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Diastereoselective Oxidation of Substituted Thietanes and Stereoselective Oxidation of Their Sulfoxides

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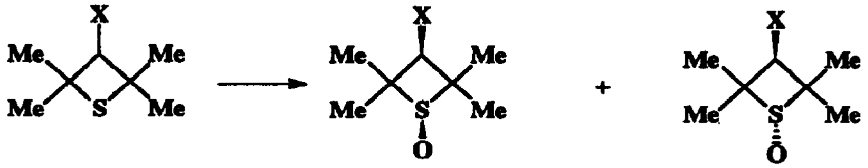
Abstract: *Oxidation of substituted thietanes 1a, b, and 6 with m-chloroperoxybenzoic acid preferentially gives the corresponding cis-sulfoxides with modest diastereoselectivity. Selective oxidation of the trans over the cis diastereomeric pairs of sulfoxides 2a, 3a; 2b, 3b; 7, 8 occurs with moderate selectivity with m-chloroperoxybenzoic acid. The basis for these selectivities is hydrogen bonding between the 3-substituent and the peracid.*

Stereochemical control in the oxidation of thioethers to sulfoxides has been much studied recently. Enantioselective oxidations, both enzymatic[1] and chemical,[2] have been reported. Diastereoselective oxidations are also well-known. However, diastereoselective oxidation of sulfoxides to sulfones is almost unknown. Recently Nakayama and coworkers[3] reported some examples. In this paper diastereoselective oxidations of sulfoxides which are more stereoselective than those of the corresponding thioethers and which have a different mechanistic basis for selectivity than those previously reported, are presented.

Oxidation of substituted thietanes **1a-d** with m-chloroperoxybenzoic acids (MCPBA) gave the corresponding diastereomeric sulfoxides **2** and **3** in the ratios reported in Table 1. To obtain accurate values the amount of peracid is limited so as to achieve partial oxidation of the starting thietane. Errors are introduced, if oxidation to the sulfone **4** occurs, for the reasons outlined below. The ratio of diastereomers was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture and after separation of the sulfoxides and starting material by preparative TLC on silica gel. The stereochemistry of the major diastereomer obtained by oxidation of **1a** was unequivocally proven to be **2a** by an X-ray crystallographic structure study. An ORTEP drawing of **2a** is shown in Figure 1.



1a, X=NHAc
b, X=NHCOPh
c, X=OH
d, X=OC(O)NHPh

2

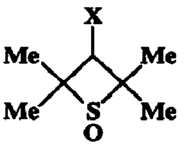
3

Table 1. Oxidation[a] of Substituted Thietanes to Sulfoxides

Compound	Ratio of Sulfoxides[b] 2(cis)	3(trans)
1a	8	3
b	2	1
c	1	1
d	1	1

[a] Oxidation using MCPA in CH_2Cl_2

[b] Determined by ^1H NMR spectroscopic analysis.



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5a, R=Me
b, R=tBu

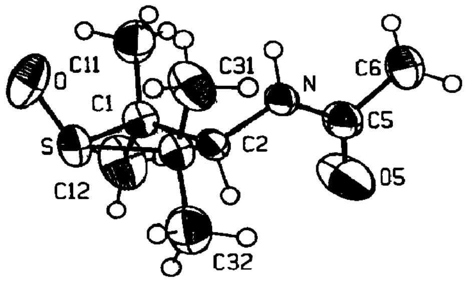


Figure 1. ORTEP Drawing of **2a**.

Thus, there is a modest diastereoselectivity in the oxidation of **1a** and **b** favoring the cis-isomer.[4,5] Siegl and Johnson reported[5] that oxidation of 3-alkylthietanes **5a** and **b** with MCPBA afforded the corresponding sulfoxides with a small preference for the trans isomer. These workers suggested that "approach to the sulfur atom of a puckered 3-alkyl thietane must be less hindered from the side trans to the substituent at C(3)."[5] Since attack on sulfur of **1a** and **b** occurs from the sterically more hindered side cis to the substituent, hydrogen bonding between this substituent and peracid must overcome this steric effect. Such a directing effect by a hydroxyl group[6] and an acetamido group[7] in the oxidation of thioethers has been reported before. Apparently, this effect is less important for **1c** and **d**. Because the directing effect of the 3-substituent would be greater in the axial position of a puckered thietane, compound **6** was prepared and its oxidation studied. An axial hydroxyl group is more favorable in this system than in **1c**. Indeed oxidation of **6** with MCPBA in CH_2Cl_2 produced the corresponding sulfoxides in a 2:1 diastereomeric ratio. The ratio of diastereomers was determined by ^{13}C NMR spectroscopic analysis. The structure of the major diastereomer was presumed to be **7**, with the hydroxyl group and sulfoxide oxygen cis. It should be noted that the 3-methyl group and sulfoxide oxygen are trans in this product, so that steric and hydrogen bonding effects both favor stereoselective formation of **7**.

Oxidation of the diastereomeric sulfoxides obtained from **1a**, **b**, and **6** proved much more selective than oxidation of the thietanes themselves. This was inadvertently discovered when an excess of MCPBA was added to thietane **1a**. Under these conditions only one diastereomeric sulfoxide was found. The results on the relative rate of oxidation of the isomeric sulfoxides are summarized in Table 2. These relative rates were

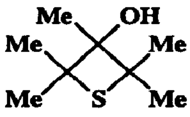
Table 2. Relative Rate of Oxidation[a] of Diastereomeric Thietane-1-Oxides

Compound	Rel. Rate of Oxidation[b]
3a:2a	13:2
3b:2b	15:2
3c:2c	1:1
3d:2d	1:1
8:7	3:1

[a]Oxidation using MCPBA in CH_2Cl_2

[b]Determined by ^1H NMR spectroscopic analysis for **3a:2a**, **3b:2b**, **3c:2c**, **3d: 2d** and ^{13}C NMR spectroscopic analysis for **8:7**.

determined by adding a limited amount of MCPBA to a mixture of diastereomers and measuring their ratio by ^1H NMR spectroscopy after partial oxidation. In the case of **7** and **8** the analysis was done using ^{13}C NMR spectroscopy.[8,9] As can be seen from Table 2 the trans isomers **3a**, **b** and **8** are much more rapidly oxidized than the corresponding cis-isomers **2a**, **b** and **7**. Consequently if excess MCPBA is added to these thietanes



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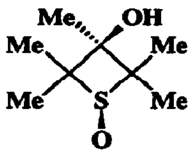

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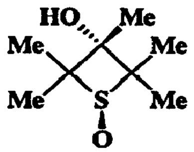

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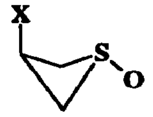
almost pure cis-sulfoxide can be obtained. The thietane is selectively oxidized to the cis-sulfoxide and the trans-sulfoxide is selectively oxidized to the sulfone leaving almost pure cis-isomer. The reason for the increased diastereoselectivity in oxidation of the sulfoxides over the thietanes is ascribed to the known preference of the sulfoxide oxygen for an equatorial orientation.[10] Consequently, the 3-substituent in the trans isomer is preferentially axial as shown in **9** and owing to hydrogen bonding it increases the rate of oxidation over the cis isomer in which the 3-substituent is equatorial as shown in **10**. As mentioned in the introduction Nakayama and coworkers reported[3] selective oxidation of isomeric sulfoxides. They ascribed the basis for this selectivity to 1,3-transannular interaction in the bridged 1,3-dithietanes they studied. The change of the



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SO stretching frequency in the IR for these compounds supported their suggestion. The SO stretching frequencies for each diastereomeric pair **1a**, **2a**; **1b**, **2b**; **7**, **8** is the same. Consequently, the basis for the diastereoselectivity reported in this paper and that for the cases reported by Nakayama and coworkers are different.

In sum the directing effect due to hydrogen bonding of 3-substituents in thietanes and their 1-oxides results in modestly diastereoselective oxidation to the cis-sulfoxide and moderately selective oxidation of the trans-sulfoxide over the corresponding cis-sulfoxide.

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9. The ratio of isomers was determined by integration of the methyl resonances in an inverse gated decoupled ^{13}C NMR spectrum of the mixture of **7** and **8** in CD_2Cl_2. The chemical shifts of the methyl groups of the major isomer were 16.04 (2Me), 22.06 (1Me), 23.42 (2Me) and for the minor isomer 17.37 (2Me), 22.42 (2Me), 22.68 (1Me) ppm at 62.9 MHz.
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