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Efficient Synthesis of Episulfones and of SO_2 with Any Variation of Oxygen Isotopes Using $HOF{\cdot}CH_3CN$

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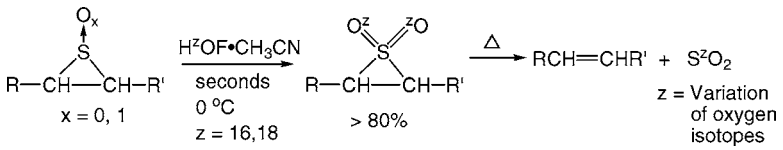
ABSTRACT



Episulfones are quite unstable and difficult to make compounds. $HOF{\cdot}CH_3CN$, a powerful oxygen transfer agent operating under very mild conditions, was successfully employed in converting episulfides to episulfones. Unlike other oxidizing agents, no episulfoxides were formed under standard conditions. Reacting $H^{18}OF{\cdot}CH_3CN$ with either an episulfide or an episulfoxide leads to the corresponding episulfone with all combinations of oxygen isotopes. Decomposition of such episulfones gives any desirable variation of $S^{18}O^xO$ (x = 16, 18).

Episulfones started to capture the attention of organic chemists almost a century ago,[1] but the interest remained somewhat abstract since all early attempts to prepare this family of compounds were unsuccessful.[2] The first oxidation of episulfides, which are relatively easy to make, resulting in episulfones was claimed in 1965,[3] but some years later it was disproved,[4] leaving these compounds on the wish list for a few more years. The root of all failures was the thermal instability of most members of this family, and since most oxidizing procedures required some heating, elimination of SO_2 took place rather easily. When this was realized, more successful attempts have appeared, but they all relied on total synthesis of episulfones from SO_2-containing starting materials.[4,5] Once available, even through cumbersome multistep procedures, they have been utilized in several useful syntheses such as vinylsilanes, vinylstannanes, and more.[5c,6] Some recent reviews on the Ramberg−Backlund reaction contain detailed description of episulfone chemistry.[7]

The first, and only successful method so far, for making some limited types of episulfones from their "natural" precursor, episulfides, was described a few years ago by Taylor, who reacted them with the remarkable oxidizer methyltrifluoromethyldioxirane (TFDO), $CH_3(CO_2)CF_3$.[8] We present here a different and general route for their formation based on the exceptional abilities of the $HOF{\cdot}CH_3CN$ complex to transfer oxygen atoms to sites where other oxygen transfer agents either encounter substantial difficulties or are completely inactive.[9] In particular, we have observed in the past that this reagent is capable of transferring two oxygen atoms to a variety of sulfur-containing compounds such as sulfides, including very deactivated ones,[10] thiophenes,[11] and even polythiophenes[12] forming the correspond-

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ing SO_2 derivatives. What is more, this very powerful oxygen transfer agent does not require prolonged reaction times (usually a few seconds to a few minutes are sufficient) or elevated temperatures. These characteristics seemed very encouraging in our quest for a general method of transforming episulfides to their corresponding episulfones.

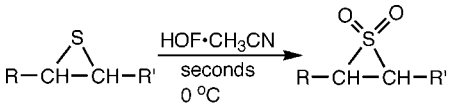
Naturally, the first set of experiments was conducted on the parent episulfide—the thiirane (**1**) itself. The synthesis of thiirane *S*,*S*-dioxide (**2**) with TFDO had been completed by Taylor in his original work[8] in 41% yield after a few hours reaction. Only a few seconds were needed for the HOF·CH_3CN to perform the same reaction and form **2** in 90% yield. The reactions of two other monoalkyl-substituted thiiranes, methyl- and decylthiiranes (**3** and **4**), with TFDO were also described in the above paper with the conclusion that the larger the alkyl group, the more difficult the reaction was going to be. Even the small methyl group in **3** was already responsible for the formation of 17% of the respective episulfoxide **5** contaminating the desired episulfone **6**, which was formed in 65% yield. With the much larger decyl group attached to the thiirane ring **4**, the major component, even after prolonged reaction time with TFDO, was the episulfoxide **7** (52%) along with only 32% of the decylthiirane *S*,*S*-dioxide (**8**). The picture was much simpler with HOF·CH_3CN. No episulfoxides were formed, and the respective episulfones **6** and **8** were obtained in 87 and 80% yield, respectively, in reaction times of a few seconds to a few minutes.

The reaction with HOF·CH_3CN could effectively deal also with thiiranes possessing substituents other than pure alkanes. Reacting epithiochlorohydrin (**9**) with 2.5 molar equiv of HOF·CH_3CN (each molar equivalent provides one oxygen atom only) for 4 min at 0 °C resulted in 80% of the hitherto unknown chloromethylthiirane *S*,*S*-dioxide (**10**), mp 59−62 °C dec, stable enough at room temperature to be fully analyzed (see the Supporting Information). Replacing the electron-withdrawing chloromethyl group with the electron-donating phenoxymethylene one (**11**) did not change the outcome much, and it took 2 min for the new 2-phenoxymethylthiirane *S*,*S*-dioxide (**12**), mp 80−83 °C dec, to be formed in 85% yield. The only difference observed between **10** and **12** was the fact that the latter tends to decompose faster then the chloromethylene derivative and it loses slowly the elements of SO_2 even at room temperature.

Remembering that the production of episulfones using TFDO is more difficult with larger alkyl chains (see above), it was of interest to find whether increasing the steric hindrance will have any effect on the route of the reaction with HOF·CH_3CN. It seems that placing two alkyl groups at positions 2 and 3 of the thiirane ring does not diminish the ability of the reagent to transfer two oxygen atoms to the sulfur atom. 1-Isopropyl-2-methylthiirane (**13**) and 2-methyl-1-pentylthiirane (**14**) produced, after a short contact (several seconds) with a cold (0 °C) solution of the acetonitrile complex of the hypofluorous acid, the corresponding new episulfones **15** (mp 29−31 °C dec) and **16** (oil) in 88 and 95% yield, respectively. As with **12**, the electron-donating alkyl groups encouraged a slow elimination of SO_2 already at room temperature, as evident also from the NMR spectra which indicated a continuous olefin formation. It should be noted, however, that the episulfone 9-thiabicyclo[6.1.0]nonane-*S*,*S*-dioxide (**17**),[8] mp 93−95 °C, produced in 90% yield from the episulfide of cyclooctene **18**, is relatively stable and does not lose the element of SO_2 as easily as its noncyclic counterparts **15** and **16**.

The episulfide of *cis*-stilbene **19** presents an interesting case. While treatment with TFDO, or any other oxygen transfer agent for that matter, produces only the stable episulfoxide **20**, treatment with HOF·CH_3CN leads to 1,2-diphenylthiirane *S*,*S*-dioxide (**21**, 80% yield) with no traces of the episulfoxide **20** (Scheme 1). Although known,[13] **21** is thermally not very stable and starts to release SO_2 slowly, forming *cis*-stilbene.

Scheme 1. Oxidation of Episulfides to Episulfones



1	R = R' = H	**2**	(90%)
3	R = H; R' = Me	**6**	(87%)
4	R = H; R' = $C_{10}H_{21}$	**8**	(80%)
9	R = H; R' = CH_2Cl	**10**	(90%)
11	R = H; R' = CH_2OPh	**12**	(85%)
13	R = Me; R' = *i*-Pr	**15**	(88%)
14	R = Me; R' = C_5H_{11}	**16**	(95%)
18	R = R' = cyclo -C_8H_{12}-	**17**	(90%)
19	R = R' = Ph (*cis*)	**21**	(80%)

The above results raise two interesting points. The first is the sharp contrast between HOF·CH_3CN and the rest of the oxygen transfer agents, the latter producing the stable episulfoxides only, while the first delivers two oxygens to the sulfur atom resulting exclusively in episulfones.[10] The second point is rather more of a challenge, and it concerns the possibility of forcing the HOF·CH_3CN complex in producing episulfoxides in a clean reaction. To relate to these issues, we reacted first the episulfide **9** with *m*-CPBA forming the episulfoxide **22**[14] in 75% yield. An equimolar mixture of **9** and **22** was then prepared and reacted with only one molar equiv of HOF·CH_3CN. The resulting reaction mixture consisted of 45% episulfoxide **22** and a similar amount of the episulfone **10**, the balance being the starting sulfide (Scheme 2). This outcome indicates that the reagent reacted almost exclusively with the episulfide **9** leaving the

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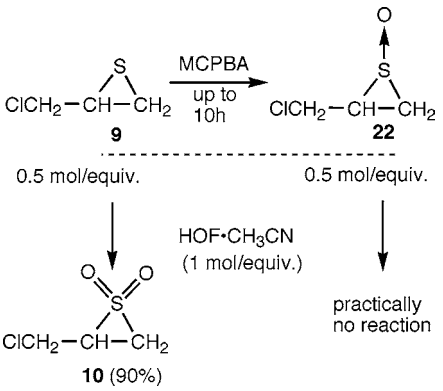
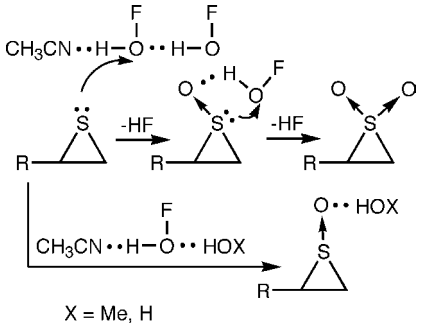
Scheme 2. Competitive Oxidation between Episulfides and Episulfoxides



episulfoxide **22** practically intact. Increasing the amount of the available electrophilic oxygen by increasing the HOF·CH_3CN concentration to nearly 1.8 molar equiv resulted in a full consumption of **9** along with the conversion of almost 40% of **22** to the episulfone **10**.

These results can be explained by the fact that HOF·CH_3CN possesses both an acidic hydrogen and a fluorine atom, a combination enabling the formation of a cluster made from the reagent's molecules by hydrogen bonding. Thus, while the episulfoxide is forming (or shortly afterward) a second molecule of the reagent is already in close proximity to the sulfur atom and can deliver the second oxygen atom before it has a chance to depart from the episulfoxide vicinity. To give experimental backing to this hypothesis, we repeated the oxidation of **9**, with both the reagent and episulfide prediluted with water and methanol, respectively. This provides additional centers for hydrogen bonding of both the HOF·CH_3CN and the resulting episulfoxide, reducing the chances for two molecules of the reagent to approach the reacting center at the same time (Scheme 3). In addition,

Scheme 3. Formation of Episulfones vs Episulfoxides

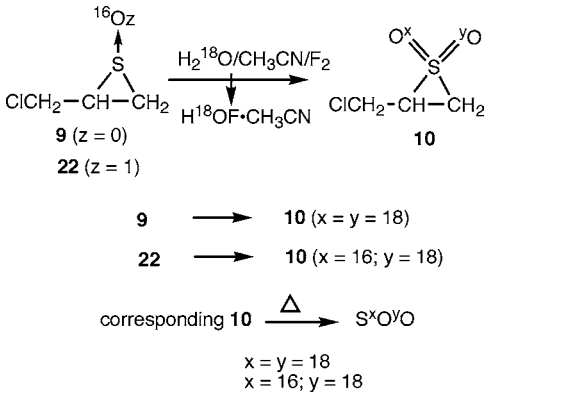


we lowered the reaction temperature to −78 °C by diluting the acetonitrile solution of the hypofluorous acid with propionitrile. The result was almost quantitative formation of the episulfoxide **22** with no detectable episulfone.[10]

Since the source of the transferred oxygen in this reaction is water, introducing any desirable oxygen isotope to the products is a relatively easy and economical process. The episulfide **9** can serve as an example. When reacted with $H^{18}OF{\cdot}CH_3CN$ it gave exclusively the [18]O episulfone **10**. The unequivocal evidence was provided by Amirav's supersonic molecular beam MS instrument,[15] using MeOH as a clustering agent[16] showing a molecular peak of m/z = 145 $(M + 1)^+$ along with the cluster peak m/z = 177 $(M + 1 + MeOH)^+$. Since any episulfoxide can also be converted to the corresponding episulfone, it is easy to show that reacting [16]O episulfoxide **22** with $H^{18}OF{\cdot}CH_3CN$ provides **10** with one of the oxygen atoms being the [16]O and the other [18]O isotope: m/z = 143 and 175 for the $(M + 1)^+$ and $(M + 1 + MeOH)^+$ ions, respectively. It should be noted that once the episulfones are made, the oxygen isotopes are not interchangeable with the oxygen atoms in the air or regular water.

While the introduction of the [18]O isotope into several organic molecules using $H^{18}OF{\cdot}CH_3CN$ has been described,[9] the labile episulfones offer an additional unique opportunity to synthesize easily and economically SO_2 with all possible oxygen isotope variations. Syntheses to this end had been performed in the past for studying many natural and other phenomena associated with SO_2.[17] Such molecules were obtained by burning sulfur in the environment of expensive $^{18}O_2$[18] (made from $H_2{}^{18}O$), difficult to control mixtures of $^{16}O_2$ and $^{18}O_2$,[19] or with the hard to get $^{18}O_3$.[20] The present reaction offers a direct way for making $S^{18}O_2$, $S^{16}O^{18}O$, and other variations simply by heating slightly the thermally unstable episulfones which decompose to SO_2 and the corresponding olefin. Here again, the supersonic cooled MS instrument helped to prove the point. The SO_2 obtained from the 16[O] episulfone **10** showed a strong molecular ion at m/z = 64 $(M)^+$, while the results from [16]O,[18]O-**10** or [18]O-**10** provided strong respective molecular ions of m/z = 66 (M^+ for $S^{16}O^{18}O$) and m/z = 68 (M^+ for $S^{18}O_2$) (Scheme 4).

Scheme 4. Incorporation of the [18]O Isotope into Episulfones and SO_2



In conclusion, HOF·CH_3CN made readily from F_2 is a powerful and versatile tool in general chemistry whenever

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transferring oxygen atoms to organic molecules is the subject. In the present work, this reagent serves as a tool for constructing the very rare family of episulfones which can, among other things, serve as a source for SO_2 with any variation of oxygen isotopes.

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Supporting Information Available: Complete experimental section including ^{1}H NMR, ^{13}C NMR, and IR data for all new compounds. Microanalysis data can also be found, although some episulfones were too unstable and started to lose weight (releasing SO_2) during the analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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