

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

Kenso Soai,* Atsuhiko Ookawa, and Hiroshi Hayashi

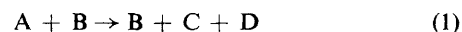
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162, Japan

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 stereoselectivity⁴ and reactivity⁵ 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.



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)].

Entry	Reactants		Products (% yield) ^b				% Recovery ^c of B
	A	B	C		D		
1	PhCONH_2	PhCONHMe	PhCH_2NH_2	(86)	PhCH_2NHMe	(14)	80
2	PhCONH_2	$\text{Me}[\text{CH}_2]_6\text{CONHMe}$	PhCH_2NH_2	(83)	$\text{Me}[\text{CH}_2]_7\text{NHMe}$	(22)	60
3	PhCONH_2	PhCO_2Na	PhCH_2NH_2	(92)	PhCH_2OH	(5)	77 ^d
4	$\text{Me}[\text{CH}_2]_6\text{CONH}_2$	PhCO_2Na	$\text{Me}[\text{CH}_2]_7\text{NH}_2$	(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
$p\text{-O}_2\text{NC}_6\text{H}_4\text{CO}_2\text{Et}^{\text{a}}$	0.5	$p\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{OH}$	90
$p\text{-ClC}_6\text{H}_4\text{CO}_2\text{Et}^{\text{a}}$	0.5	$p\text{-ClC}_6\text{H}_4\text{CH}_2\text{OH}$	91
$\text{PhCO}_2\text{Et}^{\text{b}}$	2.5	PhCH_2OH	100 ^e
$\text{PhCONH}_2^{\text{b}}$		PhCONH_2	89 ^f
$\text{PhCH}_2\text{CH}_2\text{O}^{\text{b}}$	1.5	$\text{PhCH}_2\text{CH}_2\text{OH}$	95
$\text{PhCONH}_2^{\text{b}}$		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]nonane⁶ 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.

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