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A NOVEL PROCEDURE FOR THE REDUCTION OF EPOXIDES WITH SODIUM BOROHYDRIDE

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Abstract: Epoxides were reduced to alcohols in good to high yield with a reducing system of sodium borohydride-*t*-butyl alcohol-methanol. The system had an excellent functional group selectivity.

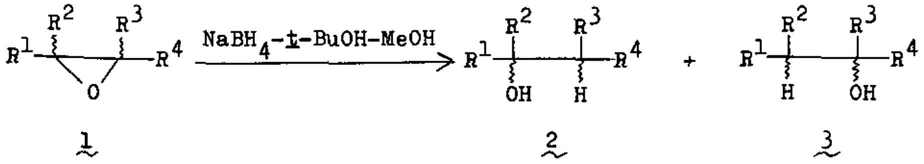
Increasing interest has been centered upon epoxides which serve as important intermediates of the syntheses of natural products.[1]

Among many types of the reactions of epoxides, reduction to alcohols by metal hydrides is one of the most fundamental reactions.[2] Several kinds of metal hydrides such as lithium aluminum hydride, diborane and aluminum hydride are usually used for this reaction.[3] However, because of a lack of a functional group selectivity of the most of these reducing agents, a selective reduction of epoxides can not be achieved in the presence of functional groups such as amide, carboxylic acid or nitrile. Though lithium borohydride($LiBH_4$) is known as a mild reducing agent of epoxides, its high cost and inflammable character prevent it from the common use.

We wish to report a novel procedure for the reduction of general epoxides with sodium borohydride($NaBH_4$).

It is generally accepted, however, that $NaBH_4$ reduces epoxides only very sluggishly. Exceptional epoxides which are reported to be reduced with $NaBH_4$ contain neighbouring functional groups which may, in some way, take part in the reductions.[4] To the best of our knowledge, no practical procedure has appeared of the reduction of general epoxides with $NaBH_4$.

We found that epoxides were reduced to alcohols in good to high yield by the



slow addition of methanol(MeOH) to the refluxing mixture of epoxide and $NaBH_4$ in t-butyl alcohol. Results are shown in Table 1. Either aliphatic, α-aryl-, mono- or di-substituted epoxides were opened reductively by this method. The more substituted alcohols were found to be formed predominantly.

A typical procedure(Entry 2) is as follows: to the refluxing mixture of $NaBH_4$(0.095g, 2.5 mmol) and 2-phenyloxirane(0.120g, 1.0 mmol) in t-BuOH(4.0 ml), MeOH(0.8 ml) was added over a period of 1 hr. After the reflux was continued for an additional 1 hr, water was added to quench the reaction. Most of the solvent was evaporated under reduced pressure at an ambient temperature, and the residue was extracted with ether. Ethereal extract was dried over anhydrous sodium sulfate. Ether was evaporated on a rotary evaporator and the residual oil was purified on silica gel TLC(methylene chloride-MeOH (10:1) as developing solvent). A mixture of 1- and 2-phenylethanol was obtained in 93% yield (0.114g).

The characteristic feature of the system of $NaBH_4$-t-BuOH-MeOH is a functional group selectivity, which was exemplified by the selective reduction of 2-phenyloxirane in the presence of functional groups such as amide, carboxylic acid, nitro or nitrile. As shown in Table 2, 2-phenyloxirane was reduced in good to high yields while other functional groups were recovered unchanged.

Table 1 Reduction of Epoxides(1) with $NaBH_4$-t-BuOH-MeOH a)

Entry	1				Yield (%)		
	R^1	R^2	R^3	R^4	2	3	
1	Ph	CH_3	H	H	73	0	b)
2	Ph	H	H	H	82	11	c)
3	H	$-(CH_2)_4-$		H	72		b)
4	$n-C_6H_{13}$	H	H	H	93	3	b)

a) Molar ratio of $NaBH_4$ to 1 were 2.5(Entry 2 and 4) or 5.0(Entry 1 and 3).
b) Yield determined by GC. c) Isolated as mixture of two alcohols.
Ratio determined by GC (88:12).

Table 2 Selective Reduction of 2-Phenyloxirane in the Presence of Various Functional Groups (**4**)

$$\underset{\left(\begin{array}{l}R^1=Ph\\ R^2=R^3=R^4=H\end{array}\right)}{\mathbf{1}} + \mathbf{4} \xrightarrow[\text{t-BuOH-MeOH}]{NaBH_4} \mathbf{2} + \mathbf{3} + \mathbf{4}$$

Entry a)	**4**	Yield(%) b) **2** + **3**	Ratio c) **2** : **3**	Recovery (%) **4**
1	$PhCONHCH_2CO_2H$	71	88 : 12	84 d)
2	$PhNO_2$	91	89 : 11	83 d)
3	PhCN	90	88 : 12	77 c)

a) Molar ratio **1** : **4** : $NaBH_4$ = 1 : 1 : 2.5~2.8

b) Isolated as mixture of **2** and **3**. c) Determined by GC. d) Isolated yield.

The exact mechanism of the present reaction is not yet obvious. We tentatively assume the actual reducing agent as one of or the aggregation of sodium mono-, di-, or tri-methoxyborohydrides(**5**) which are formed *in situ* from $NaBH_4$

$$NaBH_4 + nHOMe \longrightarrow \underset{\mathbf{5}}{NaBH_{4-n}(OMe)_n} + nH_2 \qquad (n=1,\ 2,\ 3)$$

and MeOH with the evolution of hydrogen.[5] It is known that $NaBH_4$ reacts rapidly with MeOH to form sodium tetramethoxyborate[$NaB(OMe)_4$] which doesn't have reducing power any more.[3] However, good to high yield of the products of the reduction may be explained by the relatively high content of **5** at least during the former half of the slow addition of MeOH.

As described above, the system of $NaBH_4$-*t*-BuOH-MeOH is mild and of practical utility in the reduction of general epoxides.

We are now investigating the scope and mechanism of this practical procedure.

References and Note

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