Acyl groups	Reaction Temp. °C	Products ^c			
		1 h	3 h	6 h	24 h
<i>n</i> -Hexanoyl	r.t.		93	97	100(89) ^{d, e}
	65	100(92)			
<i>n</i> -Decanoyl	r.t.	86	92	98	
	65	100			
Trimethyl-acetyl	r.t.		98 ^g		
	65	99			
Trichloro-acetyl	r.t.		13		55 ^f 70 ⁱ
	65		78	83	87
Benzoyl	r.t.	71	90	100(84)	
benzoyl	65	95	100(87)		
<i>p</i> -Methoxy-benzoyl	r.t.		90 ^g	98	
	65	98			
3,4,5-Tri-methoxy-benzoyl	r.t.	90	99 ^g		
	65	97			
<i>o</i> -Chloro-benzoyl	r.t.		(90)	(98)	
	65		(96)		
<i>p</i> -Nitro-benzoyl	r.t.		(72)	(90)	(98) ^g
	65		(98)		
2-Thiophene-carbonyl	r.t.		90	95 ^h	
	65	95			
2-Furoyl	r.t.		92	98 ^h	
	65	96			

^{a, b, c} See corresponding footnotes in Table 3. ^dThe figures in parentheses indicated isolated yields. ^eYields at 16 h. ^fYields at 20 h. ^gYields at 4 h. ^hYields at 10 h. ⁱYields at 45 h.

Reduction of Carboxylic Acids to the Corresponding Alcohols via Acyloxyborohydrides.

In order to test the generality of the reductions, we have chosen eleven representative carboxylic acids and reacted with sodium borohydride in THF at room temperature. And the resultant acyloxyborohydrides were treated with equimolar dimethyl sulfate at room temperature and at 65°. Yields were estimated by glpc analysis or isolation. Thus, the simple carboxylic acids, such as *n*-hexanoic acid, *n*-decanoic acid and benzoic acid were reduced almost quantitatively in 6 h at room temperature and in 1–3 h at 65°. And it was also possible to reduce carboxylic function quantitatively in the presence of other functional groups such as chloro nitro and heterocyclic groups such as thiophene and furan. The results were summarized in Table 4. As shown in Table 4, introduction of alkyl substituents (trimethylacetic acid) did not influence the rate of reduction (98% in 4 h at room temperature or 99% in 1 h at 65°), revealing insensitiveness of the reaction to steric effect. However, introduction of electron withdrawing substituents (trichloroacetic acid) decreased the rate of reduction, giving 70% yield in 45 h at room temperature and 87% yield in 24 h at 65°.

At present, borane is believed to be a reagent of choice for the reduction of carboxylic acids, especially under mild conditions. However, the present method has at least two

advantages over the borane reduction: (1) Sodium borohydride is cheaper and more convenient in handling than borane (2) The reduction of carboxylic acid with borane accompanies the considerable loss of borane due to the hydrogen evolution, especially in a large scale.

Conclusion

A new convenient method for the reduction of carboxylic acids to the corresponding alcohols via acyloxyborohydrides was explored. Acyloxyborohydrides, prepared from the reaction of various carboxylic acids and sodium borohydride, underwent reduction to the corresponding alcohols readily by the addition of dimethyl sulfate or Lewis acids such as boron trifluoride etherate and triphenyl borate, presumably through acyloxyboranes. This procedure should be more convenient for the reduction of carboxylic acids than that with borane, especially in a large scale. The present study provides another major application of sodium borohydride, in boron hydride reduction of organic functional groups.

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