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Journal of Molecular Catalysis A: Chemical 255 (2006) 180–183
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Short communication

Highly regioselective thiolysis of oxiranes under supramolecular catalysis involving β-cyclodextrin in water

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Received 1 March 2006; received in revised form 24 March 2006; accepted 28 March 2006
Available online 12 May 2006

Abstract

In the presence of β-cyclodextrin in water, ring opening of epoxides with various thiophenols proceeds with high regioselectivity in good yields. β-Cyclodextrin can also be recovered and reused in various runs without affecting the efficiency of the process.

Keywords: Thiolysis; Oxiranes; Thiophenoxides; β-Cyclodextrin; Water

1. Introduction

The oxirane ring opening with thiols is of great significance in the field of natural products especially for the synthesis of leukotrienes such as LTC_4 and LTD_4 [1] and various pharmaceuticals [2]. Apart from this, the resulting β-hydroxy sulfides are also versatile synthetic intermediates for allylic alcohols [3], benzoxathiepines [4], benzodiazepines [5], α-thioketones [6], α-substituted α,β-unsaturated enones [7], and different natural products [8]. However, most of the methods reported consist of Lewis acid catalysts to perform these reactions under mild conditions, but these methods suffer with various disadvantages such as drastic reaction conditions, mixtures of regioisomers [9a–c], lower yields and undesirable side products by rearrangement of oxiranes and oxidation of thiols [9d,e]. Thus, there is need for a widely applicable synthetic approach utilizing water as a solvent, which is gaining increasing importance in the present day organic synthesis.

Here in we wish to report the best choice for carrying out the thiolysis of oxiranes appeared to be through supramolecular catalysis involving cyclodextrins with water as solvent. These reactions also do not generate any toxic waste products and the catalyst can also be recovered and reused (Scheme 1).

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities and mimic enzymes in their capability to bind substrates selectively and catalyze reactions by supramolecular catalysis involving reversible formation of host–guest complexes. Complexation processes in solution depend on the size, shape and hydrophobicity of the guest molecule. The main forces operating in the complexation process are van der waals hydrophobic interactions and hydrogen bonding between the guest and cyclodextrin. Thus, mimicking of biochemical selectivity which is due to orientation of the substrates by complex formation positioning only certain region for favourable attack will be superior to chemical selectivity. In our efforts to develop biomimetic approaches involving CDs in supramolecular catalysis [10], the ring opening of various oxiranes with thiophenols in water has been attempted through the formation of β-cyclodextrin–epoxide complexes.

2. Results and discussion

The reactions were carried out by the in situ formation of the β-cyclodextrin complex of the epoxide (**1**) in water followed by the addition of thiophenoxide (**2**) and stirred at room temperature to give the corresponding β-hydroxy sulfides (**3**) in impressive yields (Table 1). The reaction goes smoothly with thiophenoxides in a span of 15 min at room temperature without the formation of any side products or rearrangements. The compounds were characterized by ^{1}H NMR, mass, IR, elemental analysis or otherwise compared with the known compounds [11,12]. The stereochemistry of the ring-opened products (18–20) has been shown to be *trans* by comparison with the known compounds [12].

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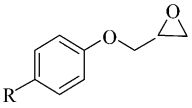
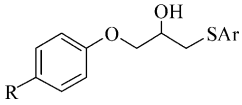
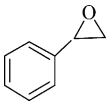
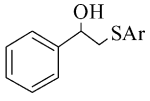
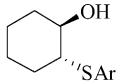
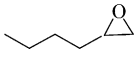
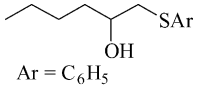
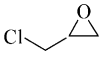
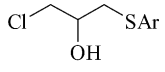
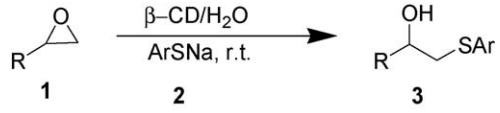
doi:10.1016/j.molcata.2006.03.063

Table 1
Ring opening of oxiranes with thiophenoxide in the presence of β-CD in water

Entry	Epoxide (**1**)	Reagent (**2**)	Product[a] (**3**)	Yield[b] (%)
				
1	R = H	C_6H_5SNa	Ar = C_6H_5	89
2		*p*-ClC_6H_4SNa	Ar = C_6H_4–p-Cl	90
3		*p*-$OMeC_6H_4SNa$	Ar = C_6H_4–*p*-OMe	92
4	R = Cl	C_6H_5SNa	Ar = C_6H_5	93
5		*p*-ClC_6H_4SNa	Ar = C_6H_4–*p*-Cl	92
6		*p*-$OMeC_6H_4SNa$	Ar = C_6H_4–*p*-OMe	89
7	R = Me	C_6H_5SNa	Ar = C_6H_5	90
8		*p*-ClC_6H_4SNa	Ar = C_6H_4–*p*-Cl	89
9		*p*-$OMeC_6H_4SNa$	Ar = C_6H_4–*p*-OMe	94
10	R = OMe	C_6H_5SNa	Ar = C_6H_5	88
11		*p*-ClC_6H_4SNa	Ar = C_6H_4–*p*-Cl	90
12		*p*-$OMeC_6H_4SNa$	Ar = C_6H_4–*p*-OMe	90
13	R = methoxy ethane	C_6H_5SNa	Ar = C_6H_5	92
14		*p*-ClC_6H_4SNa	Ar = C_6H4–*p*-Cl	89
15		*p*-$OMeC_6H_4SNa$	Ar = C_6H_4–*p*-OMe	91
16		C_6H_5SNa		88
17		*p*-ClC_6H_4SNa	Ar = C_6H_5 Ar = C_6H_4-*p*-Cl	84
18		C_6H_5SNa		80
19		*p*-ClC_6H_4SNa	Ar = C_6H_5	85
20		*p*-$OMeC_6H_4SNa$	Ar = C_6H_4-*p*-Cl Ar = C_6H_4-*p*-OMe	79
21		C_6H_5SNa		80
22		*p*-$OMeC_6H_4SNa$	Ar = C_6H_5 Ar = C_6H_4-*p*-OMe	85
23		*p*-$OMeC_6H_4SNa$		80
			Ar = C_6H_4-*p*-OMe	

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

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 [14a]. Here, the role of cyclodextrin 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.



R = Aryloxy, aryl, hexyl
Ar = C_6H_5, *p*-Cl-C_6H_4, *p*-MeO-C_6H_4

Scheme 1.

The product formation from the respective epoxides through supramolecular catalysis in these CD catalyzed reactions in water has been postulated and confirmed by spectroscopic evidence as follows: the fact that these reactions do not take place in the absence of cyclodextrins (even up to 24 h) shows the essential role of CD. Evidence to the mechanistic approach was deduced from ^{1}H NMR (200 MHz). These studies were undertaken with phenoxy epoxide as a representative example. A comparison of the ^{1}H NMR spectra (D_2O) of β-CD, β-CD–phenoxy epoxide complex and freeze-dried reaction mixtures of the CD complex with thiophenols at 4, 8 and 15 min was undertaken. It could be seen from Fig. 2 that there is a clear upfield shift of H_3 (0.021 ppm) and H_5 (0.051 ppm) protons of cyclodextrin in CD–phenoxy epoxide complex as compared to CD, indicating the formation of inclusion complex of epoxide with β-CD [14].

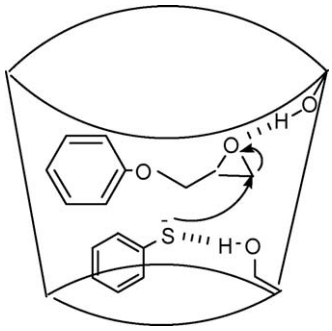


Fig. 1. β-CD catalysed thiolysis of oxiranes.

However, it is observed from the spectra of the reaction mixtures of β-CD–epoxide complex and thiophenols at 4, 8 and 15 min that these complexes apart from retaining the upfield character of H_3 and H_5 protons with subtle changes, there is also an upfield shift of H_6 proton, i.e., 0.055 ppm at 4 min, 0.078 ppm at 8 min and 0.104 ppm at 15 min reactions, indicating the complexation of thiophenol from the primary side of cyclodextrin. From these ^{1}H NMR studies it could be clearly seen that while the epoxide is still retained in the cavity, thiophenol complexes from the primary side (Fig. 1). Thus, it could be concluded from the spectral evidence of ^{1}H NMR that when the thiophenol was added to CD–epoxide complex, the epoxide while still being retained in the cavity, thiophenol complexes from the primary side (Fig. 2) for the reaction to proceed further.

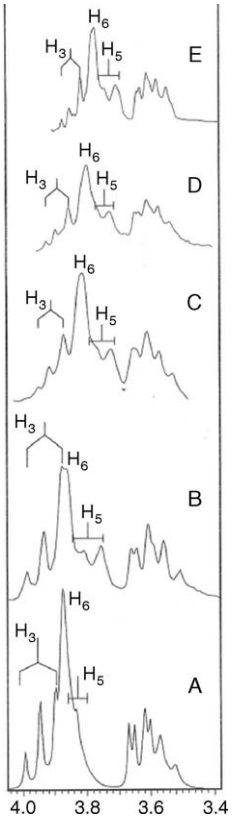


Fig. 2. (A) β-CD; (B) β-CD–phenoxy epoxide complex; (C) 4-min reaction; (D) 8-min reaction; (E) 15-min reaction.

In summary we have demonstrated a novel, mild and efficient methodology for the ring opening of epoxides with thiophenols using cyclodextrin as a catalyst resulting in single regioisomer of the product.

3. Experimental

3.1. Materials

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

3.2. Typical experimental procedure is as follows (Scheme 1)

β-Cyclodextrin (1 mmol) was dissolved in water (15 ml) at 60 °C until a clear solution was formed, epoxide (**1**) (1 mmol) dissolved in methanol (1 ml) was added and allowed to come to room temperature. Then thiophenoxide (**2**) (1 mmol) was added and the reaction mixture was stirred at that temperature until the reaction was complete (15 min). The product was extracted with ethyl acetate (3× 15 ml), the organic phase was separated, filtered, washed with brine followed by water. The organic phase was then dried (Na_2SO_4), filtered and the solvent was removed under vacuum. The crude product obtained was purified by silicagel column chromatography using *n*-hexane:ethyl acetate (8.5:1.5) as eluent. The aqueous layer was neutralized with 1N HCl, cooled to 5 °C to precipitate β-cyclodextrin, which was recovered by filtration. The recycling of recovered β-CD was observed for 10 consecutive runs without change in the yield.

The spectral (^{1}H NMR and MS) and analytical data of the unknown compounds are given below.

Entry-2. Pale yellow oil IR (KBr) 3430 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.5 (brs, 1H, OH), 3.05–3.3 (m, 2H), 3.96–4.15 (m, 3H), 6.7–7.4 (m, 9H). Mass (EI) 294 *m/z*. Anal. Calcd for $C_{15}H_{15}O_2SCl$: C, 61.12; H, 5.13; S, 10.88. Found: C, 61.08; H, 5.04; S, 10.59.

Entry-3. Yellow oil IR (KBr) 3420 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.6 (brs, 1H, OH), 2.9–3.25 (m, 2H), 3.8 (S, 3H), 3.9–4.1 (m, 3H), 6.7–7.5 (m, 9H). Mass (EI) 290 *m/z*. Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25; S, 11.04. Found: C, 66.02; H, 6.08; S, 10.99.

Entry-4. Yellow oil IR (KBr) 3430 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.55 (brs, 1H, OH), 3.05–3.3 (m, 2H), 3.9–4.2 (m, 3H), 6.8 (d, 2H, J = 9.0 Hz), 7.1–7.35 (m, 5H), 7.4 (d, 2H, J = 9.0 Hz). Mass (EI) 294 *m/z*. Anal. Calcd for $C_{15}H_{15}O_2SCl$: C, 61.12; H, 5.13; S, 10.88. Found: C, 61.08; H, 5.04; S, 10.59.

Entry-5. Light yellow solid m.p. 71–73 °C IR (KBr) 3444 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.5 (brs, 1H, OH), 3.0–3.3 (m, 2H), 3.9–4.2 (m, 3H), 6.79 (d, 2H, J = 7.6 Hz), 7.1–7.4 (m, 6H). Mass (EI) 328 *m/z*. Anal. Calcd for $C_{15}H_{14}O_2SCl_2$: C, 54.72; H, 4.29; S, 9.74. Found: C, 54.51; H, 4.10; S, 9.83.

Entry-6. Color less oil IR (KBr) 3416 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.5 (brs, 1H, OH), 2.9–3.2 (m, 2H), 3.8 (s, 3H), 3.83–4.15 (m, 3H), 6.7–6.9 (m,4H,), 7.2 (d, 2H, J = 7.8 Hz),

7.38 (d, 2H, $J = 7.8$ Hz). Mass (EI) 324 *m/z*. Anal. Calcd for $C_{16}H_{17}O_3SCl$: C, 59.16; H, 5.28; S, 9.87. Found: C, 59.01; H, 5.08; S, 9.67.

Entry-7. White solid m.p. 49–51 °C IR (KBr) 3417 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.3 (s, 3H), 2.6 (brs, 1H, OH), 3.05–3.3 (m, 2H), 3.9–4.2 (m, 3H), 6.75 (d, 2H, $J = 8.2$ Hz), 7.07 (d, 2H, $J = 8.2$ Hz), 7.15–7.5(m, 5H). Mass (EI) 276($M + 2$). Anal. Calcd for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61; S, 11.68. Found: C, 69.76; H, 6.47; S, 11.49.

Entry-8. White solid m.p. 56–58 °C, IR (KBr) 3437 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.3 (s, 3H), 2.5 (brs, 1H, OH), 3.0–3.3 (m, 2H), 3.9–4.2 (m, 3H), 6.74 (d, 2H, $J = 8.0$ Hz), 7.05 (d, 2H, $J = 8.0$ Hz), 7.2–7.4(m, 4H). Mass (EI) 308 *m/z*. Anal. Calcd for $C_{16}H_{17}O_2SCl$: C, 62.23; H, 5.55; S, 10.38. Found: C, 62.22; H, 5.54; S, 10.30.

Entry-9. Pale yellow oil IR (KBr) 3420 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.3 (s, 3H), 2.6 (brs, 1H, OH), 2.9–3.3 (m, 2H), 3.8 (s, 3H), 3.9–4.1 (m, 3H), 6.68–6.9 (m, 4H,), 7.0 (d, 2H, $J = 8.0$ Hz), 7.4 (d, 2H, $J = 8.0$ Hz). Mass (EI) 304 *m/z*. Anal. Calcd for $C_{17}H_{20}O_3S$: C, 67.08; H, 6.62; S, 10.53. Found: C, 66.99; H, 6.34; S, 10.41.

Entry-10. Yellow oil IR (KBr) 3406 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.6 (brs, 1H, OH), 3.05–3.3 (m, 2H), 3.8 (s, 3H), 3.9–4.15 (m, 3H), 6.8 (s, 4H), 7.1–7.5 (m, 5H). Mass (EI) 290 *m/z*. Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25; S, 11.04. Found: C, 66.08; H, 5.99; S, 10.87.

Entry-11. White solid m.p. 70–72 °C IR (KBr) 3476 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.6 (brs, 1H, OH), 3.0–3.3 (m, 2H), 3.8 (s, 3H), 3.9–4.2 (m, 3H), 6.8 (s, 4H), 7.2–7.5 (m, 4H,). Mass (EI) 324 *m/z*. Anal. Calcd for $C_{16}H_{17}O_3SCl$: C, 59.16; H, 5.28; S, 9.87. Found: C, 59.01; H, 5.08; S, 9.67.

Entry-12. White solid m.p. 56–58 °C IR (KBr) 3482 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.65 (brs, 1H, OH), 2.9–3.18 (m, 2H), 3.75 (s, 3H), 3.8 (s, 3H), 3.85–4.15 (m, 3H), 6.7–6.9 (m, 6H), 7.4 (d, 2H, $J = 7.2$ Hz). Mass (EI) 320 *m/z*. Anal. Calcd for $C_{17}H_{20}O_4S$: C, 63.73; H, 6.29; S, 10.01. Found: C, 63.99; H, 6.37; S, 9.87.

Entry-13. Color less oil IR (KBr) 3424 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.6 (brs, 1H, OH), 2.8 (t, 2H, $J = 7.0$ Hz), 3.05–3.32 (m, 2H), 3.35 (s, 3H), 3.53 (t, 2H, $J = 7.0$ Hz), 3.9–4.2 (m, 3H), 6.75 (d, 2H, $J = 8.2$ Hz), 7.05–7.5 (m, 7H). Mass (EI) 319($M + 1$). Anal. Calcd for $C_{18}H_{22}O_3S$: C, 67.90; H, 6.96; S, 10.07. Found: C, 67.69; H, 6.83; S, 9.85.

Entry-14. Yellow oil IR (KBr) 3444 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.5 (brs, 1H, OH), 2.78 (t, 2H, $J = 7.2$ Hz), 3.05–3.32 (m, 2H), 3.38 (s, 3H), 3.52 (t, 2H, $J = 7.2$ Hz), 3.9–4.2 (m, 3H), 6.75 (d, 2H, $J = 8.0$ Hz), 7.1 (d, 2H, $J = 8.0$ Hz), 7.16–7.4 (m, 4H). Mass (EI) 352 *m/z*. Anal. Calcd for $C_{18}H_{21}O_3SCl$: C, 61.27; H, 6.00, S, 9.09. Found: C, 61.06; H, 5.78; S, 8.97.

Entry-15. Pale yellow oil IR (KBr) 3430 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.6 (brs, 1H, OH), 2.8 (t, 2H, $J = 7.0$ Hz), 2.9–3.2 (m, 2H), 3.3 (s, 3H), 3.53 (t, 2H, $J = 7.0$ Hz), 3.8 (s, 3H), 3.9–4.1 (m, 3H), 6.7–7.2 (m, 6H), 7.35 (d, 2H, $J = 7.8$ Hz). Mass (EI) 348 *m/z*. Anal. Calcd for $C_{19}H_{24}O_4S$: C, 65.49; H, 6.94; S, 9.20. Found: C, 65.28; H, 6.64; S, 9.07.

Entry-20. Yellow oil IR (KBr) 3450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.2–1.4 (m, 4H), 1.6–1.85 (m, 2H), 1.98–2.2 (m, 2H), 2.5–2.6 (m, 1H), 3.0 (brs, 1H, OH), 3.20 (m, 1H), 3.8 (s, 3H), 6.82 (d, 2H, $J = 8.0$ Hz), 7.38 (d, 2H, $J = 8.0$ Hz). Mass (EI) 239 ($M + 1$). Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61; S, 13.45. Found: C, 65.29; H, 7.72; S, 13.26.

Acknowledgement

We thank the Indo French center for the promotion of advanced research (IFCPAR) for financial support of this project.

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