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Selective reductive cleavage of 2,3-epoxybromides by the $InCl_3$–$NaBH_4$ reagent system

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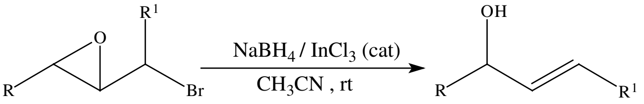
Abstract—A combination of sodium borohydride and a catalytic amount of indium(III) chloride in acetonitrile reduces 2,3-epoxybromides to the corresponding allylic alcohols in good yields involving reduction of the bromo moiety followed by selective C–O bond cleavage through a radical process. Several aromatic, cyclic and open-chain bromoepoxides successfully participated in this reaction.

The radical cleavage of epoxyhalides is very interesting from a mechanistic as well as a synthetic viewpoint. In principle, both carbon–carbon and carbon–oxygen bond cleavage is possible and with most reagents both type of cleavages occurred with C–O bond cleavage predominating. A variety of radical reducing agents such as tributyltin hydride,[1a,b] triphenyltin hydride,[1c] samarium diiodide,[1d,e] zinc–copper couple under sonication[1f,g] have been used although tributyltin hydride is the most common. However, because of the toxicity of tributyltin compounds and tedious purification to remove residual tin compounds, an alternative radical agent avoiding these drawbacks is required. Recently, chloro indium hydride (Cl_2InH), formed in situ from the combination of indium(III) chloride and sodium borohydride, has been found to show great promise as a practical and better alternative to tributyltin hydride in the dehalogenation of alkyl halides[2a] and other radical cyclizations.[2b] As part of our continued interest in indium-mediated reductions,[3] we have recently reported several selective reductions of important functionalities using the $InCl_3$–$NaBH_4$ reagent system[4] and here we disclose the selective reductive cleavage of a C–O bond in 2,3-epoxybromides using this reducing agent (Scheme 1).



Scheme 1.

The experimental procedure[5] is very simple. The epoxybromide was stirred with a solution of sodium borohydride and a catalytic amount of indium(III) chloride in anhydrous acetonitrile for the necessary period of time required to complete the reaction. Usual work up with ether followed by purification by column chromatography provided the pure product.

A variety of epoxybromides including aromatic, cyclic and open-chain systems underwent reductive cleavage of the carbon–oxygen bonds to give the corresponding allylic alcohols by this procedure. The results are summarized in Table 1. No C–C bond cleavage was observed in any of the substrates tested. The terminal monosubstituted epoxides (entries 13 and 14) produced the primary alcohols whereas the internal disubstituted epoxides provided secondary alcohols (entries 1–12). However, cleavage of trisubstituted epoxybromides was problematic as the reaction did not proceed further after reduction of the bromo functionality and thus no tertiary alcohol was obtained. An iodo epoxide (entry 2) also participated in this reaction. However, this reagent system failed to initiate the process when bromides or iodides were replaced by xanthates. When the product is not a terminal olefin, the (*E*)-isomer is formed (entry 4).

The reactions are, in general very clean, reasonably fast and high yielding. As the starting bromo epoxides were

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Keywords: Indium(III) chloride; Sodium borohydride; 2,3-Epoxybromide; Allylic alcohol; Reduction.

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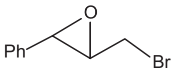
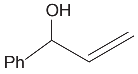
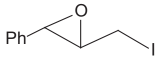
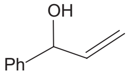
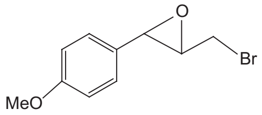
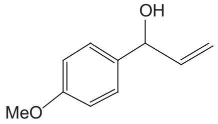
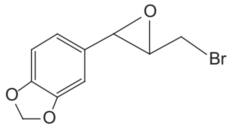
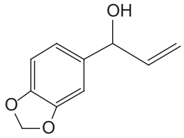
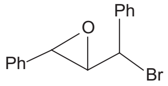
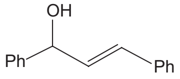
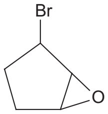
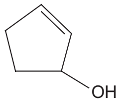
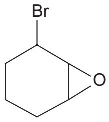
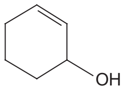
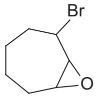
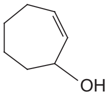
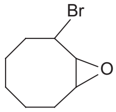
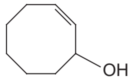
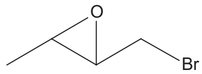
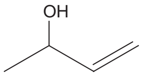
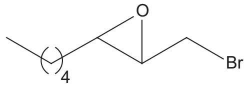
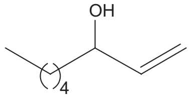
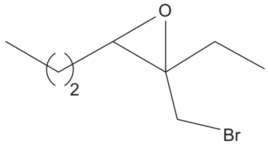
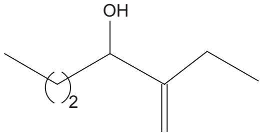
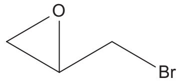
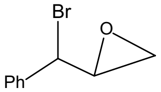
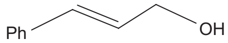
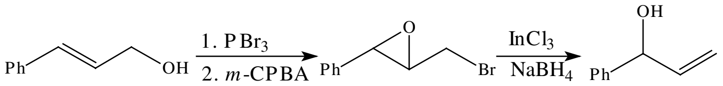
Table 1. Reductive cleavage of 2,3-epoxybromides by $InCl_3/NaBH_4$

Entry	Substrate	Product	Time (h)	Yield (%)[a]	Ref.
1			6.0	82	1e
2			6.2	80	1e
3			6.1	80	
4			6.5	75	6
5[b]			7.3	62	7
6[b]			6.5	77	8
7[b]			6.0	83	9
8[b]			7.0	78	10
9[b]			7.5	77	11
10			6.5	81	9
11			7.0	77	9
12[b]			6.5	85	12
13			7.0	70	9
14			10	50	9

[a] Yields refer to those of pure isolated products characterized by spectroscopic data (IR, ^1H and ^{13}C NMR).

[b] The epoxide used was a mixture of diastereomers.



Scheme 2.

prepared from allylic alcohols, this method provides an efficient procedure for the formal 1,3-transposition of the hydroxyl group (Scheme 2).

For comparison, when 3-phenyl-2,3-epoxybromide (entry 1) was treated with lithium aluminium hydride in ether 3-phenyl-2-propanol was obtained via reduction of the bromo as well as the epoxide moiety by hydride ion. On the other hand, sodium borohydride in acetonitrile (or methanol) without indium(III) chloride failed to cause any reaction. Thus, a combination of sodium borohydride and indium(III) chloride is essential for this reductive cleavage. Presumably, the indium hydride ($HInCl_2$) generated by transmetalation between $InCl_3$ and $NaBH_4$ acts as a radical reducing agent[2] and initiates the radical process by reduction of the C–Br bond followed by subsequent opening of the epoxy ring though selective C–O bond cleavage. The mechanism for formation of allylic alcohols by radical reaction of epoxides is well documented in the literature.[1d]

In conclusion, the indium(III) chloride–sodium borohydride reagent system provides a unique and simple method for selective reductive cleavage of the carbon–oxygen bond in 2,3-epoxyhalides via a radical pathways to produce allylic alcohols in good yields. This transformation is not possible using conventional nucleophilic hydride reducing agents. Certainly, this demonstrates the potential of indium hydride as a radical reducing agent and has great promise for further useful applications.

Acknowledgements

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5. *General experimental procedure-represented by the reductive cleavage of 3-p-methoxyphenyl-2,3-epoxybromide (entry 3).* A solution of indium(III) chloride (45mg, 0.2mmol, 20mol%) and sodium borohydride (78mg, 2mmol) in dry acetonitrile (3mL) was stirred at −10°C under nitrogen for 30min. To this was added 3-*p*-methoxyphenyl-2,3-epoxybromide (243mg, 1mmol) in acetonitrile (2mL) at that temperature. The reaction mixture was then allowed to attain room temperature and stirring was continued until completion of reaction (TLC). The mixture was then quenched with a few drops of water and extracted with diethyl ether (3 × 10mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent left the crude product, which was purified by column chromatography over silica gel (hexane–ether 4:1) to provide pure 1-*p*-methoxyphenyl-prop-2-ene-1-ol as a pale yellow liquid (132mg, 80%); IR (neat) 3365, 1641, 1580, 1245$\,cm^{-1}$; ^1H NMR (300MHz, $CDCl_3$): δ 3.76 (s, 3H), 5.07–5.33 (m, 3H), 5.90–6.08 (m, 1H), 6.88 (d, $J = 12.1$ Hz, 2H), 7.31 (d, $J = 12.1$ Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$): δ 55.5, 75.0, 114.0 (2C), 114.7, 127.9 (2C), 135.4, 140.0, 159.0. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.36. Found: C, 73.27; H, 7.31. This procedure was followed for the reductive cleavages of all the substrates listed in Table 1. All products were characterized by their IR, ^1H NMR and ^{13}C NMR spectroscopic data and were easily identified by comparison with those values reported (see references in Table 1).
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