Regio- and Stereo-selective Reductive Cleavage of Epoxides with Zinc Borohydride Supported on Silica Gel

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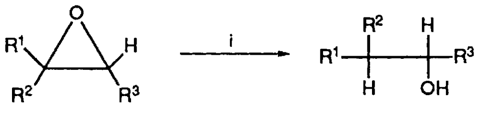
Reductive cleavage of unsymmetrical alkyl-substituted epoxides to less substituted alcohols has been achieved in a simple procedure using zinc borohydride supported on silica gel.

The reductive cleavage of epoxides to alcohols is one of the most useful reactions in organic synthesis.[1] In principle, an unsymmetrical alkyl-substituted epoxide can produce the more substituted carbinol or the less substituted alcohol depending on the cleavage of the C–O bond to the less substituted carbon atom or the more substituted one. Thus, realisation of methods for the regioselective ring opening of epoxides is of great importance. In general, more substituted alcohols are easily obtained by reduction of epoxides with nucleophilic hydride transferring reagents, whereas access to less substituted alcohols by reverse opening is not so simple.[2] Electrophilic hydride reagents have been used for this purpose, but mixtures of alcohols usually result.[2,3] Satisfactory results have been achieved only with a limited number of



R^1 = alkyl or aryl; R^2, R^3 = H or alkyl

Scheme 1. *Reagents and conditions*: i, $Zn(BH_4)_2/SiO_2$, THF, 24 h, room temp.

reagents, particularly, sodium cyanoborohydride together with boron trifluoride etherate[3h] and potassium triphenyl borohydride.[3i] But, high toxicity and the cost of these reagents often restrict their uses. In this communication, we describe a simple methodology for the reductive cleavage of unsymmetrical epoxides to the less substituted alcohols using zinc borohydride supported on silica gel (Scheme 1).

In a typical procedure, the epoxide (1 mmol) was stirred with zinc borohydride supported on silica gel† in dry THF (10 ml) at room temperature for 24 h. The reaction mixture was then decomposed with careful dropwise addition of water, and filtered. The filtrate was extracted with ether and the extract was evaporated to leave the pure product.

As shown in Table 1, the epoxides underwent cleavage of the C–O bond to the more substituted carbon atom to give the less substituted alcohols in excellent yields. Reduction of nonene-1-oxide with this reagent is completely regioselective giving nonan-1-ol exclusively (Table 1). Isolation of some of the more substituted alcohol from the cleavage of epichlorohydrin is not unexpected because of the influence of the adjacent chloromethyl group. Regioselectivity in the cleavage of aryl-substituted epoxides is also excellent. Cleavage of cyclic epoxides occurred in a stereoselective manner producing *Z*-alcohols predominantly or exclusively. Conversion of *E*-stilbene oxide to 1,2-diphenyl ethanol implies that this supported reagent is mild and does not induce any rearrangement as observed with sodium cyanoborohydride and boron trifluoride etherate.[3h]

When this cleavage reaction was carried out with zinc borohydride in THF, it was found to be very sluggish and the epoxide remained almost unaffected; although after a prolonged period, a mixture of products resulted. In earlier observations two other groups[5] also reported the inertness of epoxides towards zinc borohydride in ether during reduction of α,β-epoxy ketones to α,β-epoxy alcohols. For comparison, when an α,β-epoxy ketone was treated with silica gel supported zinc borohydride under these conditions, the corresponding 1,2-diol was obtained with the reduction of both ketone and epoxide moiety.‡ Presumably, silica gel in the supported reagent activates the epoxide towards nucleophilic attack by the hydride at the site best able to accommodate a carbonium ion. Nevertheless, this clearly demonstrates the usefulness and advantages of a supported reagent.[6]

The major advantages of this methodology are the availability of this reagent and much improved regioselectivity in the reductive cleavage of epoxides compared with other existing reagents. Moreover, with the combination of excellent methods[7] available for the synthesis of optically active epoxides, the present method can provide an easy access to optically active alcohols.

Table 1. Reductive cleavage of epoxides with $Zn(BH_4)_2/SiO_2$.

Epoxide	Product[a]	Yield (%)[b]
Nonene-1-oxide	$C_7H_{15}CH_2CH_2OH$	88
Epichlorohydrin	$ClCH_2CH_2CH_2OH$ (70%) + $ClCH_2CH(OH)CH_3$ (30%)	85
Styrene oxide	$PhCH_2CH_2OH$ + Ph $CH(OH)CH_3$ (trace, <5%)	90
α-Methyl styrene oxide	$PhCH(Me)CH_2OH$	91
trans-Stilbene oxide	$PhCH(OH)CH_2Ph$	88
1-Methylcyclohexene oxide	*cis*-2-Methylcyclohexanol + *trans*-2-Methylcyclohexanol (10%)	85
1-Methylcycloheptene oxide	*cis*-2-Methylcycloheptanol	84
Indene oxide	Indan-2-ol	90

[a] Products were characterized by comparison with authentic samples (m.p., MMP, IR, and NMR). [b] All yields refer to isolated products.

In conclusion, zinc borohydride supported on silica gel provides an inexpensive and efficient methodology for the regio- and stereo-selective cleavage of epoxides to the less substituted alcohols resulting from *anti* ring opening. Moreover, the mildness, convenience and high yield will make this simple reagent more useful and attractive in the field of organic synthesis. Further utilisation of this reagent for selective transformation is in progress and will be reported in due course.

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† Silica gel supported zinc borohydride was prepared as follows: A solution of zinc borohydride (3 mmol) in 1,2-dimethoxyethane[4] was added to silica gel HF254 (1 g) and stirred at room temperature for ½ h. Solvent was then evaporated off under vacuum to give the supported reagent which was used for reduction of epoxide (1 mmol) on the same day.

‡ Isophorone oxide was treated with zinc borohydride supported on silica gel in THF to give 3,5,5-trimethylcyclohexane-1,2-diol as a mixture of stereoisomers. A systematic and comprehensive study for the reduction of α,β-epoxy ketone and α,β-epoxy ester with this supported reagent is being carried out and will be reported presently in a full paper.