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CHEMOSELECTIVE REDUCTION OF CARBONYL COMPOUNDS WITH BOROHYDRIDE EXCHANGE RESIN IN ALCOHOLIC SOLVENTS

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Summary: Borohydride exchange resin exhibited a high chemoselectivity not only between aldehyde and ketone but also between aldehydes and between ketones.

Polymer-supported reagents have gained in popularity in the last ten to fifteen years, and have already found wide applications in organic and inorganic chemistry, biochemistry and biology[1]. Among these, borohydride exchange resin (BER) was first reported in 1977 by Gibson and Baily[2a] and has been used in solvent purification, generation of volatile metal hydrides and reductions of metal ions and some aldehydes[2b]. Now, we wish to report that BER shows high chemoselectivity in the reduction of carbonyl compounds in alcoholic solvents.

Selective reduction of one carbonyl group in the presence of other such groups is a frequent synthetic problem. In recent years, various reagents have been developed for such selective reductions[3]. These reagents are mostly capable of reducing aldehydes in the presence of ketones but the selective reductions between aldehydes[4] and between ketones[5] are rare. The chemoselectivity was studied by competitively reducing the equimolar mixture of carbonyl compounds with BER reagent. The results are summerized in Table I.

As shown in Table I, BER reagent generally reduces aldehyde much faster than ketone (entries 1, 2 and 3), and the rates of reduction are much faster in methanol than in ethanol (entries 1 and 4). As shown in entries 1, 2 and 3, BER shows a very good selectivity between aldehyde and ketone with preferential reduction of aldehyde in ethanol at 25°C. The selectivity of BER is equal to or greater than that of previously reported selective reagents[3a-3i]. For example, in the selective reduction between benzaldehyde and acetophenone, 100:8 selectivity with sodium triacetoxyborohydride[3c], 100:9 with sodium borohydride in the presence of thiol[3d], 94:2 with 9-borabicyclo[3.3.1] nonane (9-BBN)-pyridine[3e], and 100:0 with BH_3-LiCl system[3f] have been reported. The data of entries 4, 5 and 6 show a remarkable selectivity between aldehydes in methanol at -10°C. Thus aromatic aldehydes were preferentially reduced in the presence of aliphatic aldehydes with exceptional selectivity showing 93.5:6.5 between benzaldehyde and hexanal and 95.8:2.0 between p-nitrobenz-

Table I. Selective Reduction of Carbonyl Compounds with Borohydride Exchange Resin[a]

Entry	Starting mixture[b]	BH_4^-/Compd[c]	Solvent	Temp (°C)	Time (hr)	%Reduction[d]
1	Benzaldehyde Acetophenone	0.38	EtOH	25	5	99.0 1.0
2	Hexanal Acetophenone	0.38	EtOH	25	20	99.5 4.7
3	Benzaldehyde 2-Heptanone	0.38	EtOH	25	5	100.0 tr.
4	Benzaldehyde Hexanal	0.33	MeOH	-10	1	98.5 6.5
5	p-Nitrobenzaldehyde Hexanal	0.33	MeOH	-10	1	95.8[e] 2.0
6	p-Nitrobenzaldehyde p-Methoxybenzaldehyde	0.33	MeOH	-10	1	92.3[e] 5.2
7	Cyclohexanone 4-Heptanone	0.50	MeOH	0	9	95.1 3.9
8	Cyclohexanone 2-Heptanone	0.50	MeOH	0	9	92.6 7.9
9	Cyclohexanone Norcamphor	0.50	MeOH	0	9	93.4 10.8 (9.1 exo)

a: 2.0 mmol of each compound in 8 ml solvent was added to BER.

b: One drop of Et_3N to the reaction mixture to inhibit formation of acetal or ketal (entries 5, 6, 7, 8 and 9).

c: Mmoles of BH_4^-/mmol of compound.

d: Determined by GLPC[7] using an internal standard.

e: Isolated yield by column chromatography on silica gel.

aldehyde and hexanal. Recently, Gemal and Luche[4] have reported this kind of selective reduction using $NaBH_4$ in the presence of $ErCl_3$. They found 95:12 selectivity between benzaldehyde and hexanal.

More interesting chemoselectivity was observed in para-substituted benzaldehydes (entry 6) i.e. electron-withdrawing substituent enhanced the rate whereas electron-donating substituent retarded the rate. A good selectivity was also observed between ketones (entries 7, 8 and 9). Thus cyclohexanone was reduced much faster than acyclic or bicyclic ketones. However, the selectivity of BER reagent seems to be quite different from that of lithium di-n-butyl-9-BBN[5a]. As shown in entries 7 and 8, BER reagent shows a good selectivity between cyclohexanone and 2-, or 4-heptanone but a poor selectivity between 2-, and 4-heptanone[6], whereas lithium n-butyl-9-BBN was reported to show no selectivity between cyclohexanone and 2-heptanone (100:78) but a good selectivity (91:9) between 2-, and 4-heptanone.

Besides these chemoselectivity to the carbonyl compounds, BER has significant advantages over other hydride systems. Thus simple separation of BER reagent by filtration or decantation gives the alcoholic solution of products essentially free from boron moiety[8] and BER reagent can be used repeatedly, since the used reagent can be regenerated to its initial activity by treating simply with $NaBH_4$ solution.

A general procedure for preparation of reagent is as follows. 20 g (50 meq) of wet chloride-form resin (BIO-RAD, AG 1-X8, 200-400 mesh, anion exchange resin) was slurry-packed with water into a 100 ml fritted glass funnel, mounted on a filtering flask. Then 400 ml of aquous $NaBH_4$ solution (0.25 M) was slowly passed through the resin over a period of 30 minutes. The resulting resin was washed thoroughly with distilled water until free of excess $NaBH_4$. The borohydride form anion exchange resin was then dried in vacuo at 65°C for 5 hours. The dried resin was analyzed for borohydride content by hydrogen evolution on acidification with 0.8 N HCl and the average capacity of BER was found to be 3.35 meq of BH_4^- per gram. The dried resin was stored under nitrogen at room temperature. The hydride content was constant over 6 weeks.

The following competitive reduction between benzaldehyde and 2-heptanone is representative. Into an oven-dried 50 ml flask with a magnetic stirring bar, was introduced 0.224 g (3.00 mmol of hydride) of BER. And then 2 mmol each of benzaldehyde, 2-heptanone and 1-heptanol (as an internal standard) in 8 ml ethanol was added with stirring at 25°C. After 5 hours, stirring was stopped and 1 µl aliquot of the ethanol solution was withdrawn and directly analyzed by GLPC without futher work up procedure[8]. The analysis showed that benzaldehyde was completely reduced with only a trace amount of 2-heptanol.

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6. Under the same experimental conditions in entry 7, the competitive reduction between 2-, and 4-heptanone showed the selectivity of 42.5:13.8
7. 12 ft X 0.125 inch column packed with 10 % Carbowax 20M deposit on chromosorb W, 80/100 mesh and 6 ft X 0.125 inch column packed with 10 % OV 101 deposit on chromosorb W, 80/100 mesh were used for separation of reaction mixture.
8. After the reduction with BER reagent, the ethanol solution of the products are reported to be free from borohydride moiety (ref. 2b). We have also confirmed this by determining the borate content both in solution and in matrix by colorimetry using carminic acid: W. C. Smith, Jr., A. J. Goudie, and J. N. Sivertson, Anal. Chem., 27, 295 (1955).

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