Highly Regioselective C(3) Opening of an Aromatic 2,3-Epoxy Alcohol with Sodium Phenoxides or Thiophenoxides (= Benzenethiolates) Supported by β-Cyclodextrin in Water

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A simple and mild procedure was developed for the first time for the C(3)-selective ring opening of an aromatic 2,3-epoxy alcohol, *i.e.*, of *trans*-3-phenyloxirane-2-methanol (**1**), with sodium phenoxides or thiophenoxides (= benzenethiolates) **2** supported by β-cyclodextrin in H_2O at 50° to afford the corresponding 3-(aryloxy)- or 3-(arylthio)propane1,2-diols **3** in excellent yields (*Scheme*, *Table*).

Introduction. – Epoxides (= oxiranes) in general, due to their ease of formation and ready reactivity toward nucleophiles, are important starting materials and intermediates in organic synthesis [1]. Because there are two competing sites of reactivity in every epoxide, much work has gone into understanding the factors influencing the regioselectivity of epoxide opening [2] with various nucleophiles [3]. The utility of these reactions is dependent on the regioselectivity at C(2) and C(3) of the oxirane moiety [4][5]. Ring opening of 2,3-epoxyalkyl alcohols with a wide variety of nucleophiles show different ratios of C(2) and C(3) isomers [6]. There is continued interest in the regioselective ring opening of oxiranes to alkyloxy (or aryloxy)- and alkylthio (or arylthio)-substituted alcohols due to their significance as valuable synthetic intermediates in a variety of pharmaceuticals [7]. The most straightforward synthesis of such alcohols consists of the ring opening of 2,3-epoxyalkyl alcohols (= oxirane-2-methanols) with sodium phenoxides or thiophenoxides (= benzenethiolates) [8]. However, these reactions are generally carried out under hazardous solvent conditions by using *Lewis* acid catalysts [9], such as $Ti(O^iPr)_4$, with lower yields [10], or under dry reaction conditions and formation of regioisomer mixtures [6]. In view of these limitations, there is still a need for a widely applicable approach for the C(3) selective ring opening of 2,3-epoxyalkylalcohols with various substituted sodium phenoxides or thiophenoxides preferably using H_2O as a solvent with a recyclable catalyst, thus minimizing the use of harmful organic solvents as green chemistry is becoming a central issue in both academic and industrial research in the 21st century [11].

In our efforts to develop biomimetic modeling of organic chemical reactions involving cyclodextrins in aqueous medium [12], we describe, herein, the first C(3)-selective ring opening of an oxirane methanol with phenoxides and thiophenoxides to (aryloxy)- or (arylthio)-substituted diols in the presence of β-cyclodextrin in H_2O at 50° (*Scheme*).

Cyclodextrins, which are cyclic oligosaccharides, with their hydrophobic cavities have excited much interest as enzyme models due to their ability to bind substrates selectively, and catalyze chemical reactions with high regioselectivity [13]. Cyclodextrins catalyze chemical reactions by supramolecular catalysis involving reversible formation of host–guest complexes by noncovalent bonding as seen in enzyme complexation processes [14]. The complexation depends on the size, shape, and hydrophobicity of the guest molecule. Thus, mimicking of biochemical selectivity, which is due to the orientation of the substrate by complex formation exposing only certain regions for a favorable attack, will be superior to chemical selectivity, which involves random attack due to the intrinsic reactivity of different regions of the substrate. These attractive features of cyclodextrins prompted us to investigate the regioselective ring opening of an aromatic 2,3-epoxy alkyl alcohol with phenoxides and thiophenoxides, as this is one of the most useful synthetic transformations with a variety of applications.

Results and Discussion. – In general, the reactions were carried out by the *in situ* formation of a β-cyclodextrin complex of the aromatic 2,3-epoxy alcohol, *i.e.*, of *trans*-3-phenyloxirane-2-methanol (**1**), in H_2O at 50°, followed by the addition of a sodium phenoxide **2** and stirring to give the corresponding (aryloxy)diols **3** in impressive yields (82–92%) (*Scheme*). In the case of sodium thiophenoxides **2**, the reactions went to completion at room temperature. The reaction was proceeding smoothly without the formation of any by-products or rearrangements. In the presence of β-cyclodextrin, ring opening of the *trans*-2,3-epoxy alcohol with sodiumphenoxides or thiophenoxides (*Table*) yielded the C(3)-opened product as the only isomer as determined by ^{1}H-NMR analysis of the crude product. The regiospecificity was confirmed by comparison of the chemical shift and coupling constant of the benzylic proton with those reported by *Melloni et al.* [1]. The formation of a single isomer may be explained by invoking an S_N2 mechanism. Here, the role of β-cyclodextrin appears to be not only to activate the epoxide moiety but also to promote the highly regioselective ring opening due to inclusion-complex formation. These cyclodextrin-mediated reactions in H_2O proceeded under mild conditions without the need for organic solvents. The β-cyclodextrin could easily be recovered and reused. Longer reaction times (>24 h) were needed in the absence of β-CD, and the yields were also very low (20%) with the formation of product mixtures. The described reactions also took place with α-cyclodextrin (α-CD)

Scheme

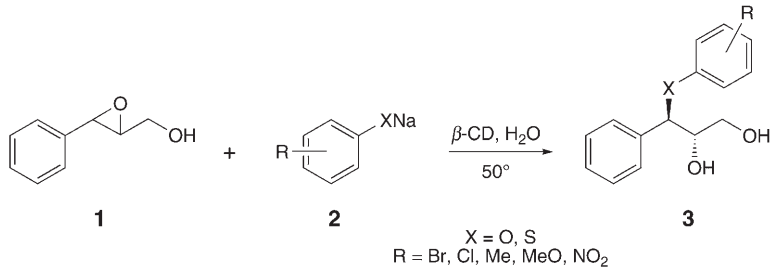

Table. *Regioselective Ring Opening of* trans-*3-Phenyloxirane-2-methanol* (**1**) *in the Presence of β-CD in Water. Conditions: β*-CD, 1 mmol; oxiranemethanol **1**, 1 mmol; sodium (thio)phenoxide **2**, 1.2 mmol, H_2O; 20 ml.

Entry	Sodium (thio)phenoxide	X	R	Product[a])	Time [h]	Yield [%][b])
1	**2a**	O	H	**3a**	7	90
2	**2b**	O	4-Br	**3b**	8	92
3	**2c**	O	4-Cl	**3c**	8	91
4	**2d**	O	2-Cl	**3d**	9	88
5	**2e**	O	4-Me	**3e**	7	90
6	**2f**	O	2-Me	**3f**	8	88
7	**2g**	O	4-MeO	**3g**	9	86
8	**2h**	O	4-NO_2	**3h**	12	88
9	**2i**	S	H	**3i**	6	84
10	**2j**	S	4-Br	**3j**	7	85
11	**2k**	S	4-Cl	**3k**	7	84
12	**2l**	S	4-MeO	**3l**	6	84
13	**2m**	S	4-NO_2	**3m**	9	82

[a]) All the products were characterized by ^{1}H-NMR and MS and compared with similar reported compounds [1][15]. [b]) Yield obtained after column chromatography.

with the same regioselectivity and stereochemistry; however, *β*-CD was chosen as the catalyst since it is inexpensive and easily accessible.

Conclusions. – For the first time, (aryloxy)- and (arylthio)-substituted diols were obtained with high regioselectivity from an easily accessible oxiranemethanol and inexpensive sodium phenoxides or thiophenoxides in the presence of *β*-cyclodextrin in H_2O. The described procedure is a simple, convenient, and highly efficient method for the synthesis of (aryloxy)- and (arylthio)diols. The notable features of this method are cleaner reaction profiles, high yields, and operational simplicity. Above all, these reactions are carried out in H_2O. This methodology will be a useful addition to the modern synthetic methodology in views of the ever-growing demand for eco-friendly chemical processes and the increasing interest in green chemistry.

We thank *CSIR*, New Delhi, India, for fellowships to *M. N.* and *M. S. R.*

Experimental Part

General. All reactions were carried out without any special precautions in an atmosphere of air. Chemicals were purchased from *Fluka* and *S. D. Fine Chemicals* and used for the synthesis of the aromatic 2,3-epoxy alcohol and sodium phenoxides and thiophenoxides. Reversed-phase HPLC: *C18* stationary phase; 40% MeCN/H_2O mobile phase, flow rate 0.5 ml/min; detection at 254 nm; t_R in min. ^{1}H-NMR Spectra: *Varian 200* or *Bruker 300* spectrometer; in $CDCl_3$; δ in ppm, J in Hz. Mass spectra: *VG Autospec*; in *m*/*z*.

(Aryloxy)diols and (Arylthio)diols from Oxiranemethanol **1**: *General Procedure*. *β*-Cyclodextrin (1135 mg, 1 mmol) was dissolved in H_2O (20 ml) by warming up to 50° until a clear soln. was formed. Then *trans*-3-phenyloxirane-2-methanol (**1**; 150 mg, 1 mmol) in acetone (1 ml) was added dropwise followed by sodium phenoxide (**2**; 139 mg, 1.2 mmol) and stirred at 50° until the reaction was complete (TLC monitoring; see the *Table*). The mixture was extracted with AcOEt (3 × 25 ml) and filtered. The

org. layer was dried (Na_2SO_4), the solvent evaporated, and the resulting product purified by column chromatography (silica gel (60–120 mesh), AcOEt/hexane 25:75). The aq. layer was cooled to 5° to recover β-CD by filtration.

3-Phenoxy-3-phenylpropane-1,2-diol (**3a**; *Table*, *Entry 1*). With sodium phenoxide (**2a**): 220 mg (90%) of **3a**. White solid. t_R 8.31 (98.72% of peak area). M.p. 106–108°. ^{1}H-NMR (200 MHz): 1.65–2.15 (br. *s*, 2 H); 3.65–4.0 (*m*, 3 H); 5.17 (*d*, *J* = 4.6, 1 H); 6.75–6.95 (*m*, 3 H); 7.1–7.5 (*m*, 7 H). EI-MS: 184, 155, 134, 120, 104, 94, 92, 77, 65, 51.

3-(4-Bromophenoxy)-3-phenylpropane-1,2-diol (**3b**; *Table*, *Entry 2*). With sodium 4-bromophenoxide (**2b**): 297 mg (92%) of **3b**. White solid. t_R 26.11 (96.63% of peak area). M.p. 109–110°. ^{1}H-NMR (200 MHz): 3.75–4.00 (*m*, 3 H); 5.13 (*d*, *J* = 4.5, 1 H); 6.70 (*d*, *J* = 6.4, 2 H); 7.25 (*d*, *J* = 6.4, 2 H); 7.30–7.40 (*m*, 5 H). EI-MS: 262, 173, 154, 134, 121, 92, 43.

3-(4-Chlorophenoxy)-3-phenylpropane-1,2-diol (**3c**; *Table*, *Entry 3*). With sodium 4-chlorophenoxide (**2c**): 253 mg (91%) of **3c**. White solid. t_R 19.01 (97.53% of peak area). M.p. 98–100°. ^{1}H-NMR (200 MHz): 3.72–4.00 (*m*, 3 H); 5.10 (*d*, *J* = 4.5, 1 H); 6.75 (*d*, *J* = 7.1, 2 H); 7.10 (*d*, *J* = 7.1, 2 H); 7.30–7.40 (*m*, 5 H). EI-MS: 218, 153, 129, 121, 92, 43.

3-(2-Chlorophenoxy)-3-phenylpropane-1,2-diol (**3d**; *Table*, *Entry 4*). With sodium 2-chlorophenoxide (**2d**): 245 mg (88%) of **3d**. White solid. t_R 19.49 (97.28% of peak area). M.p. 78–80°. ^{1}H-NMR (200 MHz): 2.90–3.60 (br. *s*, 2 H); 3.70–4.00 (*m*, 3 H); 5.75 (*d*, *J* = 4.5, 1 H); 6.65 (*d*, *J* = 7.2, 1 H); 6.80 (*t*, *J* = 7.2, 1 H); 6.96 (*t*, *J* = 7.2, 1 H), 7.20–7.40 (*m*, 6 H). EI-MS: 218, 153, 134, 128, 120, 104, 91, 77, 63.

3-(4-Methylphenoxy)-3-phenylpropane-1,2-diol (**3e**; *Table*, *Entry 5*). With sodium 4-methylphenoxide (**2e**): 232 mg (90%) of **3e**. Yellow oil. t_R 20.62 (95.24% of peak area). ^{1}H-NMR (200 MHz): 2.35(*s*, 3 H); 3.80–4.10 (*m*, 3 H); 5.30 (*d*, *J* = 4.8, 1 H); 6.60 (*d*, *J* = 9.2, 2 H); 6.83 (*d*, *J* = 9.2, 2 H); 7.30–7.55 (*m*, 5 H). EI-MS: 198, 167, 151, 107, 91, 77, 43.

3-(2-Methylphenoxy)-3-phenylpropane-1,2-diol (**3f**; *Table*, *Entry 6*). With sodium 2-methylphenoxide (**2f**): 227 mg (88%) of **3f**. Yellow oil. t_R 20.98 (96.45% of peak area). ^{1}H-NMR (200 MHz): 2.35(*s*, 3 H); 3.80–4.10 (*m*, 3 H); 5.30 (*d*, *J* = 4.8, 1 H); 6.62 (*d*, *J* = 9.1, 1 H); 6.83 (*t*, *J* = 9.1, 1 H); 6.97 (*t*, *J* = 9.1, 1 H); 7.16 (*d*, *J* = 9.1, 1 H); 7.30–7.55 (*m*, 5 H). EI-MS: 198, 151, 107, 91, 77, 43.

3-(4-Methoxyphenoxy)-3-phenylpropane-1,2-diol (**3g**; *Table*, *Entry 7*). With sodium 4-methoxyphenoxide (**2g**): 236 mg (86%) of **3g**. White solid. t_R 13.89 (95.61% of peak area). M.p. 104–106°. ^{1}H-NMR (200 MHz): 3.70 (*s*, 3 H); 3.75–3.95 (*m*, 3 H); 5.10 (*d*, *J* = 4.5, 1 H); 6.60–6.80 (*m*, 4 H); 7.20–7.40 (*m*, 5 H). EI-MS: 214, 151, 124, 110, 92, 78.

3-(4-Nitrophenoxy)-3-phenylpropane-1,2-diol (**3h**; *Table*, *Entry 8*). With sodium 4-nitrophenoxide (**2h**): 254 mg (88%) of **3h**. Yellow oil. t_R 29.22 (96.53% of peak area). ^{1}H-NMR (200 MHz): 3.30–3.80 (br. *s*, 2 H); 3.90–4.20 (*m*, 3 H); 4.70 (*d*, *J* = 4.6, 1 H); 6.93 (*d*, *J* = 7.3, 2 H); 7.15–7.50 (*m*, 5 H); 8.10 (*d*, *J* = 7.3, 2 H). EI-MS: 219, 166, 140, 123, 107, 79.

3-Phenyl-3-(phenylthio)propane-1,2-diol (**3i**; *Table*, *Entry 9*). With sodium benzenethiolate (**2i**): 218 mg (84%) of **3i**. White solid. t_R 20.90 (97.02% of peak area). M.p. 126–128°. ^{1}H-NMR (200 MHz): 1.90–2.40 (br. *s*, 2 H); 3.60–4.10 (*m*, 3 H); 4.25 (*d*, *J* = 4.5 Hz, 1 H); 7.12–7.40 (*m*, 10 H). EI-MS: 200, 165, 149, 141, 121, 91, 77, 65, 57, 43.

3-[(4-Bromophenyl)thio]-3-phenylpropane-1,2-diol (**3j**; *Table*, *Entry 10*). With sodium 4-bromobenzenethiolate (**2j**): 288 mg (85%) of **2j**. Yellow oil. t_R 35.19 (98.04% of peak area). ^{1}H-NMR (200 MHz): 2.40–2.80 (br. *s*, 2 H); 3.50–4.00 (*m*, 3 H); 4.25 (*d*, *J* = 5.0, 1 H); 7.05–7.50 (*m*, 9 H). EI-MS: 279, 188, 183, 156, 91, 77, 43.

3-[(4-Chlorophenyl)thio]-3-phenylpropane-1,2-diol (**3k**; *Table*, *Entry 11*). With sodium 4-chlorobenzenethiolate (**2k**): 247 mg (84%) of **3k**. White solid. t_R 30.59 (96.67% of peak area). M.p. 86–88°. ^{1}H-NMR (200 MHz): 2.40–2.80 (br. *s*, 2 H); 3.40–4.05 (*m*, 3 H); 4.25 (*d*, *J* = 4.7, 1 H); 7.05–7.40 (*m*, 9 H). EI-MS: 234, 217, 183, 151, 143, 91, 77, 43.

3-[(4-Methoxyphenyl)thio]-3-phenylpropane-1,2-diol (**3l**; *Table*, *Entry 12*). With sodium 4-methoxybenzenethiolate (**2l**): 244 mg (84%) of **3l**. White solid. t_R 11.34 min (97.43% of peak area). M.p. 110–112°. ^{1}H-NMR (300 MHz): 1.95–2.15 (br. *s*, 2 H); 3.75 (*s*, 3 H); 3.90–4.30 (*m*, 4 H); 6.73 (*d*, *J* = 8.0, 2 H); 7.15–7.50 (*m*, 7 H). EI-MS: 230, 169, 155, 141, 69, 57, 43.

3-[(4-Nitrophenyl)thio]-3-phenylpropane-1,2-diol (**3m**; *Table*, *Entry 13*). With sodium 4-nitrobenzenethiolate (**2m**): 250 mg (82%) of **3m**. Yellow oil. t_R 19.20 min (96.05% of peak area). ^{1}H-NMR

(200 MHz): 2.40–2.80 (br. *s*, 2 H); 3.60–4.10 (*m*, 3 H); 4.25 (*d*, *J* = 4.4, 1 H); 6.95 (*d*, *J* = 7.5, 2 H); 7.15–7.35 (*m*, 5 H); 7.75 (*d*, *J* = 7.5, 2 H). EI-MS: 245, 183, 151, 120, 91, 77.

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Received January 3, 2007