β-Cyclodextrin-Supported, Completely Regioselective Ring Opening of Thiiranes with Thiophenol in Water[1])

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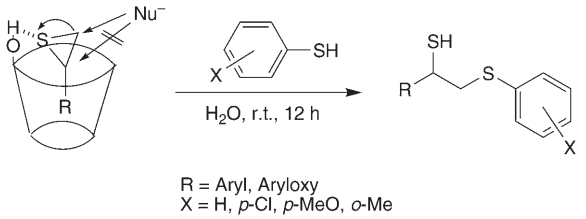
Thiolysis of thiiranes **I** with thiophenols **II** is performed efficiently in the presence of β-cyclodextrin in water with high regioselectivity (*Scheme*, *Table*).

Introduction. – Ring-opening reactions of thiiranes are rarely studied due to ready polymerization, and fundamental information is still scarce in this field. The most important reactions from the viewpoint of organic synthesis are the nucleophilic ring-opening reactions of these compounds. This type of reaction has not been investigated extensively, and only a few reports are available in the literature [1–4]. The ring-opening reactions of thiiranes usually suffer from strongly acidic conditions, high temperatures [2], long reaction times [2][5], extensive polymerization [2][5], low to very poor yields of the products [2][6], *etc*. In contrast, thiolysis under basic conditions results in polymerization and regioisomer formation [2][4]. Thus, there is a need for a widely applicable approach, preferably with H_2O as solvent, which is gaining increasing importance in present-day organic synthesis.

The best choice appeared to be through a supramolecular system involving cyclodextrins in H_2O as solvent since such reactions do not generate any toxic-waste products. Thus a new, attractive procedure for the ring opening of thiiranes with thiophenols, different from the classical approach, is presented here, consisting of a supramolecular system involving β-cyclodextrin in H_2O, and showing no signs of polymerization (*Scheme*).

Scheme



R = Aryl, Aryloxy
X = H, *p*-Cl, *p*-MeO, *o*-Me

[1]) IICT Communication No. 061122.

Cyclodextrins (CDs) are cyclic oligosaccharides with hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions. The reactions by a supramolecular system involve noncovalent bonding such as those seen in enzyme reactions [7]. The high selectivity is due to the orientation of the substrate by complex formation exposing only certain regions of the substrate to a favorable attack. Complexation processes in solution depend on the size, shape, and hydrophobicity of the guest molecule. Our earlier expertise in the field of biomimetic modeling of organic reactions involving cyclodextrins [8] prompted us to develop the ring opening of various thiiranes with thiophenols in H_2O through the formation of β-cyclodextrin–thiirane complexes.

Results and Discussions. – The reactions were carried out by dissolving β-cyclodextrin in H_2O followed by the subsequent addition of a thiirane **I** and a thiophenol (ArSH) **II**. The optimum ratio of β-cyclodextrin was 1 mmol per mmol of substrate **I**. After 12 h stirring at room temperature and workup, the α-(arylthio)thiols **I/II** were obtained (*Table*). The ^{1}H-NMR of the crude products established the presence of only one regioisomer. All products were characterized by ^{1}H-NMR, MS, IR, and elemental analysis. Reactions were carried out with a variety of substrates **I**, and the yields of products **III** were in the range of 80–90% (*Table*).

Complexes of **I** were formed with β-cyclodextrin since the latter is easily accessible and the least expensive among the cyclodextrins. The ring-opening reactions of **I** did not take place in the absence of β-cyclodextrin. Here, the role of the cyclodextrin appears to be not only the activation of the thiirane but also the promotion of a highly selective ring opening due to inclusion-complex formation. No optical induction was observed in these reactions.

In conclusion, we presented for the first time a simple methodology for the regioselective ring opening of thiiranes in a supramolecular system in H_2O at room temperature. Thiophenols readily reacted with the thiiranes at the least hindered position to give a single regioisomer in high yield without polymerization of the thiiranes. This approach may be considered as environmentally benign with a high potential for a variety of applications.

We thank *CSIR*, New Delhi, India, for the award of a research fellowship.

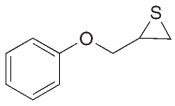
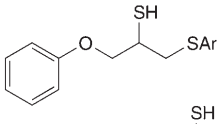
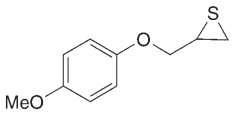
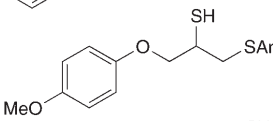
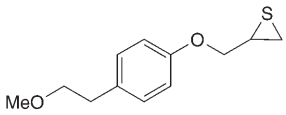
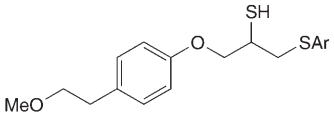
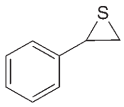
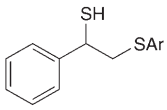
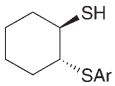
Experimental Part

General. All reactions were carried out under N_2 and monitored by TLC (silica gel (60–120 mesh, *Merck*)). IR Spectra: *FT-IR-Thermo-Nicolet-Nexus-670* spectrometer; in cm^{-1}. NMR Spectra: *Bruker* (300 MHz) and *Varian* (200 MHz) NMR spectrometers; $CDCl_3$ as solvent; δ in ppm, J in Hz. Mass spectra: *LC-MSD-Trap-SL* spectrometer (*Agilent* technologies); in cm^{-1}.

General Procedure. To a soln. of β-cyclodextrin (1 mmol) in dist. H_2O (15 ml) at 60°, thiirane **I** (1 mmol) in acetone or MeOH (1 ml) was added slowly with stirring. The mixture was cooled to r.t., thiophenol **II** (1 mmol) was added, and the mixture stirred at r.t. for 12 h. The product was extracted with AcOEt (3×50 ml), the org. phase dried (Na_2SO_4) and concentrated, and the residue subjected to column chromatography (silica gel (60–120 mesh), AcOEt/hexane 85:15): product **III**.

Data for 1-[(4-Chlorophenyl)thio]-3-[4-(2-methoxyethyl)phenoxy]propan-2-thiol (**III** of *Entry 8*, *Table*): Yellow liquid. IR (KBr): 2921.5, 1951.9, 1580.9, 1053.8, 695.1. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.78 (t, $J = 6.7$, 2 H); 3.01–3.27 (m, 3 H); 3.32 (s, 3 H); 3.51 (t, $J = 6.7$, 2 H); 3.96–4.24 (m, 2 H); 6.62–6.81 (m, 2 H); 6.97–7.29 (m, 6 H). ESI-MS: 391 ($[M + Na]^+$).

Table. *Ring Opening of Thiiranes* **I** *with Thiophenols* **II** *in the Presence of β-Cyclodextrin in Water*

Entry	Substrate **I**	Reagent **II**	Product **I/II**[a])	Ar	Yield[b]) [%]
1		PhSH		Ph	89
2		*p*-ClC_6H_4SH		*p*-ClC_6H_4	86
3		*p*-$MeOC_6H_4SH$		*p*-$MeOC_6H_4$	88
4		PhSH		Ph	90
5		*p*-ClC_6H_4SH		*p*-ClC_6H_4	83
6		*o*-MeC_6H_4SH		*o*-MeC_6H_4	85
7		PhSH		Ph	88
8		*p*-ClC_6H_4SH		*p*-ClC_6H_4	81
9		*o*-MeC_6H_4SH		*o*-MeC_6H_4	80
10		PhSH		Ph	89
11		*p*-ClC_6H_4SH		*p*-ClC_6H_4	90
12		PhSH		Ph	88
13		*p*-ClC_6H_4SH		*p*-ClC_6H_4	83

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

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Received October 26, 2006