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Selective Reduction of α,β -Unsaturated Ketones with Borohydride Exchange Resin-CuSO₄ in Methanol

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Borohydride exchange resin (BER)-CuSO₄ system readily reduces α,β -unsaturated ketones to the corresponding saturated alcohols quantitatively. This reduction tolerates many functional groups such as carbon-carbon multiple bonds, chlorides, epoxides, esters, amides and nitriles.

Introduction

Although many metal hydride systems are reported to be effective on the selective reduction of α,β -unsaturated ketones to the saturated ketones¹ or to the corresponding allylic alcohols,² the clean one step reduction to the saturated alcohols is rare. Only a few borohydrides are reported to be effective on specific enones.³ Other reagents are hydrogenation over Rh/Al₂O₃,⁴ hydrogenation with LaNi₅H₆,⁵ hydrogenation over Nic in ethanol,⁶ and lithium metal in liquid ammonia.⁷ Recently we have found borohydride exchange resin (BER)-CuSO₄-MeOH^{8,9} system reacts slowly with terminal olefins and is inert to many other functional groups, however reacts rapidly with α,β -unsaturated ketones to give the corresponding saturated alcohols. BER is a quaternary ammonium borohydride supported on an anion exchange resin,⁸ and unlike NaBH₄-MeOH system, BER-MeOH system decomposes slowly at room temperature in the presence of copper. In this paper, we wish to report BER-CuSO₄ system is capable of reducing enones almost quantitatively with excellent chemoselectivity.

Results and Discussion

Preparation and Stability of BER-CuSO₄ System in Methanol. Borohydride exchange resin was prepared as described previously.⁸ When BER was added to copper sulfate solution in methanol, the resin turned black, presumably by copper coating. The stabilities of BER in methanol was studied in the presence and absence of a catalytic amount of copper, and compared with those of NaBH₄ in Figure 1. As shown in Figure 1, this polymeric quaternary ammonium borohydride, BH₄⁻ being attached on the surface of resin (BER) is much more stable in methanol than NaBH₄ itself, both in the presence and absence of copper. Thus in

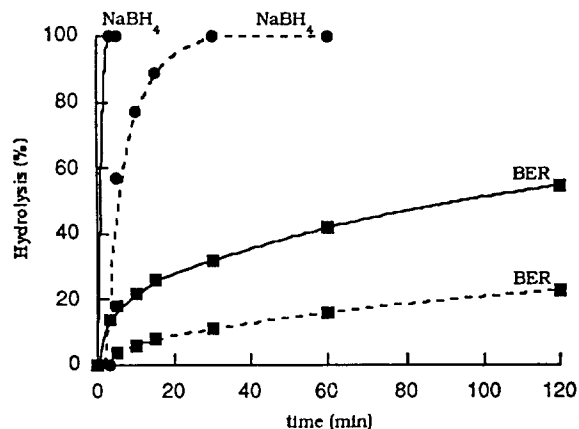


Figure 1. Rate of Hydrolysis of BER and NaBH₄ in Methanol in the Presence (solid line) and Absence (dotted line) of CuSO₄ (2.0 mol%).

the presence of 2.0 mol% of CuSO₄, NaBH₄ decomposed completely in 5 min, whereas BER retained ca. 60% of hydride after 1.0 h at room temperature. Therefore NaBH₄ reduction in methanol had to be carried out by adding solid NaBH₄ portionwise especially in the presence of transition metal salts.^{9,10}

Standard Procedure. Procedure adapted was to add substrate (1.0 mmol) to the mixture of BER (5.0 mmol) and CuSO₄ (0.1 mmol) in methanol (20 mL). The reductions were usually completed in 1 h at room temperature, and the products were analyzed by Glpc. When the reduction was slow at the standard conditions, reduction was accelerated by increasing the reagents. In the case of preparative runs, substrate (10.0 mmol) was reacted with BER (50.0 mmol)-CuSO₄ (1.0 mmol) and after the reduction, BER-Cu was filtered and methanol was evaporated to get nearly pure product.

Table 1. Reduction of α,β -Unsaturated ketones with BER-CuSO₄ in Methanol at Room Temperature

Entry	Enone	Product	Time (h)	Yield (%) ^c
1	ethyl vinyl ketone	3-pentanol	1.0	99
2	benzalacetone	4-phenyl-2-butanol	1.0	99(95)
3	chalcone	1,3-diphenyl-1-propanol	1.0	100
4	mesityl oxide ^b	4-methyl-2-pentanol	3.0	99
5	mesityl oxide ^c	4-methyl-3-penten-2-ol	8.0	95
6	mesityl oxide ^d		3.0	N.R.
7	cyclopentenone	cyclopentanol	1.0	100
8	cyclohexenone	cyclohexanol	1.0	98(91)
9	isophorone	3,3,5-trimethylcyclohexanol	1.0	98(93) ^e

^aYields are estimated by Glpc using appropriate internal standards. Isolated yields are in parenthesis. ^bBER (10.0 eq)-CuSO₄ (0.1 eq). ^cReduction with BER in MeOH. ^dReduction with BER-CuSO₄ in EtOH. ^eCis/trans ratio was 8/92.

Reduction of α,β -Unsaturated Ketones. Seven representative α,β -unsaturated ketones were reacted at the standard conditions. As shown in Table 1, all the enones tested, either aliphatic or aromatic, were reduced to the corresponding saturated alcohols quantitatively in 1 h at room temperature with only one exception, mesityl oxide. However in this case also, hydride attack occurred exclusively on β -carbon of mesityl oxide, and the resulting ketone, 4-methyl-2-pentanone was reduced in 3 h using 10 mmol of BER (entry 4). However, in the absence of copper, BER reduced mesityl oxide to the corresponding allylic alcohols (entry 5). It is impressive that the presence of catalytic amount of copper changes the point of hydride attack exclusively from carbonyl carbon to β -carbon, and BER-CuSO₄ could not reduce this enone at all in ethanol (entries 5 and 6). Although NaBH₄ in EtOH at 78^o_{3a} and NaBH₄-MeOH at -10^o_{3b} were effective to give cyclopentanol from 2-cyclopentenones, NaBH₄ usually gives a mixture of allylic alcohol and saturated alcohol.¹¹ The reduction products with Ks-Bu₃BH vary depending upon the structure of α,β -unsaturated ketones.^{1c,3c} On the other hand, hydrogenations over Rh/Al₂O₃,⁴ NaNi₅H₅⁵ and Ni⁶ would proceed simultaneous hydrogenation of double bonds, and lithium metal in liq. NH₃ may not tolerate ester^{7b} or benzene ring.¹²

Selectivity of BER-CuSO₄ System in Methanol. In order to find out the selectivity of this reduction in organic synthesis, we explored briefly the reduction property of BER-CuSO₄-MeOH system. As shown in Table 2, 1-heptene was reduced slowly but internal olefins such as cyclohexene and 2-octene were almost inert (entries 1, 3 and 5). Benzalacetone and mesityl oxide could be reduced selectively in the presence of 1-heptene and cyclohexene respectively (entries 2 and 4). 1-Heptyne was also reduced very slowly and 2-cyclohexenone was reduced selectively (entries 6 and 7). 1-Chlorooctane, 1,2-epoxydecane, ethyl hexanoate and benzamide were all inert to this system (entries 8, 10, 11 and 13), however, 1-bromooctane was rapidly reduced to octane, and ethyl crotonate and crotononitrile were readily reduced to the corresponding saturated compounds (entries 12 and 15). Hexanenitrile was reduced slowly, however 2-cyclopentenone was reduced in the presence of hexanenitrile with very good selectivity (entries 14 and 16).

Table 2. Reducing Characteristics of BER-CuSO₄ system and Some Competitive Reductions with Enones in Methanol at Room Temperature

Entry	Substrate	Product	Time (h)	Yield (%) ^c
1	1-heptene	<i>n</i> -heptane	1.0	42
			3.0	50
2 ^b	1-heptene	<i>n</i> -heptane	1.0	5
	benzalacetone	4-phenyl-2-butanol		98
3	cyclohexene	cyclohexane	3.0	0
4 ^b	cyclohexene	cyclohexane	3.0 ^c	0
	mesityl oxide	4-methyl-2-pentanol		99
5	2-octene	<i>n</i> -octane	3.0	0
6	1-heptyne	1-heptene	3.0	8
7 ^b	1-heptyne	1-heptene	0.5 ^d	6
	2-cyclohexenone	cyclohexanol		98
8	1-chlorooctane		3.0	N.R. ^e
9	1-bromooctane	<i>n</i> -octane	1.0	99
10	1,2-epoxydecane		3.0	N.R.
11	ethyl hexanoate		3.0	N.R.
12	ethyl crotonate	ethyl butyrate	1.0	100
13	benzamide		3.0	N.R.
14	hexanenitrile	hexylamine	3.0	13
15	crotononitrile	butyronitrile	1.0	99
16 ^b	hexanenitrile	hexylamine	1.0	2
	2-cyclopentenone	cyclopentanol		100

*Same as Table 1. ^bA mixture of one mmol each of substrates was reacted. ^cBER (10.0 eq)-CuSO₄(0.1 eq) was used. ^dBER (5.0 eq)-CuSO₄(0.2 eq) was used. ^eNo reaction.

Table 3. Reduction of α -Ionone with BER-Transition Metal Salts in Methanol at Room Temperature

Ber(5) ^a -	1 h	52	17	24 ^b
CuSO ₄ (0.1)	3 h	23	17	58
BER(5)-	1 h	18	36	28
Ni(OAc) ₂ (0.1)	3 h	1	43	56
BER(5)-	1 h	4	4	91
CuSO ₄ (0.1)-	3 h	0	4	96(85) ^c
Ni(OAc) ₂ (0.1)				

*Mmol per mmol of α -ionone. ^bYield by Glpc. ^cIsolated yield.

tenone was reduced in the presence of hexanenitrile with very good selectivity (entries 14 and 16).

The selectivity was also tested with α -ionone. As shown in Table 3, the double bond of cyclohexene was intact, however 58% of expected alcohol was contaminated with 17% of allylic alcohol together with substantial amount of saturated ketone even after 3 h in our standard conditions. However we could get 96% yield of expected alcohol in 3 h using BER-CuSO₄(0.1 eq)-Ni(OAc)₂(0.1 eq). BER-Ni(OAc)₂(0.1 eq) gave more allylic alcohol (43%) than BER-CuSO₄(0.1 eq).

Finally BER-CuSO₄-MeOH system has another advantage

of simple work up. As shown in Table 1, simple filtration of BER-Cu and evaporation of methanol gave a quantitative yield of almost pure product (entry 2, 8 & 9). Therefore we believe BER-CuSO₄ system in methanol is a reagent of choice for the selective reduction of α,β -unsaturated ketones to the corresponding saturated alcohols.

Experimental

Materials

NaBH₄ (98% Nisso Ventron) was used without further purification. Anion exchange resin (Amberlite IRA-400) was used for supporting polymer of BER. All 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.

Instruments

The Glpc analysis was performed on a Hewlett-Packard 5890A chromatograph equipped with FID detector and Spectra Physics 4290 integrator. NMR spectra were obtained on a Varian Gemini 200 (200 MHz) spectrometer.

Preparation of BER.⁸

A slurry of 60 g of wet chloride form-anion exchange resin (Amberlite IRA-400, 20-50 mesh) was slurry-packed with water into 300 mL glass column connected to a water aspirator. Then 500 mL aqueous solution of NaBH₄ (10 g) was slowly passed through the resin over a period of 30 min. The resulting resin was washed thoroughly with distilled water until free of excess NaBH₄. The borohydride form anion exchange resin was then dried *in vacuum* at 60°C for 5 h. The dried resin was analyzed for borohydride content by hydrogen evolution on acidification with 2 N HCl and the average capacity of BER was found to be 3.3 mmol of BH₄⁻ per gram. The dried resin was stored under nitrogen in refrigerator (0-4°C). The hydride content was constant over 6 weeks.

Stability of BER in Methanol in the Presence and Absence of Copper Sulfate

For the hydrolysis, a 50 mL flask fitted with a rubber syringe cap on an inlet port, a magnetic stirrer and reflux condenser connected to a gas buret was used. The reaction flask, charged with 2.0 mmol of BER (8.0 mmol of hydride) was purged with N₂ gas for 10 min, then 0.04 mmol of CuSO₄ solution in 8 mL methanol or 8 mL methanol was injected. BER evolved 3.4 mmol (42%) and 4.4 mmol (55%) of hydrogen in 1 h and 2 h respectively in the presence of copper sulfate and 1.3 mmol (16%) and 1.8 mmol (23%) of hydrogen in 1 h and 2 h respectively in the absence of copper sulfate.

Reduction of Benzalacetone

Reduction of benzalacetone is described as a representative.

Analytical. BER (1.61 g, 5.0 mmol) was added to the reaction flask containing a solution of copper sulfate (0.025 g, 0.1 mmol) in 20 mL of methanol. After the addition, yellowish BER particle turned black. One mmol each of benzalacetone and mesitylene (internal standard) in methanol (2 mL) was then added. After the reaction mixture was stirred for 1 h at room temperature, the Glpc analysis of the mixture on column HP-FFAP showed 99% of 4-phenyl-2-butanol.

Isolation. BER (15.2 g, 50.0 mmol) was added to the reaction flask containing a solution of copper sulfate (0.249 g, 1.0 mmol) in 120 mL of methanol. Benzalacetone (10.0

mmol) in methanol (20 mL) was then added. After the reaction mixture was stirred for 1 h at room temperature, the resin was removed by filtration and methanol was evaporated under reduced pressure to give 1.42 g of 4-phenyl-2-butanol (95%); ¹H NMR (CDCl₃+TMS) δ 1.20-1.25 (d, 3H), 1.71-1.87 (m, 2H), 2.12-2.32 (s, 1H), 2.59-2.85 (m, 2H), 3.75-3.90 (sextet, 1H), 7.15-7.35 (m, 5H).

Competitive Reduction

BER (1.61 g, 5.0 mmol) was added to the reaction flask containing a solution of copper sulfate (0.025 g, 0.1 mmol) in 20 mL of methanol. One mmol each of benzalacetone, 1-heptene, and mesitylene (internal standard) in methanol (2 mL) was then added. After the reaction mixture was stirred for 1 h at room temperature, the Glpc analysis of the reaction mixture on column HP-1 showed 98% of 4-phenyl-2-butanol and 5% *n*-heptane.

Reduction of α -Ionone

Analytical. BER (1.67 g, 5.0 mmol) was added to the reaction flask containing a solution of copper sulfate (0.025 g, 0.1 mmol) and nickel acetate (0.025 g, 0.1 mmol) in 20 mL of methanol. One mmol each of α -ionone and *n*-octyl alcohol (internal standard) in methanol (2 mL) was then added. After the reaction mixture was stirred for 3 h at room temperature, the Glpc analysis of the reaction mixture on column HP-FFAP showed the corresponding saturated alcohol (96%) and allylic alcohol (4%).

Isolation. BER (15.2 g, 50.0 mmol) was added to the reaction flask containing a solution of copper sulfate (0.249 g, 1.0 mmol) and nickel acetate (0.249 g, 1.0 mmol) in 120 mL of methanol. α -Ionone (10.0 mmol) in methanol (20 mL) was then added. After the reaction mixture was stirred for 3 h at room temperature, the resin was removed by filtration and methanol was evaporated under reduced pressure. After the allylic alcohol was transformed to the corresponding epoxy alcohol by MCPBA,¹³ separation by silica gel column chromatography afforded 1.67 g of expected alcohol (85%); ¹H NMR (CDCl₃+TMS) δ 0.85-0.88 (s, 3H), 0.90-0.92 (s, 3H), 1.14-1.21 (d, 3H), 1.30-1.58 (m, 8H), 1.65-1.69 (s, 3H), 1.89-2.02 (m, 2H), 3.66-3.78 (m, 1H), 5.25-5.35 (s, 1H).

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