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A new and efficient method for the synthesis of thiiranes from oxirane–β-cyclodextrin complexes and thiourea in water☆

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Abstract—Oxiranes react smoothly with thiourea in the presence of β-cyclodextrin in water at room temperature under neutral conditions to afford the corresponding thiiranes in excellent yields; the β-cyclodextrin can be recycled.

Thiiranes, which are the simplest sulfur heterocycles and occur in nature, are useful from both theoretical and synthetic points of view. They are used in the pharmaceutical, polymer, pesticide and herbicide industries.[1] A variety of methods have been developed for the preparation of thiiranes.[2] Amongst these, the most important method is the conversion of oxiranes to thiiranes by an oxygen–sulfur exchange reaction. Various sulfur introducing reagents such as inorganic thiocyanates,[3] phosphine sulfide,[4] 3-methylbenzothiazole-2-thiirane,[5] dimethylthioformamide in the presence of trifluoro acetic acid,[6] silica gel supported potassium thiocyanate,[7] indium halides/KSCN[8] and polymeric cosolvent/NH_4SCN,[9] together with solvent-free conditions[10] and ionic liquids,[11] etc., have been reported to produce thiiranes from oxiranes. However, many of these methods suffer from undesirable side reactions due to rearrangement or polymerization of the oxiranes resulting in low yields of the thiiranes especially for the conversion of cyclohexene oxide to cyclohexene sulfide, and styrene oxide to styrene sulfide as well as the synthesis of other higher thiiranes.[2]

Although thiourea has been one of the most widely used reagents for this transformation,[12] it suffers from various disadvantages such as long reaction times, low yields and desulfuration of the resulting episulfide to olefin in some cases.[12f] In reports with aqueous solvents the control of pH was important if the episulfide was to be obtained without polymerization.[13,2b] Epoxides have been transformed to episulfides by the action of thiourea in aqueous acidic solutions followed by basic workup in methanolic solutions.[14] So far no success has been achieved in carrying out these reactions exclusively in water under neutral conditions.[15] Water as a solvent is safe, economical and environmentally benign.[16] In view of the advantages of using water as a solvent, we explored the synthesis of thiiranes from oxiranes and thiourea in water in the presence of β-cyclodextrin.

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates 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. This mimicking of biochemical selectivity, which involves orientation of the substrate by complex formation thereby positioning only certain regions for favourable attack, is superior to chemical selectivity where the attack is due to the intrinsic reactivity of the substrate at different regions. Our earlier expertise in the field of biomimetic modelling of organic chemical reactions involving cyclodextrins,[17] prompted us to attempt the regioselective ring opening of oxiranes with thiourea in the presence of β-cyclodextrin (β-CD) (Schemes 1 and 2).

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 thiourea **2** and stirring at

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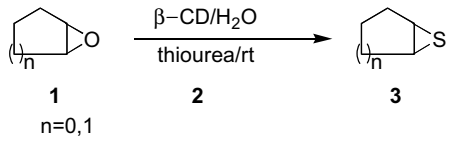
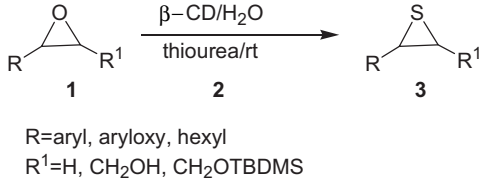


Scheme 1.

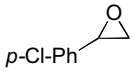
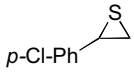
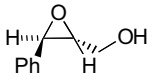
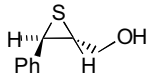
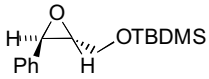
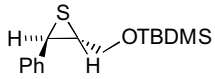
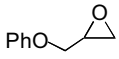
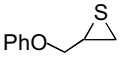
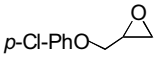
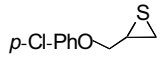
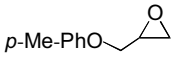
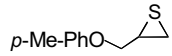
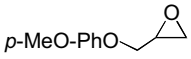
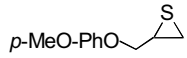
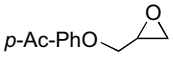
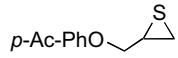
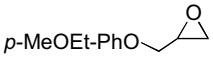
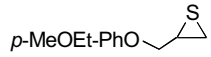
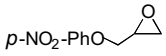
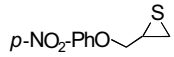
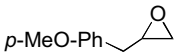
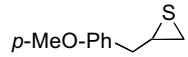
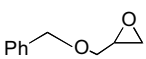
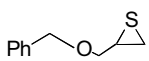
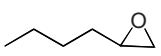
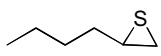


Scheme 2.

room temperature to give the corresponding thiiranes **3** in impressive yields.[18] These reactions take place at room temperature and no side product or rearrangement was observed. The β-cyclodextrin can be recovered and reused. The reactions also take place using α-cyclodextrin with the same results. However, β-cyclodextrin was chosen as the catalyst since it is inexpensive and readily available. When a catalytic amount of cyclodextrin (0.1 mmol per 1.0 mmol of substrate) was used in the reaction, the yields were only 15%.

The reactions are clean and high yielding compared to conventional methods. The reaction with styrene epoxides (Table 1, entries 3–4), *trans*-cinnamyl epoxides (Table 1, entries 5–6) and phenoxy-epoxides (Table 1, entries 7–13) were complete within 4 h whereas the cyclic epoxides (Table 1, entries 1–2) required 6 h. Reactions were carried out on a wide range of epoxides. All

Table 1. β-Cyclodextrin catalyzed synthesis of thiiranes from oxiranes and thiourea in water

Entry 1	Substrate	Product[a]	Time (h)	Yield (%)[b]
1			6.0	80
2			6.0	82
3			3.5	93
4			3.5	94
5			4.0	85
6			4.0	81
7			3.0	94
8			3.0	96
9			3.5	96
10			4.0	91
11			4.0	90
12			3.5	94
13			4.0	88
14			3.5	91
15			4.0	94
16			6.0	80

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

products were characterized by ^{1}H NMR, MS, IR and elemental analysis or by comparison with known compounds.[6,7,11]

These reactions do not take place in the absence of cyclodextrin. It appears that cyclodextrin not only activates the epoxide but also forms a cyclodextrin–epoxide complex through hydrogen bonding. Evidence for association between the epoxide and cyclodextrin is supported by ^{1}H NMR spectroscopy. The studies were undertaken with *p*-chlorophenoxy epoxide as a representative example. A comparison of the ^{1}H NMR spectra (D_2O solutions) of β-CD, the β-CD-epoxide complex and the freeze-dried reaction mixture after 3 h was undertaken. It can be seen from Figure 1 that there is a upfield shift of H-3 (0.03 ppm) and H-5 (0.057 ppm) of cyclodextrin in the CD-epoxide complex in comparison to CD indicating the formation of an inclusion complex of the epoxide with β-CD.[19] It was further observed from the spectra of the reaction mixtures of the β-CD-epoxide complex and thiourea (after 3 h) that the complex retains the upfield character of the H-3 and H-5 protons showing retention of the epoxide in the cavity.

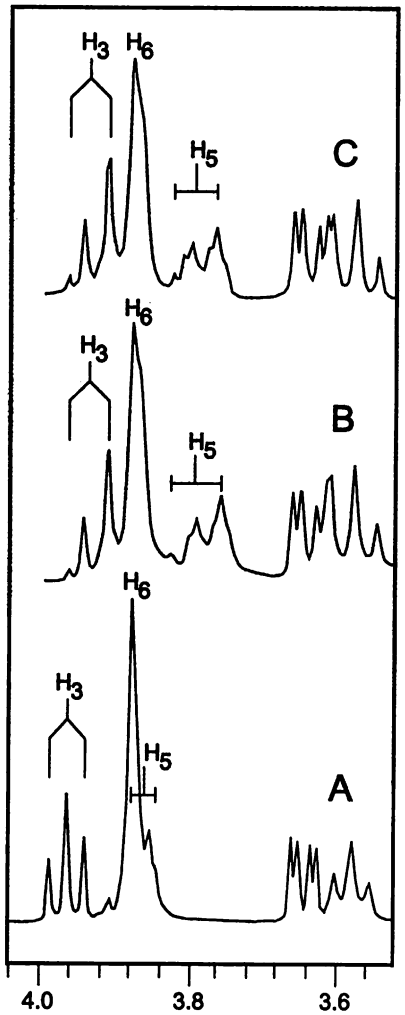


Figure 1.

Thus, it can be seen that the reaction takes place through supramolecular catalysis. An upfield shift of the H-3 and H-5 protons was also observed in the β-CD-cyclohexene epoxide complex.

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18. General procedure: β-Cyclodextrin (1.0 mmol) was dissolved in water (15 mL) at 60 °C and the epoxide (1.0 mmol) dissolved in acetone (1 mL) was added slowly with stirring. Then the mixture was cooled to room temperature, thiourea (1.5 mmol) was added and the reaction mixture was stirred for 4–6 h. (Table 1). The reaction mixture was extracted with ethyl acetate, and the extract was filtered and the solvent was removed under vacuum. The product thus obtained was purified by silica gel column chromatography with ethyl acetate–*n*-hexane (5:95) as eluent. The filtrate was cooled to 5 °C in order to precipitate β-cyclodextrin.
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