Novel Functional Group Selectivity in Reductions with Lithium Borohydride in Mixed Solvents Containing Methanol

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Primary amides were reduced selectively in the presence of carboxylic acid salts or secondary aliphatic amides by lithium borohydride in diglyme–methanol, and esters and epoxides were selectively reduced rapidly by $LiBH_4$ in the presence of nitro, chloro, or amide groups in ether containing a small amount of methanol.

Functional group selective reduction is an important synthetic method,[1] and we were surprised that, to the best of our knowledge, the selective reduction of primary amides in the presence of carboxylic acid salts has not been reported. Though it has been considered that diborane performs this reduction formally,[2] it has recently been shown that diborane does reduce acid salts.[3]

During our continuing study of the stereoselectivity[4] and reactivity[5] of sodium borohydride, we have found that lithium borohydride in diglyme–methanol mixtures performed the selective reduction of primary amides in the presence of acid salts. When an equimolar mixture of benzamide and sodium benzoate in diglyme was reduced by $LiBH_4$ with the slow addition of methanol, benzamide was reduced selectively to afford benzylamine (92%), and sodium benzoate was recovered as the corresponding benzoic acid (77%) after acidic treatment. This method thus provides a new route for the selective reduction of primary amides in the presence of carboxylic acids. Moreover, under similar conditions, primary amides were reduced more rapidly than secondary amides. Thus benzamide was reduced to benzylamine (86%) selectively in the presence of *N*-methylbenzamide which was recovered (80%). The results are summarized in Table 1.

$$A + B \rightarrow B + C + D \qquad (1)$$

It was also found that $LiBH_4$ in refluxing ether containing a small amount of MeOH reduced esters and epoxides rapidly and selectively in the presence of nitro, chloro, or amide groups (Table 2). Though $LiBH_4$ has greater selectivity than lithium aluminium hydride, it reduces esters relatively slowly.[6]

Table 1. Chemoselective reduction of primary amides (A) in the presence of acid salts or secondary amides (B) by $LiBH_4$–MeOH–diglyme[a] [reaction (1)].

	Reactants		Products (% yield)[b]				
Entry	A	B	C		D		% Recovery[c] of B
1	$PhCONH_2$	$PhCONHMe$	$PhCH_2NH_2$	(86)	$PhCH_2NHMe$	(14)	80
2	$PhCONH_2$	$Me[CH_2]_6CONHMe$	$PhCH_2NH_2$	(83)	$Me[CH_2]_7NHMe$	(22)	60
3	$PhCONH_2$	$PhCO_2Na$	$PhCH_2NH_2$	(92)	$PhCH_2OH$	(5)	77[d]
4	$Me[CH_2]_6CONH_2$	$PhCO_2Na$	$Me[CH_2]_7NH_2$	(90)	$PhCH_2OH$	(38)	60[d]

[a] 1 mmol of A and B, 3 mmol of $LiBH_4$, 4 ml of diglyme, 0.45 ml of MeOH, slow addition, at reflux. [b] Determined by gas chromatography. [c] Isolated. [d] Isolated as the corresponding acid.

Table 2. Rapid selective reduction of esters and an epoxide in the presence of nitro, chloro, and amide groups by $LiBH_4$ in refluxing ether containing MeOH.

Substrate(s)	Time /h	Product(s)	% Yield[d]
p-$O_2NC_6H_4CO_2Et$[a]	0.5	p-$O_2NC_6H_4CH_2OH$	90
p-$ClC_6H_4CO_2Et$[a]	0.5	p-$ClC_6H_4CH_2OH$	91
$PhCO_2Et$[b]	2.5	$PhCH_2OH$	100[e]
$PhCONH_2$[b]		$PhCONH_2$	89[f]
$\mathrm{Ph\overline{CH.CH_2.O}}$[b]	1.5	[c]	95
$PhCONH_2$[b]		$PhCONH_2$	99[f]

[a] Substrate : $LiBH_4$: MeOH, 1 : 1.5 : 1.5. [b] Substrate : $PhCONH_2$: $LiBH_4$: MeOH, 1 : 1 : 3 : 3. [c] Mixture of 1- and 2-phenylethanol. [d] Isolated. [e] Determined by gas chromatography. [f] Recovery.

Catalysts such as 9-methoxy-9-borabicyclo[3.3.1]nonane[6] or high-temperature conditions (*ca.* 100 °C)[7] are normally required for the practical reduction. The present procedure provides a mild and facile selective reduction of esters and epoxides.

Received, 28th March 1983; Com. 405

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