# Synthesis of Thiiranes from Oxiranes in the Presence of β-Cyclodextrin in Water

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**Abstract:** A mild and highly efficient, user-friendly procedure has been developed for the conversion of oxiranes to thiiranes under supramolecular catalysis in the presence of β-cyclodextrin in water at ambient temperature in excellent yields. The use of β-cyclodextrin in this transformation overcomes the use of heavy metal halides as promoters and chlorinated hydrocarbons and other hazardous organic solvents.

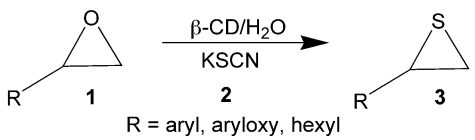
**Keywords:** β-cyclodextrin; oxiranes; potassium thiocyanate; thiiranes; water

Oxiranes are one of the most versatile intermediates in organic synthesis and a large variety of nucleophiles is known for the ring opening of these compounds.[1] Amongst various possibilities, easily accessible oxiranes have opened up routes for the synthesis of thiiranes of high synthetic utility. Although a variety of methods has been developed for the synthesis of thiiranes,[2] using inorganic thiocyanate,[3] thiourea,[4] phosphine sulfide,[5] 3-methylbenzothiazole-2-thione,[6] dimethylthioformamide,[7] indium tribromide/KSCN,[8] etc., many of these methods have serious limitations such as extended reaction times, strongly acidic or oxidizing conditions, low yields, elevated temperatures, hazardous reagents and solvents, and undesirable side products. At times protic acids such as trifluoroacetic acid or strong Lewis acids had also to be employed. Furthermore, most of these methods are of limited synthetic scope when applied to multifunctional compounds.

The toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons, that are widely used in organic synthesis has posed a serious threat to the environment. Just recently, there was a report of carrying out the synthesis of thiiranes in a mixture of ionic liquid and water (2:1) with potassium thiocyanate.[9] However, there are few drawbacks associated with this methodology such as liberation of hazardous HF during recycling of the solvent. Moreover, these reactions were unsuccessful in water alone. Some of the methods reported in the literature which were carried out in pure water were not successful.[10] So far no success has been achieved in carrying out these reactions exclusively in water. Since green chemistry is becoming a central issue in both academic and industrial research in the 21st century,[11] with water as solvent because it is safe, economical and environmentally benign,[12] we have explored these reactions using water as the reaction medium.

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. Thus, an attractive procedure for the synthesis of thiiranes from oxiranes, different from the classical approach, was developed for the first time under supramolecular catalysis in water in presence of β-cyclodextrin.

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. They promote reactions by supramolecular catalysis involving reversible formation of host-guest complexes by non-covalent bonding as seen in enzymes. Complexation depends on the size, shape and hydrophobicity of the guest molecule. Thus mimicking biochemical selectivity, which involves orientation of the substrate by complex formation positioning only certain region for favorable attack, will be superior to chemical selectivity where the attack is 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,[13] prompted us to attempt the highly selective ring opening of oxiranes with potassium thiocyanate in the presence of β-cyclodextrin (β-CD) as this is one of the most useful synthetic transformations with a variety of applications.




**Scheme 1.**

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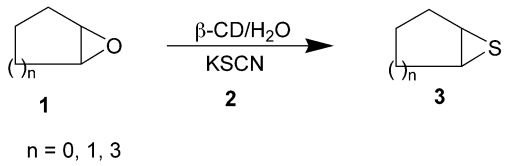



**Scheme 2.**

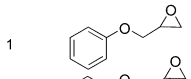
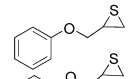
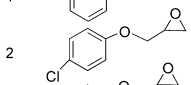
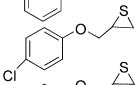
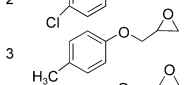
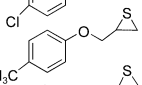
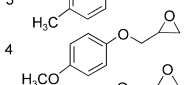
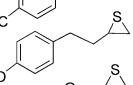
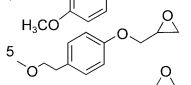
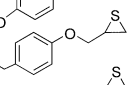
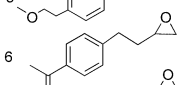
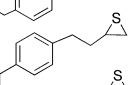
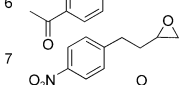
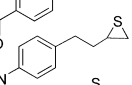
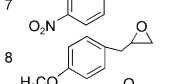
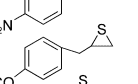
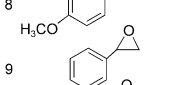
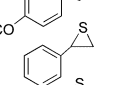
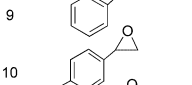
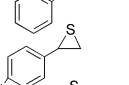
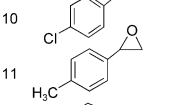
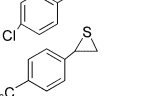
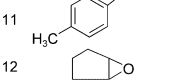
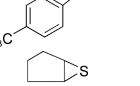
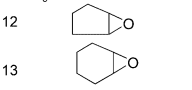
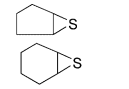
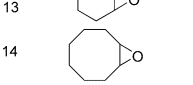
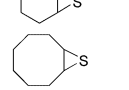
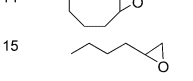
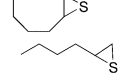
The reactions were carried out by the *in situ* formation of the β-cyclodextrin complex of the epoxide (**1**) in water followed by the addition of potassium thiocyanate (**2**) and stirring at room temperature to give the corresponding thiiranes (**3**) in impressive yields. These reactions take place at room temperature and no side products or rearrangements were observed. β-Cyclodextrin can be easily recovered and reused a number of times. These reactions do take place with α-cyclodextrin as well with the same results, however, β-cyclodextrin was chosen as the catalyst since it is inexpensive and easily accessible. When catalytic amount of cyclodextrin (0.1 mmol per 1 mmol of substrate) was used in the reaction, the yields were only to the extent of 10%. These reactions do not proceed in the absence of β-cyclodextrin.

The reactions are clean and high yielding compared to conventional methods. The reactions with phenoxy epoxides and styrene epoxides were complete within 3.5 to 4 hours whereas with cyclic epoxides the reaction times were extended upto 6 to 7 hours. Reactions were carried out with a wide range of epoxides. All the compounds were characterized by $^1$H NMR, mass, IR and elemental analysis or otherwise compared with the known compounds.[7,9,14]

The formation of thiiranes occurs through *in situ* formation of a β-cyclodextrin inclusion complex. However, these inclusion complexes have been isolated and characterized by powder X-ray[15] and $^1$H NMR studies.[16] There is a clear upfield shift of the H-3 and H-5 protons of cyclodextrin indicating the formation of a supramolecular entity with the epoxide. In this type of complexes the α-position of the epoxide will be more hindered and β-attack dominates to give the product. Here the role of cyclodextrin appears to be not only to activate the oxiranes but also to promote highly selective ring opening due to inclusion complex formation with cyclodextrin in this new biomimetic methodology (Fig. 1). Thiiranes might be formed through the intermediacy of the corresponding β-hydroxythiocyanate, however this intermediate could not be isolated due to its rapid conversion to the corresponding thiiranes as already observed.[3d,17]

In summary, this methodology describes a simple, convenient and highly efficient method for the conversion of oxiranes to thiiranes. The notable features of this method are cleaner reaction profiles, high yields of products, short reaction periods and operational simplicity. Above all, the reactions are carried out in water. The ever-growing demand for eco-conscious chemical processes and increasing interest in green chemistry has prompted us to carry out the synthesis of these versatile thiiranes in water.

**Table 1.** Synthesis of thiiranes from oxiranes in the presence of β-CD in water.

| Entry | Epoxide (**1**) | Reagent (**2**) | Product (**3**)[a] | Time | Yield [%][b] |
|---|---|---|---|---|---|
| 1 |  | KSCN |  | 4.0 | 94 |
| 2 |  | KSCN |  | 4.0 | 95 |
| 3 |  | KSCN |  | 4.0 | 92 |
| 4 |  | KSCN |  | 3.5 | 94 |
| 5 |  | KSCN |  | 4.0 | 92 |
| 6 |  | KSCN |  | 4.0 | 90 |
| 7 |  | KSCN |  | 4.5 | 90 |
| 8 |  | KSCN |  | 5.0 | 92 |
| 9 |  | KSCN |  | 3.5 | 90 |
| 10 |  | KSCN |  | 3.5 | 94 |
| 11 |  | KSCN |  | 3.5 | 92 |
| 12 |  | KSCN |  | 6.0 | 80 |
| 13 |  | KSCN |  | 6.0 | 84 |
| 14 |  | KSCN |  | 7.0 | 81 |
| 15 |  | KSCN |  | 6.5 | 80 |

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

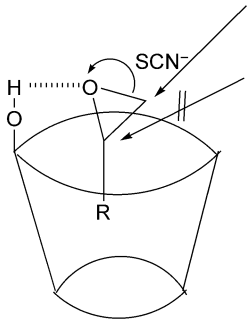



**Figure 1.**

## Experimental Section

### General Information

$^1$H NMR spectra were recorded on Gemini-200 MHz spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. IR spectra were recorded on Nicolet FT-IR spectrometer. Melting points were recorded on Büchi R-535 apparatus and are uncorrected. CH analyses were recorded on a Vario EL analyser.

### General Procedure

β-Cyclodextrin (1 mmol) was dissolved in water (25 mL) at 60 °C, and the epoxide (1 mmol) dissolved in acetone (2 mL) was added slowly with stirring. The mixture was cooled to room temperature, potassium thiocyanate (1.5 mmol) was added and the reaction was stirred at that temperature (Table 1). The reaction mixture was extracted with ethyl acetate, filtered and washed with brine. The organic phase was dried ($Na_2SO_4$), filtered and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography with ethyl acetate:*n*-hexane (5:95) as eluent.

### Spectroscopic Data of New Compounds

**2-[4-(2-Methoxyethyl)phenoxymethyl]thiirane (Table 1, entry 5):** Colorless oil; IR (neat): $\nu = 2923$, 1600, 1507, 1246, 1107 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta = 2.25$ (m, 1H), 2.50 (m, 1H), 2.75 (t, 2H, $J = 5.8$ Hz), 3.12 (m, 1H), 3.25 (s, 3H), 3.38 (t, 2H, $J = 5.8$ Hz), 3.72 (m, 1H), 4.20 (m, 1H), 6.71 (d, 2H, $J = 7.9$ Hz), 7.05 (d, 2H, $J = 7.9$ Hz); MS (EI): $m/z = 224$; anal. calcd. for $C_{12}H_{16}O_2S$: C 64.25, H 7.19, S 14.29; found: C 64.29, H 7.22, S 14.31.

**1-[4-(2-Thiiranylmethoxy)phenyl]-1-ethanone (Table 1, entry 6):** Colorless oil; IR (neat): $\nu = 2924$, 1691, 1584, 1245, 1153, 838 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta = 2.20$ (m, 1H), 2.50 (s, 3 H), 2.59 (m, 1H), 3.18 (m, 1H), 3.82 (m, 1H), 4.20 (m, 1H), 6.89 (d, 2H, $J = 8.0$ Hz), 7.89 (d, 2H, $J = 8.0$ Hz); MS (EI): $m/z = 208$; anal. calcd. for $C_{11}H_{12}O_2S$: C 63.44, H 5.81, S 15.39; found: C 63.48, H 5.84, S 15.41.

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