

Selective Reduction of Carbonyl Group with Borohydride Exchange Resin (BER)-LiCl System

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The reduction rate of borohydride exchange resin (BER) was greatly enhanced in the presence of lithium salts. Thus 2-heptanone was reduced completely with BER-LiCl in 1 h at room temperature however, no reduction was observed with BER alone under the same conditions. With this system, organic compounds containing various functional groups were examined in ethanol at room temperature. This study revealed that BER-LiCl system exhibits an excellent chemoselectivity for carbonyl group in the presence of other functional groups. Keto esters and epoxy ketones were reduced with BER-LiCl to give the corresponding hydroxy esters and epoxy alcohols with excellent yields. Selective reductions of carbonyl groups were also possible in the presence of other organic compounds containing functional groups such as 1-iodooctane, 1-bromooctane, caproamide, hexanenitrile, nitrobenzene, *n*-butyl disulfide, dimethyl sulfoxide and 1-dodecene.

Introduction

Since its original discovery¹, borohydride exchange resin (BER) has proven to be an excellent chemoselective² and regioselective³ reducing agent of carbonyl and α, β -unsaturated carbonyl compounds.

In a previous paper², we reported that BER exhibited a high chemoselectivity not only between aldehydes and ketones but also between different aldehydes and between different ketones. Besides, BER offers a significant advantage of simple work-up procedure for the isolation of products. However compounds such as 2-heptanone, acetophenone and norcamphor were reduced sluggishly with BER alone, showing only 30% reductions in 24 h at room temperature.

Searching for the methods to increase the reducing power of BER, we have investigated the effect of metal salts⁴ such as LiCl, LiNO₃, CaCl₂, and MgCl₂ on the reduction with BER. Among these metal salts, lithium salts showed an excellent catalytic effect on the reduction of ketones with BER. In order to better understand this reducing system, we examined the reductions of BER-LiCl with organic compounds containing various functional groups and explored several selective reductions.

Results and Discussion

The catalytic effects of some metal salts such as lithium chloride, lithium nitrate, calcium chloride and magnesium chloride on the reduction of 2-heptanone with BER have been investigated. Thus two mmol of 2-heptanone was reacted with BER, containing 1 mmol of BH₄⁻ (4 mmol of hydrides) in the presence of 2 mmol of metal salts, and the reaction was followed by the GLC estimation of 2-heptanol. As shown in Table 1, the order of catalytic activity of metal salts was as follows: LiCl > LiNO₃ > CaCl₂ > MgCl₂.

The effect of lithium chloride and lithium nitrate was particularly superior to those of other metal salts. Thus, 2-heptanone was completely reduced with BER-lithium salt in 1.0 h, whereas only 30% yield was observed with BER in

Table 1. The Effect of some Metal Salts on the Reduction of 2-Heptanone with BER in 95% Ethanol at Room Temperature^a

metal salts	reduction ^b , %				
	0.5	1.0	3.0	12.0	24.0
LiCl	96	98			
LiNO ₃	91	100			
CaCl ₂	13	33	93	100	
MgCl ₂	0	3	7	43	81
none	0	0	2	12	30

^aTwo mmoles of 2-heptanone in 2 ml ethanol were added to BER (1 mmol of BH₄⁻) and metal salts (2 mmol) in 6 ml ethanol. ^bDetermined by GLC.

24 h in the absence of lithium salt. Calcium and magnesium chloride also influenced the reduction of 2-heptanone but their catalytic effects were inferior to lithium salts, showing a 90% reduction in 3 h and a 81% reduction in 24 h respectively. There are two possible effects of the metal salts that would influence the reducing ability of BER. First, chloride (or nitrate) anion may exchange with the borohydride anion bounded on resin, and the unbound metal borohydride may influence the reduction of 2-heptanone. However, we detected⁵ only 0.2% boron moiety in the solution after 1h reaction of 2-heptanone with BER in the presence of equimolar LiCl. Thus this possibility was ruled out. Another possibility would be the influence of the metal cation on the reactivity of carbonyl group by coordination. Such coordination of lithium ion on the oxygen of carbonyl group would doubtless increase the electron deficiency of the carbonyl carbon and makes it more receptive to the transfer of a hydride moiety from the borohydride anion. Brown et al.⁶ also observed that the reactivities in the borohydride reduction of esters were in the following order: LiBH₄ > Ca(BH₄)₂ > NaBH₄.

We examined the effect of LiCl concentration on the reduction of 2-heptanone in the protic solvents such as ethanol and methanol. The concentration of LiCl was varied

Table 2. The Effect of LiCl concentration on the Reduction of 2-Heptanone with BER in protic solvents at Room Temperature^a

concentration (M)			reduction ^b , %			
LiCl	2-heptanone	solvent	1.0	3.0	12.0	24.0
0.25	0.25	ethanol	96	98		
0.125	0.25	ethanol	16	62	74	89
0.025	0.25	ethanol	6	13	27	52
0	0.25	ethanol	0	2	12	30
0	0.25	methanol	7	9	31	51
0.25	0.25	methanol	93 ^c	93		

^aTwo mmoles of 2-heptanone in 2 ml ethanol was added to BER (1 mmol of BH_4^-) and LiCl in 6 ml ethanol. ^bDetermined by GLC. ^cBER was destroyed by the rapid evolution of hydrogen gas and 2-Heptanone was recovered in a 7% yield.

Table 3. Reaction of BER-LiCl with Selected Organic Functional Compounds in 95% Ethanol at Room Temperature^a

compd	reaction ^b , %			
	0.5	1.0	3.0	24.0
2-heptanone	96	98		
norcamphor	94	100		
acetophenone	68	83	101	
ethyl caproate	0	2	3	19
1-bromooctane	0	0	1	4
styrene oxide	0	0	1	4
caproamide	0	0	0	10
hexanenitrile	1	3	3	10
nitrobenzene	0	0	0	8
<i>n</i> -butyl disulfide	0	0	0	4
dimethyl sulfoxide	0	0	1	3

^aTwo mmoles of compound of 2 ml in ethanol was added to BER (1 mmol of BH_4^-) and 2 mmoles of LiCl in 6 ml of ethanol. ^bDetermined by GLC. The reaction of ketones were followed by the yields of alcoholic products, however those of other substrates were estimated by the decrease of the substrates.

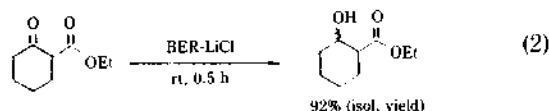
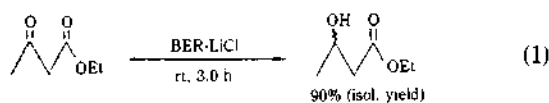
from 0.25 M, to 0.125 M and 0.025 M, while the concentration of 2-heptanone was fixed to 0.25 M. In ethanol solvent, 98%, 47% and 4% of 2-heptanone was reduced in 1 h when the concentration of LiCl was 0.25 M, 0.125 M, and 0.025 M respectively. Reduction rate was faster with higher concentration of LiCl. In changing the solvent from ethanol to methanol, somewhat faster reduction of 2-heptanone by BER was observed. Thus 2-heptanone was reduced to 2-heptanol in the yield of 54% in methanol and 30% in ethanol in 24 h. However, in the presence of LiCl, 93% of 2-heptanone was reduced in 0.5 h and further reduction did not proceed in methanol. The reaction was accompanied by the rapid evolution of hydrogen gas. These results can be attributed to the destruction of borohydride anion during the reaction. Therefore, we chose ethanol as solvent for the reduction by BER in the presence of LiCl.

Reduction of Selected Organic Compounds. In order to understand the reducing properties of this system, we studied the reactions of BER-LiCl with a series of selected organic compounds containing various functional groups. In

general, 2.0 equiv of BER ($\text{BH}_4^-/\text{compd} = 0.5$) was used in the presence of 1.0 equiv LiCl to the substrate. The reactions were all carried out in 95% ethanol (commercial grade) at room temperature and the results are summarized in Table 3. As shown in Table 3, ketones such as 2-heptanone, norcamphor and acetophenone were reduced completely in 3 h with this system, whereas ethyl caproate, 1-bromooctane, styrene oxide, caproamide, hexanenitrile, nitrobenzene, *n*-butyl disulfide and dimethyl sulfoxide were all inert to this system. The rate study of functional groups show the high selectivity of this system permitting the reduction of carbonyl group in the presence of many other functional groups.

Selective Reduction

Keto esters. Selective reduction of a carbonyl group in the presence of an ester functional group was examined. We tested two keto esters, namely ethyl acetoacetate and ethyl 2-cyclohexanecarboxylate. BER-LiCl system reduced these esters with an excellent selectivity. Thus ethyl 3-hydroxy butyrate and ethyl 2-hydroxy cyclohexanecarboxylate were obtained in the isolated yields of 90% and 92% respectively (eq 1 and 2).



Sodium borohydride⁷, zinc borohydride⁸ or alkyl boranes such as disiamyl borane⁹ are used for the reduction of carbonyl group in the presence of ester group. These hydrides are known to reduce carbonyl group readily, but they are inert or very sluggish for the reduction of ester group under normal conditions. However sodium borohydride has to be used in alkaline stabilized hydroxylic solvents in order to reduce ketone group smoothly, and this alkaline solution could cause complication such as hydrolysis¹⁰, racemization¹¹ etc. Sometime ago, we have demonstrated that we could overcome these difficulties using zinc borohydride⁸. However BER-LiCl system should have advantages over zinc borohydride for isolation of product. Disiamyl borane is expected to do this selective reduction nicely, but it is a much more expensive reagent than the borohydrides, and the oxidation of organoborane should be included in the work-up procedure.

Epoxy Ketones. Similarly, the inertness of epoxides toward this system allows the chemoselective reduction of α,β -epoxy ketones. Thus, isophorone oxide and 3,4-epoxy-4-methyl-2-pentanone were reduced with BER-LiCl to give the corresponding epoxy alcohols in the yields of 95% and 82% respectively (eq 3 and 4).

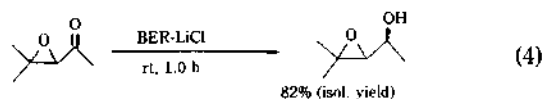
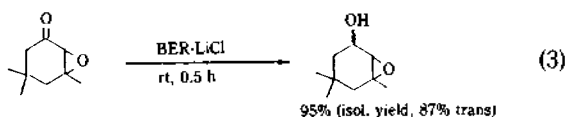


Table 4. Competitive Reduction of 2-Heptanone in the Presence of Other Functional Group Compounds with BER-LiCl in 95% Ethanol at Room Temperature^a

compd	product ^b , %
2-heptanone 1-iodooctane	2-heptanol, 100
	1-iodooctane, 96
2-heptanone 1-bromooctane	2-heptanol, 100
	1-bromooctane, 100
2-heptanone caproamide	2-heptanol, 100
	caproamide, 100
2-heptanone nitrobenzene	2-heptanol, 99
	nitrobenzene, 98
2-heptanone 1-dodecene	2-heptanol, 100
	1-dodecene, 99
2-heptanone hexanenitrile	2-heptanol, 100
	hexanenitrile, 100
2-heptanone <i>n</i> -butyl disulfide	2-heptanol, 100
	<i>n</i> -butyl disulfide, 100
2-heptanone dimethyl sulfoxide	2-heptanol, 100
	dimethyl sulfoxide, 100

^aTwo mmoles of each compounds in 2 ml ethanol were added to BER (1mmol of BH_4^-) and LiCl (2 mmol) in 6 ml ethanol. ^bAfter 1 hour reaction, the products were determined by GLC.

α , β -Epoxy ketones are known to isomerize easily in the presence of acids or bases¹². Accordingly, mild and neutral reducing agent should be employed for this kind of selective carbonyl reduction. Sodium borohydride and zinc borohydride have been reported for the selective reduction of α , β -epoxy ketones. However, sodium borohydride seems to be inadequate since it has been reported to reduce epoxides slowly¹³ and to be sufficiently basic to induce epimerization of α -substituent of a ketone¹¹. Zinc borohydride¹⁴ also shows a very good selectivity as BER-LiCl system, but BER-LiCl should be a preferred reagent, because of the simple work-up procedure.²

Competitive Reduction. In order to demonstrate the selective reduction of carbonyl groups with BER-LiCl in the presence of functional groups other than esters and epoxides, eight competitive reductions were carried out. Thus equimolar mixture of 2-heptanone and other organic compounds, such as 1-iodooctane, 1-bromooctane, caproamide, hexanenitrile, nitrobenzene, *n*-butyl disulfide, dimethyl sulfoxide and 1-dodecene, were competitively reduced with BER-LiCl. In typical cases, the concentration of each reactant was 0.5 M and the hydride to 2-heptanone ratio was fixed 2. After 1.0 h reaction, the reaction mixture was analyzed by GLC and the results are listed in Table 4. As shown in Table 4, BER-LiCl showed an excellent selectivity with a clean reduction of 2-heptanone to the corresponding alcohol, whereas 1-iodooctane, 1-bromooctane, caproamide, hexanenitrile, nitrobenzene, *n*-butyl disulfide, dimethyl sulfoxide and 1-dodecene were completely inert to BER-LiCl. In conclusion, we have demonstrated that BER-LiCl is a reagent of choice for the selective reduction of carbonyl groups in the presence of many other functional groups because of its excellent selectivity, ready availability, and the simple work-up procedure.

Experimental

Materials. NaBH_4 (98%, Nisso Ventron) was used without further purification. Anion exchange resin (Amberlite IRA-400) was used for supporting polymer of BER. Commercial grade, 95% ethanol was used as such. 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. Hypodermic syringes were used to introduce and transfer the solution.

Preparation of BER. A slurry of wet chloride-form anion exchange resin (Amberlite IRA-400, 10 g, 19 meq) was slurry-packed with water into a 100 ml fritted glass funnel and mounted on a filtering flask which connected to a water aspirator. Then 200 ml of aqueous NaBH_4 solution (0.1 M) was slowly passed through the resin over a period of 30 min. The resulting resin was then dried in vacuo at 60°C for 5 h. The dried resin was analyzed for borohydride with 2.0 M HCl solution and the average capacity of BER was found to be 13.6 mmol of hydride (3.4 mmol of BH_4^-) per gram of resin. The dried resin was stored under nitrogen at room temperature. The hydride content was constant over 6 weeks.

General Procedure for the Rate Study. The reduction of 2-heptanone is described as representative. BER (294 mg, 1.0 mmol of BH_4^-) was placed in a 50 ml flask with rubber-capped side arm, a magnetic stirring bar and a reflux condenser connected to a mercury bubbler. After 2 ml of ethanol and 4 ml of LiCl solution (0.5 M in ethanol) was added, 2 mmol each of 2-heptanone and 1-heptanol (as an internal standard) in 2 ml ethanol were introduced into the reaction flask with stirring at room temperature. At the end of appropriate time intervals, stirring was stopped and then 0.5 ml of aliquot was withdrawn and analyzed by GLC after drying over anhydrous K_2CO_3 . GLC analysis indicated that 2-heptanone was reduced to 2-heptanol in a 96% yield at 0.5 h and a 98% yield at 1.0 h.

Procedure for the Reduction of Ethyl 2-cyclohexanonecarboxylate. BER (2.94 g, 10 mmol of BH_4^-) was placed in a 250 ml flask fitted with rubber-capped side arm and a magnetic stirring bar, connected to a mercury bubbler. After adding 30 ml of ethanol, 40 ml of LiCl solution (0.5 M, 20 mmol) in ethanol was added. The reaction was started by adding 3.4 g (20 mmol) of ethyl 2-cyclohexanonecarboxylate at room temperature. After 0.5 h, the resin was separated by filtering and washed with ethanol (5 ml \times 5). Then 50 ml of ether and 100 ml of water was added to divide organic layer from aqueous layer. The organic layer was separated and aqueous layer was extracted with ether (50 ml \times 2). The combined extracts were dried over anhydrous MgSO_4 . After the solvent was removed by distillation, the residue was fractionally distilled under reduced pressure to provide 3.1 g (92.4%) of ethyl 2-hydroxy cyclohexanecarboxylate: bp 118-9°C (20 mm) (lit.¹⁵ 100-3°C (10 mm)); ¹H NMR (Neat) 1.27 (t, 3H, CH_3), 1.4-2.5 (m, 9H), 2.97 (s, 1H, OH), 4 (m, 1H, H), 4.15 (q, 2H, CH_2); n_D^{20} 1.4599.

Reduction of Ethyl Acetoacetate. The general procedure was followed, and 2.38 g (90%) of ethyl 3-hydroxy butyrate was obtained: bp 167-171°C (lit.¹⁶ 76-77°C (15 mm)); ¹H NMR (Neat) 1.32(t, 3H, CH_3), 1.7 (t, 3H, CH_3), 2.41 (q, 2H, CH_2), 3.41 (m, 1H, OH), 4.18 (q, 2H, CH_2), 4.03-4.22 (m, 1H, H); n_D^{20} 1.4179 (lit.¹⁶ n_D^{20} 1.4182).

Reduction of Isophorone Oxide. Isophorol oxide was obtained in a 95% (2.79 g) yield and GLC analysis showed that the ratio of cis-and trans isophorol oxide was 13:87.; bp 103-106°C (5 mm) (lit.¹⁴ bp 97-99 °C (4 mm)); ¹H NMR (Neat) 0.99 (s, 3H, CH₃), 1.06 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.63 (t, 2H, CH₂), 2.18 (m, 1H, OH), 2.88 (s, 1H, H), 4.14 (m, 1H, H); n_D^{20} 1.4632 (lit.¹⁴ n_D^{20} 1.4635).

Reduction of 3,4-Epoxy-4-Methyl-2-Pentanone. 1.9g (82%) of 3,4-epoxy-4-methyl-2-pentanol was obtained: bp 52-55°C (4mm) (lit.¹⁴ bp 58-60 (6mm)); ¹H NMR (Neat) 1.2-1.4(m, 9H, CH₃), 2.50 (d, 1H, H), 3.48 (m, 1H, OH), 3.95 (s, 1H, H); n_D^{20} 1.4193 (lit.¹⁴ n_D^{20} 1.4180).

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A Route for Sulfuranyl Radical by an Electron Transfer from Sodium Naphthalenide to a Triarylsulfonium Salt ¹

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Reaction of 5-(2-thianthreniumyl)thianthrene perchlorate with sodium naphthalenide in the presence of benzenethiol in tetrahydrofuran at -78°C proceeded via a formation of a sulfuranyl radical to give thianthrene (66%), 2-phenylthiothianthrene (33%), phenyl 2-(2-thianthrenylthio)phenyl sulfide (traceable amount), and some unknowns, along with naphthalene and very small amount of 1,4-dihydronaphthalene.

Sulfuranyl radicals have been mainly suggested in reactions involving radical substitution at sulfur.² However, little is known about generation of sulfuranyl radical *via* an electron transfer to arylsulfonium salts. McEwen and co-worker³ studied reactions of triarylsulfonium salts with sodium alkoxides, and rationalized their results on the basis of an electron transfer from alkoxides to the sulfonium salts, yielding sulfuranyl and alkoxy radicals. Since triarylsulfuranyl radicals are too reactive to be detected by ESR techniques, and in particular, it is necessary to obtain clearly information about sulfuranyl radicals which might be involved in the reactions of triarylsulfonium salts with organolithiums⁴ or thiolates⁵, investigations on reactions of triarylsulfonium salts with an good electron donor are needed.

Results and Discussion

We have chosen sodium naphthalenide (**1**) as an electron donor and carried out the reaction of **1** with 5-(2-thianthreniumyl)thianthrene perchlorate (**2**). By treatment of **2** with **1** in tetrahydrofuran (THF) under nitrogen at -78°C were obtained naphthalene, thianthrene (**3**), and a great number of unidentified products. Since one of the reasons for the complexity was conceived of diverse reactions of radicals formed by the decomposition of sulfuranyl radical, the same reaction was carried out in the presence of benzenethiol so as to quench the possible secondary radical reactions. The results are summarized in Table 1.

The fact that only a trace amount of 1,4-dihydrona-