

NaBH₄-(C₆H₅O)₃B계에 의한 몇가지 유기화합물의 환원법

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Reductions of Some Representative Organic Compounds with NaBH₄-(C₆H₅O)₃B System

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요 약. 테트라히드로프란 용액에서 수소화붕소나트륨과 붕산트리페닐을 사용해서 카르복시산, 카르복시산염, 3차아미드 및 술폭시드를 환원하는 새로운 방법을 개발하였다. 즉 카르복시산은 실온에서 6~12시간에 정량적으로 환원될 수 있으며, 지방족 카르복시산염은 실온에서 6시간에 정량적으로 환원되나 방향족 산염은 65°C에서 24시간이 소요되었다. 3차 아미드는 실온에서 3~6시간에 88~100%의 좋은 수율로 환원되었으며, 조사한 대부분의 술폭시드는 실온에서 1~6시간에 98~100% 수율로 환원되었으나, 디페닐술폭시드는 보다 격렬한 조건에서 48시간에 환원할 수 있었다.

ABSTRACT. New procedures for the reduction of carboxylic acids, carboxylic acid salts, tertiary amides, and sulfoxides with sodium borohydride and triphenyl borate in tetrahydrofuran were developed. Thus carboxylic acids were reduced quantitatively in 6~12 h at 25°C. Aliphatic acid salts were quantitatively reduced to the corresponding alcohols in 6h at 25°C whereas aromatic acid salts required 24 h at 65°C. Tertiary amides were reduced to the corresponding amines in 88~100% yields in 3~6 h at room temperature. Most sulfoxides examined were reduced to the corresponding sulfides in 98~100% yields in 1~6 h at 25°C and completely reduced at 65°C; however, diphenyl sulfoxide required 48 h in a more vigorous condition.

INTRODUCTION

Sodium borohydride is a remarkably mild reducing agent, reducing readily only aldehydes, ketones and acid chlorides¹. Recently we have carried out a systematic study of the approximate rates and stoichiometries on the reduction of representative organic functional groups² with sodium borohydride-triphenyl borate

system. In this study, by measuring the number of mmoles of hydride consumption per mmole of organic compound, we have found that carboxylic acids, carboxylic acid salts, tertiary amides and sulfoxides were readily reduced with this reducing system in THF at 0°C. Therefore, it was decided to study these reductions more in detail in THF at room temperature in order to develop new procedures for these

reductions.

EXPERIMENTAL SECTION

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. Some compounds such as triphenyl borate³, N,N-dimethylbenzamide⁴, benzylphenyl sulfoxide⁶, diethyl sulfoxide⁵ and carboxylic acid salts were prepared by the known methods. Sodium borohydride (98% Aldrich Chem. Co) was used without further purification, but dried out in a vacuum oven at 120°C for 12 h.

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

All reduction experiments were carried out under a dry nitrogen atmosphere. Hypodermic syringes were used to transfer the solution.

Gpc analysis was performed on Hewlett Packard Model 5840 A instrument equipped with flame ionization detector. The yields of products were determined by gpc, utilizing suitable internal standards and authentic mixtures. All analyses were carried out on 10% carbowax 20 M on chromosorb WHP, 6 ft, 0.125 inch column (A), 20% carbowax 20 M on chromosorb W, 10 ft, 0.125 inch column (B) and 10% OV-1 on chromosorb WHP, 6 ft, 0.125 inch column (C).

Potentiometric titrations were measured by using Metrohm Herisau Dosimat 535 potentiometer equipped with potentiograph E 536 recorder.

Melting points were measured with Mettler Model FP-5 melting point apparatus equipped with Mettler Model FP-51 furnace.

Preparation of Triphenyl Borate Solution in Tetrahydrofuran. Phenol (244g, 2.6 mol) and boric acid (31g, 0.5 mol) were placed in a dry 500 ml flask with a magnetic stirring bar and heated until water-phenol azeotrope was distilled off at 98~99°C. The remaining phenol was removed at low pressure (62°C, 1~2 mm Hg), and the triphenyl borate² was distilled by a vacuum distillation (192~210°C 1~2 mmHg). The crude yield was 80% (116g). 104g (72%) of pure triphenyl borate was obtained by a fractional vacuum distillation (210°C, 1 mmHg). (lit.³ 177~178°C, 0.5 mmHg). The triphenyl borate (104g) was dissolved in THF to give 200 ml. Thus, the solution was found to be 1.8M.

Preparation of Sodium Salt of Carboxylic Acids. The preparation of sodium *n*-hexanoate is described as a representative. To a solution of *n*-hexanoic acid (2.323g, 20 mmol) in 50 ml of ethanol, 1 N sodium hydroxide (20ml, 20 mmol) was added slowly with stirring at room temperature until the reaction mixture was clear solution. Then the solvents were evaporated to dryness under reduced pressure. The product was washed with a small portion of cold ethanol. 2.68g (67%) of sodium *n*-hexanoate was obtained. Potentiometric titration indicated 99% purity.

Preparation of *tert*-Amides. The preparation of N,N-dimethylbenzamide from benzoyl chloride is described as a representative⁴. A mixture of 14.3g of benzoyl chloride and 15g of N,N-dimethylformamide was heated together at 150°C for 4 h. The product was distilled under reduced pressure and yielded 14.0g(93%) of N,N-dimethylbenzamide, b.p. 157~158°C (35 mm) (lit.⁴ 157~158°C), mp 40~41°C

(*lit.*⁴ 40~41°C).

Preparation of Sulfoxides. The preparation of benzylphenyl sulfoxide from benzylphenyl sulfide is described as a representative⁵. Benzylphenyl sulfide (50g, 0.25 M) was dissolved in 250 ml of acetone. The solution was filtered to remove undissolved substances. After adding 41g of 30% hydrogen peroxide, the solution was stirred for 8 h at 10~15°C and allowed to stand at room temperature for 72 h. The acetone was evaporated. The crude sulfoxide was recrystallized from 60% ethanol, to give 38g (70%) of benzylphenyl sulfoxide, mp 119~120°C (*lit.*⁵ 122~123°C).

Reaction of Sodium Monoacyloxyborohydrides with Triphenyl Borate in THF at Room Temperature. The reaction of sodium mono-*n*-decanoyloxyborohydride with triphenyl borate is described as a 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 (0.416 g, 11 mmol) was introduced, followed by THF (14.5 ml) and diphenyl ether (5 mmol, 10 ml) in THF to serve as an internal standard for glpc analysis. Finally, 10 ml of 1M solution of *n*-decanoic acid (10mmol) in THF was added slowly. 10 mmol of hydrogen gas was evolved immediately. To the resulting sodium mono-*n*-decanoyloxyborohydride, was added 5.5 ml of 1.82M solution of triphenyl borate (10 mmol) in THF. The reaction mixture was stirred at room temperature. After 1h, 3 h, and 6 h, 1 ml of the reaction mixture was withdrawn, hydrolyzed acid with 1M sulfur (1ml), made alkaline with 3 N sodium hydroxide (2ml), extracted with ether and analyzed by glpc using column A. The 88% (1 h), 92% (3 h), and 97% (6 h) yields of *n*-decanol were realized respectively.

The results are summarized in Table 1.

Reaction of Carboxylic Acid Salts with Sodium Borohydride-Triphenyl Borate System in THF at 65°C

The reduction of sodium benzoate with sodium borohydride triphenyl borate (1 : 2) system in THF at 65°C is described as a representative. The experimental set-up was the same as in the previous experiments. Into the 50 ml, oven-dried flask were introduced sodium benzoate (721 mg, 5 mmol) and sodium borohydride (193 mg, 5 mmol). Then, THF (9.5 ml) and 1 M diphenyl ether (5 ml, 5 mmol) in THF to serve as an internal standard were added. Finally, triphenyl borate in THF (10 mmol, 5.5 ml) was added. The reaction mixture was stirred at reflux for 24 h. An aliquot (2 ml) was withdrawn, hydrolyzed with dilute sulfuric acid, made alkaline with dilute sodium hydroxide, extracted with ether and the combined extracts were analyzed by glpc using column A. The analysis indicated the formation of benzyl alcohol in 98% yield. The results are summarized in Table 2.

Reaction of *tert*-Amides with Sodium Borohydride-Triphenyl Borate (2 : 3) System in Tetrahydrofuran at Room Temperature.

The reduction of *N*-benzoylpiperidine with sodium borohydride-triphenyl borate (2 : 3) system is described as a representative. The experimental set-up and the work-up procedure for analysis of product were the same as in the previous experiments. Into a 50 ml flask was charged 232 mg (6 mmol) of sodium borohydride, followed by 3.7 ml of THF and 3 ml of 1.0 M *N*-benzoylpiperidine solution in THF and 5.3 ml of 1.7 M triphenyl borate solution in THF. The reaction mixture was stirred at room temperature. After 3 h and 6 h, the yields of the corresponding amines were estimated to be 90% (3 h) and 98% (6 h) by glpc analysis using column B. The results are summarized in Table 4.

Reduction of Sulfoxides with Sodium Borohydride-Triphenyl Borate System.

The reduction of diethyl sulfoxide with sodium borohydride-triphenyl borate (1:2) system is described as a representative. Into a 50 ml flask was introduced 189 mg (5 mmol) of sodium borohydride followed by 4.4 ml of THF and 5.6 ml of 1.8 M solution of triphenyl borate in THF (10 mmol) and 5 ml of 0.5 M solution of toluene in THF, to serve as an internal standard. Finally, 5 ml of 1 M solution of diethyl sulfoxide was added. The reaction mixture was 0.25 M both for the sulfoxide and sodium borohydride and 0.5 M for triphenyl borate. The reaction mixture was maintained at room temperature. At 3 h, the reaction mixture was hydrolyzed with 5 ml of 1 M sulfuric acid. Then, 10 ml of 6 N sodium hydroxide was added to remove free phenol. The THF layer was separated and the water layer was extracted twice with 10 ml of ether. The organic layer was combined and checked by glpc analysis using column C. A 100% yield of diethyl sulfide was found. The results are summarized in Table 5.

RESULTS AND DISCUSSION

Reactions were usually carried out using sodium borohydride and triphenyl borate³ solution in tetrahydrofuran(THF) at room temperature. Yields of the product at appropriate intervals of time were determined by glpc. When necessary, optimum molar equivalents of sodium borohydride and triphenyl borate per mole of substrate were determined, before five structurally different substrates from each class, namely, carboxylic acid, carboxylic acid salt, tertiary amide, and sulfoxide, were tested for the generality.

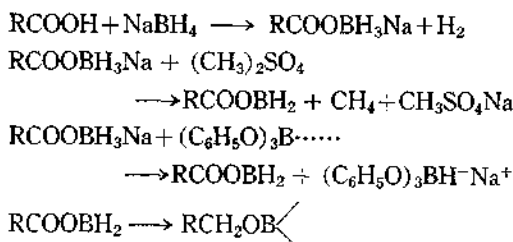
Reduction of Carboxylic Acids. Carboxylic acids react readily with a slurry of sodium borohydride in THF and the resulting acyloxyborohydrides can be converted by dimethyl sulfate to the corresponding alcohols through reactive intermediates, acyloxyboranes.^{6,7} We have also observed that the reduction proceeded readily with triphenyl borate, (C₆H₅O)₃B in place of dimethyl sulfate.

Table 1. Reaction of sodium monoacyloxyborohydrides with triphenyl borate in THF at room temperature. ^{a, b}

Carboxylic acids	Alcohols(%) ^c				
	1.0h	3h	6h	10h	24h
<i>n</i> -Decanoic acid	88	92	97		
Trimethylacetic acid	88	93	98		
Benzoic acid	64	78	94	100	
<i>o</i> -Chlorobenzoic acid	53	70	94	100 ^d	
<i>p</i> -Nitrobenzoic acid	46	60	72		100

^a To sodium acyloxyborohydrides prepared from the reaction of 10 mmol of carboxylic acids and 11 mmol of sodium borohydride was added 10 mmol of triphenyl borate; ^b The reaction mixtures were both 0.25 M in acyloxyborohydrides and triphenyl borate; ^c Percent yields estimated by glpc; ^d Yield at 24 h.

xyborohydrides can be converted by dimethyl sulfate to the corresponding alcohols through reactive intermediates, acyloxyboranes.^{6,7} We have also observed that the reduction proceeded readily with triphenyl borate, (C₆H₅O)₃B in place of dimethyl sulfate.



Therefore, we have investigated an alternate procedure for the reduction of carboxylic acid with sodium borohydride and triphenyl borate. Five representative carboxylic acids, namely, *n*-decanoic acid, trimethylacetic acid, benzoic acid, *o*-chlorobenzoic acid and *p*-nitrobenzoic acid, were reacted with an equimolar amount of sodium borohydride (10% excess) in THF to give a slurry of acyloxyborohydrides and hydrogen gas. The slurry of acyloxyborohydrides was reacted with an equimolar amount of triphenyl borate in THF at room temperature. At appropriate reaction times, the yields of

alcohols were estimated by glpc analysis. The results are summarized in *Table 1*.

As shown in *Table 1*, aliphatic acids such as *n*-decanoic acid and trimethylacetic acid were reduced rapidly in 3~6 h at room temperature. The bulky *tert*-butyl group did not show any steric effect in the reduction of trimethylacetic acid. The reduction of aromatic acids was somewhat slower than that of aliphatic acids, completing the reduction in 10~24 h. The presence of electron withdrawing groups in *o*-chlorobenzoic acid and *p*-nitrobenzoic acid decreased the rate of reduction, presumably due to the difficulty of forming acyloxyboranes of these stronger acids⁸.

Reduction of Carboxylic Acid Salts. The reduction of carboxylic acid salts to the corresponding alcohols has been a rather neglected area of research. There are few reports for this conversion in the literature.⁹ Therefore, we investigated an alternative procedure for such reduction with NaBH₄ and (C₆H₅O)₃B. Thus, sodium benzoate was chosen as a representative carboxylic acid salt and reacted with an equimolar amount of sodium borohydride in the presence of 1, 2, and 4 molar equivalents of triphenyl borate in THF at room temperature and at 65°C. The yields of benzyl alcohol at appropriate intervals of time were estimated by glpc analysis. The results are summarized in *Fig. 1*.

As shown in *Fig. 1*, no reduction was realized with one equiv. of triphenyl borate and the rate of reduction was enhanced by the increase of molar equivalents of triphenyl borate. However, the slow reduction could also be overcome by raising the reaction temperature to 65°C (*Table 2*). In order to test the generality of the reaction, four more representative carboxylic acid salts were reduced with sodium borohydride-triphenyl borate (1 : 2) system in

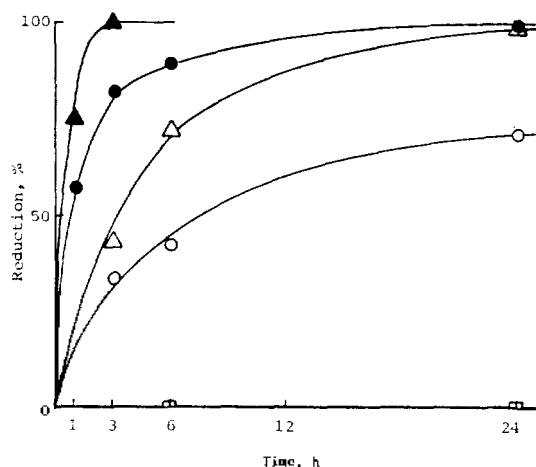


Fig. 1. Reduction of sodium benzoate with NaBH₄-(C₆H₅O)₃B system. [NaBH₄] = (C₆H₅CO₂Na) = 0.25 M. At 25°C NaBH₄: (C₆H₅O)₃B = 1 : 1 (□); 1 : 2 (○); 1 : 4 (△), and at 65°C NaBH₄: (C₆H₅O)₃B = 1 : 2 (●); 1 : 4 (▲).

Table 2. Reduction of representative sodium salts of carboxylic acids with sodium borohydride-triphenyl borate (1 : 2) system in THF.

Compounds ^a	Temp °C	Alcohols ^b			
		1h	3h	6h	24h
Sodium hexanoate	r. t.		91	100	
	65°	96	100		
Sodium trimethylacetate	r. t.		90	100	
	65°	100			
Sodium trichloroacetate	r. t.			5	26, 62 ^d
	65°			32	73
	65°		(32) ^c	(79)	
Sodium benzoate	r. t.		34	42	71
	65°	57	82	89	98
	65°	(75)	(100)		
Sodium <i>o</i> -chlorobenzoate	r. t.		11	18	37
	65°		48	60	78
	65°		(78)	(82)	(96)

^a The reaction mixtures were 0.25 M both for compounds and NaBH₄, and 0.05 M for triphenyl borate; ^b Percent yields of the corresponding alcohols estimated by glpc; ^c The figures in parentheses indicate the percent yields with sodium borohydride-triphenyl borate (1 : 4); ^d Yield at 48 h.

THF. The results are summarized in Table 2.

As shown in Table 2, aliphatic acid salts (sodium hexanoate) was reduced rapidly in 3~6 h in contrast to the slow reduction of aromatic acid salt. The bulky *tert*-butyl group did not influence the rate of reduction as observed in sodium trimethylacetate. However, introduction of three electron withdrawing groups at α -carbon in sodium trichloroacetate decreased the rate tremendously. Similarly, it was observed that *ortho*-chloro substituent in sodium *o*-chlorobenzoate decreased the rate of reduction, giving *o*-chlorobenzyl alcohol in 78% yield in 3 h at 65°C in contrast to the quantitative reduction of sodium benzoate under the same condition. The slow reduction of stronger acid salts may be rationalized due to the difficulty of forming acyloxyboranes.⁸

Reduction of *tert*-Amides. Reduction of *tert*-amides to the corresponding amines has been accomplished by diborane¹⁰, lithium aluminum hydride¹¹, and aluminum hydride¹². Recently¹³ it was reported that reduction of *tert*-amides with borane-dimethyl sulfide is rapid in the presence of boron trifluoride. But this procedure required high reaction temperature (100°C). Now we have developed an alternate procedure using NaBH₄ and triphenylborate. As shown in Table 3, N,N-dimethylbenzamide was reduced to the corresponding amine in various conditions. The best yield of amine was obtained in shorter period of time (88%, 3 h) with NaBH₄-(C₆H₅O)₃B (2 : 3) at room temperature.

Therefore, four more *tert*-amides, namely, N,N-dimethyl-*p*-nitrobenzamide, N-benzoylpiperidine, N,N-dimethylcaproamide and N,N-dimethylpivalamide were reduced under the same condition. As shown in Table 4, all the *tert*-amides examined were reduced in 88~100% yields in 3~6 h at room temperature.

Table 3. Effect of triphenyl borate on the reduction of N,N-Dimethylbenzamide with sodium borohydride-triphenyl borate system in THF at room temperature^a.

Time (h)	Product ^b					
	NaBH ₄ (Solid) : (C ₆ H ₅ O) ₃ B ^c					
	1.5 : 1	1.5 : 2	1.5 : 3	2 : 2	2 : 3	2 : 4
1.0		54				
3.0	57	67	69	66	88	87
6.0		80	83	83	86	86
12.0	65		87	81	89	
24.0		79				

^a The reaction mixtures were 0.25M in *tert*-amide;

^b Percent yields of N,N-dimethylbenzylamine were estimated by glpc; ^c Molar ratio of sodium borohydride and triphenyl borate, per mole of compound.

Table 4. Reduction of representative *tert*-amides with sodium borohydride-triphenyl borate (2 : 3) system in THF at room temperature.^a

Compounds	Amines ^b		
	3h	6h	24h
N,N-Dimethylbenzamide	88	86	
N,N-Dimethyl- <i>p</i> -nitrobenzamide	100	—	
N-Benzoylpiperidine	90	98	
N,N-Dimethylcaproamide	73	92	
N,N-Dimethylpivalamide	89	91	100

^a The reaction mixtures were 0.25M in *tert*-amide and 0.5M in sodium borohydride; ^b Percent yields of the corresponding amines estimated by glpc.

Reduction of Sulfoxides. It has been reported that sulfoxide is essentially inert to sodium borohydride¹⁴, lithium borohydride¹⁵, zinc borohydride¹⁶, and lithium triethylborohydride¹⁷, and it is slowly reduced with lithium aluminum hydride¹¹, borane¹⁸, alkylborane¹⁹ and catechoborane⁸; however, recently sulfoxides are reported to be reduced rapidly with dichloroborane with excellent chemoselectivity²⁰. Now, we have found an alternative method using NaBH₄ and triphenyl borate. Thus, as shown in Table 5, aliphatic sulfoxi-

Table 5. Practical procedure for the reduction of representative sulfoxides with sodium borohydride-triphenyl borate system in THF^a.

Compounds ^b	Sulfoxides ^d					
	0.5h	1h	3h	6h	24h	28h
Tetramethylene sulfoxide	81	100				
Diethyl sulfoxide			90	100		
Dibenzyl sulfoxide				84	100	
Benzylphenyl sulfoxide				77	98	
Diphenyl sulfoxide ^c					87	99

^a With sodium borohydride-triphenyl borate (1:2) system, sulfoxides were reacted at room temperature, unless otherwise indicated; ^b The reaction mixtures were 0.25M in both sulfoxide and sodium borohydride; ^c With sodium borohydride-triphenyl borate (1:4) system, the sulfoxide was reacted at 65°; ^d Percent yields of the corresponding sulfides estimated by glpc analysis.

des and benzylphenyl sulfoxide were reduced readily in 1~6 h at room temperature with equimolar NaBH₄ and two mole equiv of (C₆H₅O)₃B. However, diphenyl sulfoxide required 48 h reaction at 65°C using 4 mole equiv of (C₆H₅O)₃B. The reaction of dichloroborane and diphenyl sulfoxide were also slow.²⁰

CONCLUSION

We have developed convenient reducing procedures for carboxylic acids, carboxylic acid salts, tertiary amides, and sulfoxides by using sodium borohydride-triphenyl borate system were developed. Yields were essentially quantitative.

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