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Highly Regioselective Ring Opening of Oxiranes with Phenoxides in the Presence of β-Cyclodextrin in Water†

K. Surendra, N. Srilakshmi Krishnaveni, Y. V. D. Nageswar, and K. Rama Rao*

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad- 500 007, India

ramaraok@iict.res.in

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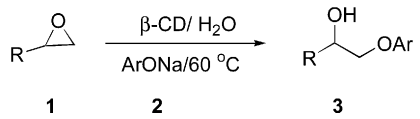
Abstract: Highly regioselective ring opening of oxiranes to β-hydroxy ethers with phenoxides has been achieved in impressive yields in the presence of β-cyclodextrin as catalyst and water as solvent.

There is continued interest in the regioselective ring opening of oxiranes to β-hydroxy ethers due to their significance as valuable synthetic intermediates in a variety of pharmaceuticals.[1] Oxiranes are well-known carbon electrophiles and their synthetic potential is enhanced by their ability to undergo regioselective ring-opening reactions[2] with various nucleophiles such as CN^-,[3] N_3^-,[4] NO_3^-,[5] halides,[6] amines,[7] thiols,[8] etc.

The most straightforward synthesis of β-hydroxy ethers consists of the ring opening of glycidol with phenols in the presence of tertiary amines or under alkaline conditions at 80−130 °C.[9] However, there is a recent report of the synthesis of a variety of hydroxy ethers with phenoxide anions in micellar media with use of $Ce(OTf)_4$.[10] Even in this methodology, regioisomers were obtained and the yields reported were particularly lower when the reaction was carried out in aqueous medium. Thus, there is a need for a widely applicable approach preferably with water as a solvent, which is gaining increasing importance in present day organic synthesis.

SCHEME 1



R = aryloxy, aryl, hexyl
Ar = C_6H_5, 4Cl-C_6H_4, 4CH_3O-C_6H_4.

The best choice appeared to be through supramolecular catalysis involving cyclodextrins with water as solvent since such reactions do not generate any toxic waste products (Scheme 1).

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. They catalyze reactions by supramolecular catalysis involving reversible formation of host−guest complexes by noncovalent bonding as seen in enzymes. Complexation depends on the size, shape, and hydrophobicity of the guest molecule. Thus mimicking of biochemical selectivity, which is due to orientation of the substrate by complex formation positioning only certain region for favorable attack, will be superior to chemical selectivity, which involves random attack due to intrinsic reactivity of the substrate at different regions. Our earlier expertise in the field of biomimetic modeling of organic chemical reactions involving cyclodextrins[11] prompted us to attempt the regioselective ring opening of oxiranes with phenoxides in the presence of β-cyclodextrin (β-CD) as this is one of the most useful synthetic transformations with a variety of applications.

The reaction was carried out by the in situ formation of the β-CD complex of the epoxide (**1**) in water followed by the addition of phenoxide (**2**) and stirring for 8 h at 60 °C to give the corresponding β-hydroxy ethers (**3**) in impressive yields. Several examples illustrating this simple and practical methodology are summarized in Table 1. The reaction goes smoothly at 60 °C without the formation of any side products or rearrangements. These reactions also take place at room temperature to give the corresponding β-hydroxy ethers but the reaction times were longer (18−24 h). The catalyst β-cyclodextrin can be easily recovered and reused. These reactions do not proceed in the absence of cyclodextrin. The compounds were characterized by ^1H NMR, mass, IR, and elemental analysis or otherwise compared with the known compounds.[10] The stereochemistry of the ring-opened products (**19**−**21**) has been assigned trans configuration by comparison with the known compounds.[12]

These reactions do take place with α-CD as well with the same regioselectivity and sterochemistry; however, β-CD was chosen as the catalyst since it is inexpensive

† IICT communication no. 030410.

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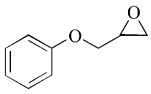
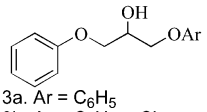
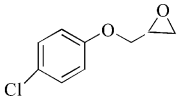
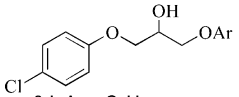
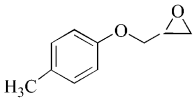
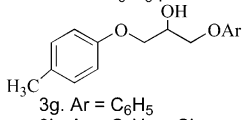
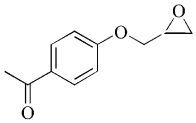
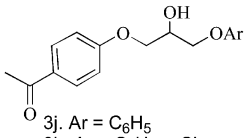
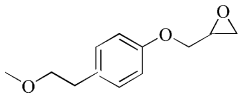
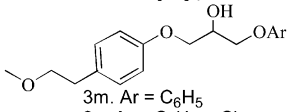
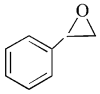
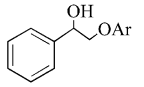
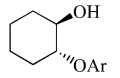
TABLE 1. Ring Opening of Oxiranes with Phenoxide in Presence of β-CD in Water

Entry	Epoxide (1)	Reagent (2)	Product[a] (3)	Yield[b](%)
1		C_6H_5ONa p-ClC_6H_4ONa p-$OMeC_6H_4ONa$	 3a. Ar = C_6H_5	94
2			3b. Ar = C_6H_5-p-Cl	90
3			3c. Ar = C_6H_5-p-OMe	88
4		C_6H_5ONa p-ClC_6H_4ONa p-$OMeC_6H_4ONa$	 3d. Ar = C_6H_5	96
5			3e. Ar = C_6H_5-p-Cl	92
6			3f. Ar = C_6H_5-p-OMe	90
7		C_6H_5ONa p-ClC_6H_4ONa p-$OMeC_6H_4ONa$	 3g. Ar = C_6H_5	92
8			3h. Ar = C_6H_5-p-Cl	90
9			3i. Ar = C_6H_5-p-OMe	88
10		C_6H_5ONa p-ClC_6H_4ONa p-$OMeC_6H_4ONa$	 3j. Ar = C_6H_5	90
11			3k. Ar = C_6H_5-p-Cl	89
12			3l. Ar = C_6H_5-p-OMe	84
13		C_6H_5ONa p-ClC_6H_4ONa p-$OMeC_6H_4ONa$	 3m. Ar = C_6H_5	92
14			3n. Ar = C_6H_5-p-Cl	90
15			3o. Ar = C_6H_5-p-OMe	88
16		C_6H_5ONa p-ClC_6H_4ONa p-$OMeC_6H_4ONa$	 3p. Ar = C_6H_5	89
17			3q. Ar = C_6H_5-p-Cl	84
18			3r. Ar = C_6H_5-p-OMe	80
19		C_6H_5ONa p-ClC_6H_4ONa p-$OMeC_6H_4ONa$	 3s. Ar = C_6H_5	84
20			3t. Ar = C_6H_5-p-Cl	80
21			3u. Ar = C_6H_5-p-OMe	77

[a] All the products were characterized by ^{1}H NMR, IR, and mass spectroscopy. [b] Isolated yields after purification.

and easily accessible. Though inclusion complexation takes place in situ during the reaction, the complexes have been isolated and characterized by powder X-ray[13] and ^{1}H NMR studies.[14] Here, the role of CD appears to be not only to activate the oxiranes but also to promote highly regioselective ring opening due to inclusion complex formation with cyclodextrin in this new biomimetic methodology.

Thus, it has been shown for the first time that β-hydroxy ethers with high synthetic potential can be made in a biomimetic fashion with high regioselectivity from the easily accessible oxiranes and inexpensive phenoxides in the presence of β-cyclodextrin in water. Further potential applications of this reaction are under study.

Experimental Section

Materials. Oxiranes were either purchased commercially or synthesized[15a] and phenoxides were synthesized as reported in the literature.[15b]

General Procedure. β-Cyclodextrin (1 mmol) was dissolved in water (25 mL) at 60 °C, and epoxide (1 mmol) dissolved in acetone (2 mL) was added slowly with stirring. After 15 min at that temperature, sodium phenoxide(1 mmol) was added and stirred for 8 h at 60 °C. The organic material was extracted with ethyl acetate. The organic phase was separated, filtered, and washed with brine. The organic phase was then dried (Na_2SO_4) and filtered and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography with ethyl acetate:hexane (2:8) as eluent.

Supporting Information Available: Experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

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