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The First Preparation of Episulfones from Episulfides: Oxidation Using Oxone®/Trifluoroacetone

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Abstract: For the first time, episulfones have been prepared by oxidation of the corresponding episulfides. Seven examples are given, most of which proceed in good to excellent yield. The first oxidation of an episulfoxide to an episulfone is also reported as part of a preliminary mechanistic study.
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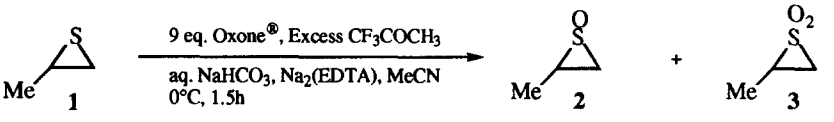
A wide range of organic sulfides, both acyclic and cyclic, are easily oxidised to give the corresponding sulfoxides and sulfones.[1] Episulfides (thiiranes), however, have proved anomalous:[2] under controlled conditions they can be oxidised to episulfoxides[2] but there are no authenticated[3] reports of episulfones being prepared from either episulfides or episulfoxides by an oxidative pathway. This is not through lack of effort: a range of oxidants including nitric acid,[4,5] potassium permanganate,[4,6,10] peroxides and peracids,[6-11] ozone,[11] and singlet oxygen[12] have been employed without success. In cases where by-products have been isolated they have resulted from nucleophilic ring opening of the intermediate episulfoxide followed by further oxidation[7,9] or from loss of SO/SO_2 from the oxidised product giving the corresponding alkene.[12]

In view of our interest in the synthetic applications of episulfones,[13] we required a straightforward route to this class of compound. They are available *via* the addition of diazoalkanes to sulfenes[4,14] or, as we have recently shown, from α-halosulfones under modified Ramberg-Bäcklund conditions.[15] Both approaches have limitations, however, and given the accessibility of episulfides,[16] we decided to reinvestigate their oxidation. The choice of oxidant was prompted by the recent report[17] that methyl(trifluoromethyl)dioxirane (TFDO) converts sulfides directly into sulfones *via* sulfurane intermediates, and does not proceed by way of sulfoxides. Such a procedure seemed to be ideally suited to the preparation of episulfones from episulfides, particularly as a convenient *in situ* method for preparing TFDO from Oxone® ($KHSO_5$ triple salt) and 1,1,1-trifluoroacetone has been described by Yang *et al.*[18] We therefore studied the oxidation of propene episulfide **1**, which is commercially available and gives a reasonably stable and well characterised episulfoxide **2**.[19]

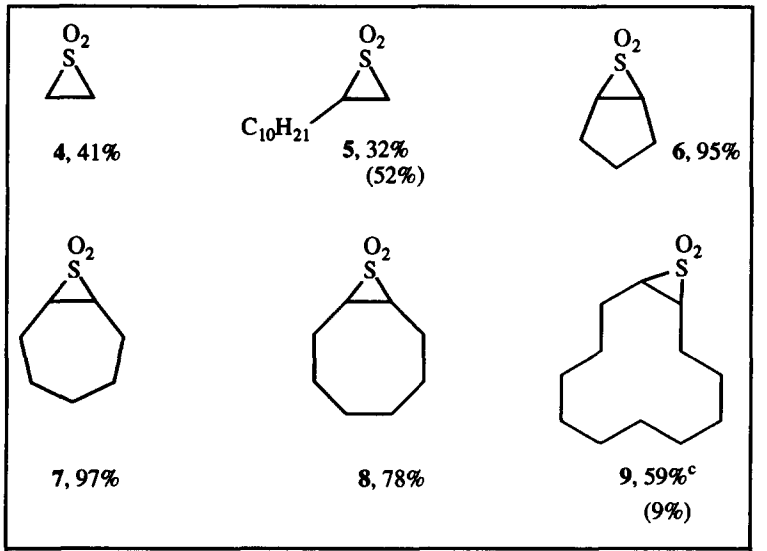
Equation 1



To our delight, and somewhat surprisingly in view of previous studies, treatment of propene sulfide **1** with Oxone®/trifluoroacetone under Yang's conditions, followed by work up and chromatography, gave the corresponding episulfone **3** in 65% isolated yield, together with 17% of episulfoxide **2** (Equation 1).[20]

$^1H/^{13}C$ NMR and IR spectroscopic data were entirely consistent with these assignments and an accurate mass measurement was obtained for episulfone **3** [Found (CI): $(M + NH_4)^+$, 124.043352. $C_3H_{10}NO_2S$ requires 124.043225 (1 ppm error)]. For confirmation purposes, we also prepared propene episulfoxide **2** by a literature[19] procedure and established that it was identical to the minor product of this oxidation but differed chromatographically and spectroscopically from the major product of the reaction [*e.g.* **3**: δ_C ($CDCl_3$) 13.2 (Me), 38.4 (CH_2SO_2), 40.2 ($CHSO_2$); **2**: δ_C ($CDCl_3$) 14.7 (Me), 42.8 (CH_2SO), 44.8 (CHSO)]. Having made this discovery, we went on to demonstrate that a range of episulfones can be prepared by the Oxone®/trifluoroacetone oxidative procedure (Figure).

Figure Oxone®/trifluoroacetone preparation of episulfones **4** - **9**[a,b]



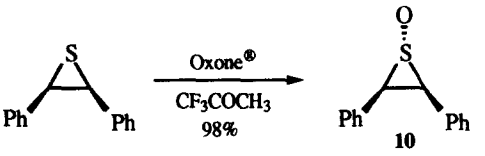
[a]MeCN, $(EDTA)Na_2$, aq. $NaHCO_3$, 0°C (see representative experimental procedure)

[b]Yield of episulfoxide co-product (if obtained) shown in parentheses

[c]*Cis:trans* ratio = 74:26 (the starting-episulfide was also an isomeric mixture with the *cis*-isomer predominating); a small amount of the epoxide corresponding to **9** is also formed (presumably by episulfone desulfonylation followed by *in situ* epoxidation)

Thiirane is commercially available; the other episulfides required for this study were prepared from the corresponding epoxides by treatment with triphenylphosphine sulfide.[21] In the monocyclic series, thiirane underwent oxidation to give the corresponding episulfone **4** in 41% isolated yield, decomposition to ethene and sulfur dioxide presumably accounting for the low recovery. Dodecene episulfide gave a separable mixture of episulfone **5**, and the corresponding episulfoxide, both of which are novel compounds, in good combined yield. With *cis*-stilbene episulfide, however, the standard reaction conditions gave only the known[19] episulfoxide **10**, even after extended reaction times (Equation 2). The stilbene episulfoxide **10** has been assigned the *anti*-configuration[19] and it seems likely that dodecene episulfoxide, which is a single diastereoisomer, is also *anti*. These results indicate that increasing steric hindrance around the episulfide leads to reduced amounts of the episulfone.

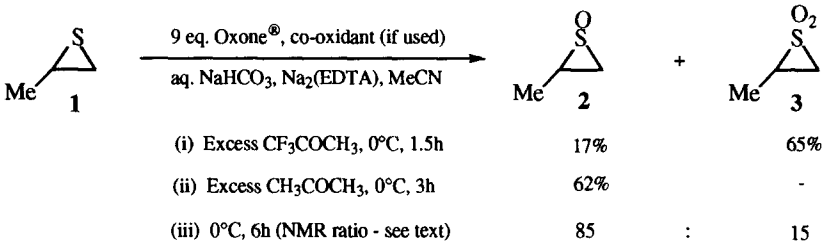
Equation 2



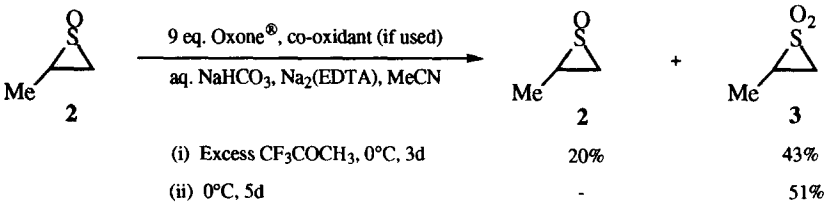
We next turned our attention to bicyclic episulfides (Figure). Cyclopentene episulfide was converted into the corresponding episulfone **6** in excellent yield (95%) and it was surprising, therefore, that the oxidation of cyclohexene episulfide under identical conditions gave neither episulfoxide nor episulfone. The ease with which the 7-thiabicyclo[4.1.0]heptane dioxide system undergoes loss of SO_2 has been noted before,[15b] however, and it seems likely that the expected episulfone was formed but underwent facile desulfonylation; evidence for this proposal came from the ^1H NMR spectrum of the crude product mixture which indicated the presence of cyclohexene. By contrast, the episulfides derived from cycloheptene, cyclooctene and cyclododecene were converted into episulfones **7-9** in excellent (59-97%) yields.

Preliminary mechanistic investigations have also been carried out (Equations 3 and 4). The oxidation of propene episulfide **1** was carried out using Oxone® with acetone in place of trifluoroacetone (Equation 3, ii), and Oxone® in the absence of a ketone co-oxidant (Equation 3, iii). Both reactions proceeded much more slowly compared to the Oxone®/trifluoroacetone process (Equation 3, i), and gave episulfoxide **2** as the major product. With Oxone® alone (entry iii), the reaction was monitored by ^1H NMR spectroscopy for an extended period of time: an 85:15 mixture of episulfoxide **2** and episulfone **3** was observed after 6 hours whereas after 5.5 days episulfone **3** was the only observable product.

Equation 3



Equation 4



The oxidation of episulfoxide **2** was also studied (Equation 4). With Oxone®/trifluoroacetone or Oxone® alone the reaction was extremely slow producing reasonable amounts of episulfone **3** only after reaction times of several days. These results indicate that both Oxone® and Oxone®/trifluoroacetone can produce episulfones from episulfides, and that the presence of trifluoroacetone has a dramatic accelerating effect in the episulfide oxidation but not in the oxidation of episulfoxide **2**. These observations support the proposal that sulfide oxidation using Oxone®/trifluoroacetone proceeds directly to the episulfone and not *via* the intermediacy of the corresponding episulfoxide.[17] A preliminary study using "isolated" TFDO, which readily oxidises a range of sulfides to sulfones, has revealed that it converts episulfide **1** into episulfoxide **2**

in good yield (66%), but that, surprisingly, episulfone **3** is not formed in any significant amount. More research is needed, but it seems likely that the active oxidant in the Oxone®/trifluoroacetone mixture which promotes episulfone production is not TFDO but some other peroxidic species.[22]

In summary, we have demonstrated that a range of episulfones can be prepared by oxidation of the corresponding episulfides using a simple Oxone®/trifluoroacetone procedure. The ease with which bicyclic episulfones can be obtained is particularly noteworthy as the standard diazoalkane/sulfene methodology[4,14] is not readily applicable to such systems. We are currently examining other episulfides and oxidants in order to optimise this new route to episulfones, as well as continuing with the mechanistic studies.

Representative Experimental Procedure: *9-Thiabicyclo[6.1.0]nonane dioxide* (**8**)
1,1,1-Trifluoroacetone (1 mL, 1.25 g, 11.15 mmol) and aq. disodium EDTA solution (0.4 *mM*, 10 mL) were added to a stirred solution of cyclooctene episulfide (142 mg, 1 mmol) in acetonitrile (15 mL) at 0°C. A mixture of Oxone® (3.07 g, 5 mmol) and sodium hydrogencarbonate (1.26 g, 15 mmol) were then added in portions over 1 h. After 2 h at 0 °C, water (20 mL) was added and extraction effected with dichloromethane (3 x 20 mL). *The temperature was kept as low as possible during the work-up and chromatographic purification.* The combined extracts were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The resulting oil was purified by chromatography (silica; dichloromethane) to give the title episulfone **8** (135 mg, 78%) as a white solid, dec. pt. 94-96°C, R_f 0.33 (CH_2Cl_2); δ_H (270 MHz, $CDCl_3$): 1.47-1.87 (10 H, m, remainder), 2.20-2.27 (2 H, m, H-3,8), 3.17-3.25 (2 H, m, $CHSO_2$); δ_C (67.5 MHz, $CDCl_3$): 20.8 (C-5,6), 25.6 (C-4,7), 27.3 (C-3,8), 47.8 ($CHSO_2$); IR (Nujol): $\nu/(cm^{-1})$ 1358, 1321, 1284 (SO_2), 1167 (SO_2); HRMS (CI): Found $(M + NH_4)^+$: 192.10657. $C_8H_{18}NO_2S$ requires 192.10583 (3.9 ppm error).

Acknowledgements

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