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수소화 붕소리튬을 이용한 다중작용기를 가진 화합물에서 할라이드의 선택환원

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Selective Reduction of Halides with Lithium Borohydride in the Multifunctional Compounds

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요 약. 한 분자내에 클로로, 니트로, 에스테르 및 니트릴기를 포함하는 할로겐 화합물에서 수소화붕소리튬을 이용한 할로겐의 선택환원이 논의되었다. 1-브로모-4-클로로부탄은 96 %의 수득율로 1-클로로부탄으로, 브롬화 *p*-니트로벤질은 98 %의 수득율로 *p*-니트로 톨루엔으로 환원되었으나 요오도프로피온산 에틸에스테르나 4-브로모부티로니트릴의 경우 선택환원의 수득율이 낮았다. 그러나 당량의 피리딘 존재하에서 이 반응을 시키면 프로피온산 에틸에스테르는 93 %, 부티로니트릴은 88 %로서 각각 선택환원의 수득율이 향상되었다.

ABSTRACT. Selective reduction of halide (Br, I) with lithium borohydride in halogen compounds containing chloro, nitro, ester and nitrile groups was achieved satisfactorily. 1-bromo-4-chlorobutane was reduced to 1-chlorobutane in 96% yield and the reduction of *p*-nitrobenzyl bromide gave *p*-nitrotoluene in 98 % yield. However, the selectivity on the reduction of ethyl 3-iodopropionate and 4-bromobutyronitrile required the presence of equimolar pyridine to give good yields of ethyl propionate (93 %) and *n*-butyronitrile (88 %), respectively. In competitive reduction of 1-bromoheptane and 2-bromoheptane, lithium borohydride reduced 1-bromoheptane preferentially in the molar ratio of 93:7.

INTRODUCTION

It was reported that both lithium aluminum hydride and lithium triethylborohydride exhibited exceptional utility for the reduction of alkyl halides and tosylates.[1,2] However, they may be inadequate for selective reduction of halides in the multifunctional compounds, since they are powerful reducing agents, capable of reducing many functional groups, such as ester, nitrile, nitro and all kinds of halides (primary and secondary iodides, bromides, chlorides).

On the other hand, it was also realized that remarkably mild reducing agents, sodium borohydride and sodium cyanoborohydride reduced successfully alkyl halides in dimethyl sulfoxide or hexamethyl phosphoramide.[3~6] However, they reduced smoothly both alkyl bromides and alkyl chlorides (for example, with both 2 equiv. sodium borohydride in dimethyl sulfoxide at 85°, 95 % reduction of 1-bromododecane in 1.5h and 91% reduction of 1-chlorododecane

in 4 h[4]) It is difficult to expect selective reduction of bromide with these reducing agents in the presence of chloride.

Recently it was reported that lithium borohydride reduced alkyl iodides and alkyl bromides in moderate yields in tetrahydrofuran at room temperature, whereas alkyl chlorides were essentially inert to lithium borohydride under the same conditions.[2,7] And it was found that lithium borohydride was a mild reducing agent which could reduce readily only few organic functional groups such as aldehydes, ketones and acyl chlorides at room temperature. Therefore, we decided to examine selective reduction of bromide and iodide with lithium borohydride in compounds containing the other functional groups, such as chloride, nitro, ester and nitrile groups, less susceptible to this reducing agent.

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 4 Å 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 atmosphere. Hypodermic syringes were used to transfer the solution.

Glpc analysis was performed on Hewlett Packard Model 5840 A 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, 6 ft, 0.125 inch (Column A), 10 % OV-17 on chromosorb WHP, 6 ft, 0.125 inch (Column B) and 10 % OV-1 on chromosorb WHP, 6 ft, 0.125 inch. (Column C)

Lithium Borohydride Solution in Tetrahydrofuran. A 250 m*l*, oven-dried flask, equipped with a side arm, fitted with a silcon rubber cap, and a magnetic stirring bar, was cooled down to room temperature under a dry stream of nitrogen. In the flask were placed 6.37 g (98 %, 165 mmol) of finely divided sodium borohydride and 6.3885 g (150 mmol) of lithium chloride. Then, the flask was fitted with a reflux condenser connected to a mercury bubbler and heated at about 150° for 1h with stirring under a stream of nitrogen. Thereafter, the flask was cooled down to room temperature under a dry stream of nitrogen, and 160 m*l* of distilled THF was introduced to provide a solution of about 1.0 *M* in lithium borohydride, 4 *M* in hydride. The flask was heated at a rate sufficient to maintain a gentle reflux for 5 days with continuous stirring. After 5 days, the solution was cooled down to room temperature under a dry stream of nitrogen, and allowed to stand to permit sodium chloride and unreacted sodium borohydride to settle down. The upper solution was stored under dry nitrogen in a 250 m*l* flask with a side arm, closed with a rubber cap for removing aliquots. The solution was standardized by removing a known aliquot with a hypodermic syringe, hydrolyzing with a THF-water-2 *N* sulfuric acid (1 : 1 : 1) mixture and measuring the hydrogen evolved. The concentration was found to be 0.91 *M* solution of lithium borohydride in THF.

Reaction of Alkyl Halides with Lithium

Borohydride in THF at Room Temperature or at 65°. The reduction of n-heptyl iodide at 65° is described as a representative. A clean 100 m*l*, oven-dried flask with a side arm, fitted with a silicon rubber cap, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler, was cooled down to room temperature under a stream of dry nitrogen. Then 9 m*l* of THF was introduced into the flask by a hypodermic syringe, followed by 11 m*l* (10 mmol) of a 0.91 *M* THF solution of lithium borohydride and 5 m*l* (5 mmol) of a 1.0 *M* THF solution of toluene and 5 m*l* (5 mmol) of a 1.0 *M* THF solution of dodecane to serve as internal standards. Finally, 10 m*l* (10 mmol) of 1*M* THF solution of *n*-heptyl iodide was added. The mixture was heated to reflux in an oil bath. At appropriate intervals of time, 1 m*l* of the reaction mixture was withdnawn by a hypodermic syringe, quenched with 1 m*l* of 1 *M* sulfuric acid, saturated with anhydrous potassium carbonate and extracted with 2 m*l* of ether, and the upper layer was checked by glpc analysis using a column C. At 1 h, glpc analysis indicated that *n*-heptane was formed in the yield of 92 % and 8 % *n*-hepthyl iodide remained. The results were summarized in *Table* 1. In all cases of incomplete reduction for 24 h, the reaction mixture were oxidized and worked up as a usual procedure. Glpc examination revealed the complete absence of heptanols. Starting materials were recovered.

Selective Redution of Bromide in the Presence of Chloride with Lithium Borohydride. The reduction of 1-bromo-4-chlorobutane was carried out as a representative. The experimental set-up and work-up procedure for analysis of product were the same as in the previous experiments. 9 m*l* of THF, 11 m*l* (10 mmol) of 0.91 *M* THF solution of lithium borohydride and 10 m*l* (5 mmol) of 0.5 *M* solution of *n*-dodecane in THF to serve as an internal standard were introduced into a reaction flask. And then 10 m*l* (10 mmol) of 1.0 *M* solution of 1-bromo-4-chlorobutane in THF was added. The reaction mixtures were heated to reflux. After 18 h, g lpc analysis on column C indicated the formation of 96 % 1-chlorobutane. (*Table* 2)

Selective Reduction of Bromide in the Presence of Nitro Group with Lithium Borohydride. The reduction of *p*-nitrobenzyl bromide was carried out as a representative. The experimental set-up and work-up procedure for analysis of the product were performed as described in the previous experiments. Into a 100 m*l* flask, 9 m*l* of THF, 11 m*l* (10 mmol) of 0.91 *M* THF solution of lithium borohydride and 10 m*l* (5 mmol) of 0.5 *M* solution of diphenyl ether in THF to serve as an internal standard were introduced. Finally, 10 m*l* (10 mmol) of 1.0 *M* *p*-nitrobenzyl bromide solution in THF was added.

The reaction mixtures were maintained at room temperature. After 3 h, glpc analysis using column C revealed the presence of 98 % *p*-nitrotoluene. (*Table* 2)

Selective Reduction of Iodide in the Presence of Ester Group with Lithium Borohydride. The following procedure for the reduction of ethyl 3-iodopropionate was carried out as a representative. The experimental set-up was the same in the previous experiments. 4 m*l* of THF was introduced into the reaction flask by a hypodermic syringe, followed by 5 m*l* (10 mmol) of 2 *M* solution of pyridine in THF, 11 m*l* (10 mmol) of 0.91 *M* lithium borohydride THF solution and 10 m*l* (2.5 mmol) of 0.25 *M* THF solution of *n*-octane to serve as an internal standard. Finally, 10 m*l* (10 mmol) of 1.0 *M* ethyl 3-iodopropionate solution in THF was added. The reaction mixture was maintained at

room temperature. After 3 h, the reaction mixture was quenched with 10 m*l* of 1*N* sulfuric acid, saturated with anhydrous potassium carbonate and extracted with 20 m*l* of ether. The upper layer was checked by glpc analysis using column C for determination of ethyl propionate. The result revealed ethyl propionate in the yield of 93 %. For the same compound, the above procedure was performed without pyridine under the same reaction condition. In this case, the yields of ethyl propionate was 33 % at 1 h, 27 % at 3 h, 25 % at 6 h, and 19 % at 24 h, showing the reaction underwent over-reduction. The results were summarized in *Table* 2.

Selective Reduction of Bromide in the Presence of Nitrile Substituents with Lithium Borohydride. The reduction of 4-bromobutyronitrile was representative. The experimental set-up, reaction procedure and work-up procedue for analysis of product were the same as in the previous experiments. Into the flask, THF (4 m*l*), pyridine in THF (10 mmol, 5 m*l*), lithium borohydride in THF (11 m*l*, 10 mmol) and *n*-octane in THF (2.5 mmol, 10 m*l*) to serve as an internal standard were introduced. Finally, 4-bromobutyronitrile in THF (10 mmol, 10 m*l*) was added. The reaction mixture was maintained at room temperature. After 24 h, glpc examination using column B revealed the formation of *n*-butyronitrile in the yield of 88 %. For the same compound, the above procedure was performed without pyridine at the same reaction condition. In this case, the yields of *n*-butyronitrile was 20 % at 1 h, 28 % at 3 h, 35 % at 6 h, and 27 % at 24 h, showing the reaction underwent over-reduction. The results were summarized in *Table* 2.

Competitive Reduction of Primary Bromide in the Presence of Secondary Bromide with Lithium Borohydride. The reduction of 1-bromoheptane in the presence of 2-bromoheptane was carried out as a representative. The experimental set-up and work-up procedure for analysis of products were the same as in the previous experiments. In to a 100 m*l* flask, 9 m*l* of THF, 11 m*l* (10 mmol) of 0.91 *M* lithium borohydride solution in THF, and both 5 m*l* (5 mmol) of 1.0 *M* THF solution of *n*-dodecane and 1.0 M THF solution of toluene (5 mmol) to serve as internal standards were introduced. And then 5 m*l* (10 mmol) of 2.0 *M* THF solution of 1-bromoheptane and 5 m*l* (10 mmol) of 2.0 *M* THF solution of 2-bromoheptane were added. The reaction mixtures were heated to reflux in an oil bath. After 6 h, glpc analysis indicated the presence of 2-bromoheptane (93 %), 1-bromoheptane (7%) and *n*-heptane (100 %). (*Table* 2)

RESULTS AND DISCUSSION

Firstly, in order to investigate the selectivity of alkyl iodides, alkyl bromides and alkyl chlorides in the reduction with lithium borohydride, nine representative alkyl halides, na-

Table 1. Reaction of Representative Alkyl Halides with Lithium Borohydride in THF.[a,b]

Compounds	Products[c]			
	1 h	3 h	6 h	24 h
Benzyl chloride	11	21(1.5)	46(3)	67(10)[d]
Benzyl bromide	79(52)	97(64)	(77)	(90)
Benzyl iodide	93(84)	100(93)	(100)	
n-Heptyl chloride			2	12(0)
n-Heptyl bromide	50	70(11)	95(18)	100[e](39)
n-Heptyl iodide	92	100(51)	(63)	(79)
2-Bromoheptane		6	11(1.3)	34(3)
2-iodoheptane	24	48(3)	59(8)	80(15)
Cyclohexyl iodide		5	6	16(0)

a. Reaction mixtures were 0.25 M in compounds; *b*. The molar ratio of hydride to compounds was 4.0; *c*. Percent yields of alkanes estimated by glpc at 65°, unlessotherwise indicated; *d*. The figures in parentheses indicated the percent yields at room temperature; *e*. Yield at 12 h.

mely benzyl chloride, benzyl bromide, benzyl iodide, *n*-heptyl chloride, *n*-heptyl bromide, *n*-heptyl iodide, 2-bromoheptane, 2-iodoheptane and cyclohexyl iodide were chosen and were examined at room temperature and at 65° in tetrahydrofuran. Thus, each alkyl halide was reacted with lithium borohydride at room temperature and at 65°. The concentration of both alkyl halides and lithium borohydride was 0.25 *M*. And the approximate rate of each reaction was followed by the yield of the corresponding hydrocarbons estimated by glpc. The results were summarized in *Table* 1. These results confirmed that the reaction of alkyl halides with lithium borohydride in tetrahydrofuran was a typical S_N2 displacement reaction.[8] Thus, the rates of reduction were as the following: benzyl halides > primary alkyl halides > secondary alkyl halides and iodides > bromides > chlorides. As shown in *Table* 1, the reduction of benzyl iodide and benzyl bromide was essentially complete in 3 h at 65°, whereas benzyl chloride was reduced in the yield of 21 % under the exactly same condition, *n*-heptyl bromide was reduced completely in 12 h, and the reduction of *n*-heptyl iodide was faster than the other halides, giving 100 % yield in 3 h. However, the reduction of secondary alkyl halide was quite slow, compared with the corresponding primary alkyl halides. Thus, 2-bromoheptane and 2-iodoheptane were reduced in the yield of 34 % and 80 % both in 24 h, respectively. The reduction of cyclohexyl iodide was still very sluggish, giving cyclohexane in the yield of 16 % in 24 h. These results suggested that lithium borohydride possessed the possibilties for selective reduction of primary alkyl iodides or bromides in the presence of alkyl chlorides, secondary bromides and cyclohexyl iodide in tetrahydrofuran.

Table 2. Selective reduction of halides with lithium borohydride in the multifunctional compounds in THF[a,b]

Compounds	Procedure	Time (hour)	Products	Yield[c]
1-Brom-4-chloro-butane	A	3.0 6.0 18.0	1-Chlorobutane	68 84 96
p-Nitrobenzyl bromide	B	0.5 1.0 3.0	p-Nitrotoluene	85 93 98
Ethyl 3-iodopropionate	B	3.0 6.0 24.0	Ethyl propionate	27 25 19
Ethyl 3-iodopropionate	C	1.0 3.0 6.0	Ethyl propionate	85 93 89
4-Bromobutyronitrile	B	3.0 6.0 24.0	n-Butyronitrile	28 35 27
4-Bromobutyronitrile	C	3.0 6.0 24.0	n-Butyronitrile	76 82 88
1-Bromoheptane and 2-bromoheptane[d]	A	6.0	2-Bromoheptane 1-Bromoheptane Heptane	93 7 100

a.b. See corresponding footnotes in *Table* 1. *c.* Yields by glpc. *d* To the mixture of 1-bromoheptane (10 mmol) and 2-bromoheptane (10 mmol) was added to lithium borohydride (10 mmol). Procedure A.: Under reflux condition in THF. Procedure B.: At room temperature in THF. Procedure C.: At room temperature in the presence of equimolar pyridine.

Selective Reduction of Halides with Lithium Borohydride. In order to investigate selective reduction of halides with lithium borohydride in the multifunctional compounds, four representative compounds, namely 1-bromo-4-chlorobutane, *p*-nitrobenzyl bromide, ethyl 3-iodopropionate and 4-bromobutyronitrile were chosen and were reacted with lithium borohydride at room temperature or at 65°. And competitive reduction of 1-bromoheptane and 2-bromoheptane with lithium borohydride was also examined. The results were summarized in *Table* 2.

A. Selective Reduction of Bromide in the

Presence of Chloride. In order to investigate selective reduction of compound containing both bromide and chloride in a molecule, 1-bromo-4-chlorobutane was chosen as a representative compound and reacted with lithium borohydride in tetrahydrofuran at 65°. At appropriate time intervals, the reaction mixture was hydrolyzed with dilute sulfuric acid, neutralized with dilute sodium hydroxide, extracted with ether and the organic layer was analyzed by glpc. Glpc examination revealed the formation of 4-chlorobutane in the yields of 68 % at 3 h, 84 % at 6h and 96 % at 18 h.

B. Selective Reduction of Bromide in the Presence of Nitro Group. *p*-Nitrobenzyl bromide was chosen as a representative compound and reacted with lithium borohydride in tetrahydrofuran. Since nitro group was relatively susceptible to lithium borohydride,[7,9] the reaction was performed at room temperature. Glpc examination indicated the formation of *p*-nitrotoluene in the yields of 85 % at 0.5 h, 93 % at 1 h and 98 % at 3 h. It is considered that the faster reduction of *p*-nitrobenzyl bromide in comparison with benzyl bromide (64 % reduction in 3 h, see *Table* 1) under the same condition is attributed to electron withdrawing effect of nitro group.

C. Selective Reduction of Iodide in the Presence of Ester Group. The selective reduction of iodide with lithium borohydride in ethyl 3-iodopropionate was examined. Since lithium borohydride reduces ester moderately in tetrahydrofuran at 65°,[7] we examined the reaction at room temperature. However, the results were not satisfactory to give ethyl propionate in the yields of 33 % at 1 h, 27 % at 3 h, 25 % at 6 h, and 19 % at 24 h. The low yields of ethyl propionate were presumably resulted due to the reduction of the ester group with borane produced by the reaction of halide with lithium borohydride[2,10].

$$RX + LiBH_4 \longrightarrow RH + BH_3 + LiX$$
$$X = \text{halogen.}$$

Such undesirable reaction could be overcome by the addition of one molar equivalent of pyridine to the reaction mixture, presumably trapping the borane as pyridine borane, a very weak reducing agent[11]. Thus, in the presence of equimolar pyridine, ethyl propionate was obtained at room temperature in the yields of 85 % at 1 h, 93 % at 3 h and 89 % at 6 h.

D. Selective Reduction of Bromide in the Presence of Nitrile Group. 4-Bromobutyronitrile was chosen as a representative and reacted with lithium borohydride in tetrahydrofuran. Since nitriles were susceptible to borane,[13] the reaction was also performed in the presence of equimolar pyridine in tetrahydrofuran at room temperature as described in the preceding section. Thus, *n*-butyronitrile was obtained in the yields of 76 % at 3h, 82 % at 6 h and 88 % at 24 h. The reaction without pyridine gave n-butyronitrile at room temperature in the yields of 20 % at 1 h, 28 % at 3 h, 35 % at 6 h and 27 % at 24 h, respectively.

E. Selective Reduction of Primary Bromide in the Presence of Secondary Bromide. In order to examine the reducing selectivity between primary halides and secondary halides, lithium borohydride (10 mmol) was reacted with the mixture of 1-bromoheptane (10 mmol) and 2-bromoheptane (10 mmol) in tetrahydrofuran at 65°. After 6 h, glpc analysis indicated that lithium borohydride reduced 1-bromoheptane preferentially in the molar ratio of 93:7.

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