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Highly Chemoselective Oxidation of Dithioester Enethiolates to Sulfenates: Application to the Synthesis of Ketene Dithioacetal *S*-Oxides

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Abstract: Enethiolates derived from dithioesters were efficiently converted into the corresponding vinyl sulfenates by oxidation with a unique *N*-sulfonyloxaziridine **1a** derived from pinacolone. Subsequent alkylation with alkyl halides led to ketene dithioacetal *S*-oxides in good to excellent yields.

Ketene dithioacetal mono-*S*-oxides have proven to be useful intermediates in organic synthesis.[1] They can act as good Michael acceptors for a variety of nucleophiles, including enamines, enolates, and carbanions derived from imines or nitroalkanes.[2] In addition, they are efficient precursors of carboxylic acid derivatives[3] or thiocarbonyl compounds.[4] An original and high-yielding transformation into γ-hydroxyvinyl sulfides, which can serve as synthetic equivalents of β-hydroxy aldehydes, has also been reported.[5]

The two conventional preparative methods for these sulfoxides are based upon (i) oxidation[6] of the corresponding ketene dithioacetal, the best reagents being *m*-CPBA and $NaIO_4$, and (ii) the use of methyl (methylsulfanyl)methyl sulfoxide or functionalized derivatives as starting materials and creation of the double bond by Knoevenagel-type reactions,[7] Wittig−Horner condensations,[8] or elimination reactions.[9] A high (*E*)-stereoselectivity is generally achieved. A completely different approach involving a sulfine from a dithioester has also been described by the group of Zwanenburg, but is limited to a single substrate.[10] In this synthesis, α-deprotonation of the thiocarbonyl *S*-oxide generates a vinyl sulfenate that is captured in situ at the sulfur center by an alkyl halide.[11] This deprotonation/alkylation sequence suffers, however, from a few drawbacks such as the instability of the starting sulfine[5,12] and the requirement of a thallium base [thallium(I) ethoxide].[10,11] With all other bases, *O*-alkylation of the ambident sulfenate surprisingly occurs. The development of an efficient and general alternative pathway to the sulfenate intermediates could allow further investigation of this sequence.

We have previously reported[13] a highly efficient approach to aromatic sulfenates (ArSOLi) through oxidation of the corresponding thiolates (ArSLi) in which the unusual racemic *N*-sulfonyloxaziridine **1a**, derived from pinacolone,[14] was introduced as the optimal reagent (Scheme 1). Subsequent *S*-alkylation with aliphatic

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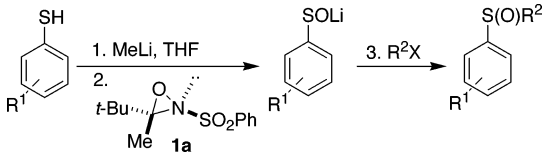
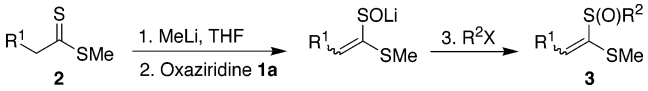
SCHEME 1. Aromatic Sulfoxides via Sulfenates



SCHEME 2. Ketene Dithioacetal *S*-Oxides 3 via Vinyl Sulfenates



halides led to sulfoxides in good to excellent yield. Earlier examples of this oxidation reaction in the sulfur series are scarce, the few oxidizing reagents that were tested (*m*-CPBA, hydroperoxides) having proven insuitable.[15] As a consequence, applications of this concept in organic synthesis have hitherto remained unexploited. The mild conditions we have developed (−78 °C) have broadened the scope of this reaction quite considerably, with good chemoselectivity and tolerance of a wide range of substrates.

These results suggested to us that α,*β*-unsaturated sulfenates could, in principle, be prepared by oxidation of the corresponding enethiolates, which are readily available by deprotonation[16] of dithioesters (Scheme 2). An important feature of this sequence would be to start this time from a stable thiocarbonyl compound. Furthermore, if the overall sequence proceeds with retention of the enethiolate geometry, the (*Z*)-isomer should be predominantly produced.[17] Inadequate chemoselectivity is, however, a potential problem as there could be competitive oxidation of two other sites in the molecule, namely the alkylthio substituent and the monosubstituted carbon atom of the double bond. The latter is known to occur readily at low temperature in the corresponding oxygenated series, thereby yielding α-hydroxy carbonyl compounds.[18,19] In contrast, the thioether function should be unaffected, as oxidation of the methylsulfanyl functionality in thioanisole with oxaziridine **1a** (1 equiv) took more than 1 day at room temperature to go to completion.[13a] In this paper we present the results obtained with this oxidation approach.

The choice of base for the generation of the enethiolate followed an extensive study that identified methyllithium as the optimal reagent. Use of amides such as LDA, NaHMDS, or KHMDS led to complex mixtures, suggesting unwanted side reactions with the liberated secondary amine. We began our investigations by examining a simple example in which the stereochemistry was not a concern. Dropwise addition of oxaziridine **1a** (1 equiv) to the anion of dithioacetic acid methyl ester **2a** (R^1 = H), generated by deprotonation with methyllithium at −78 °C, resulted in a spontaneous reaction in which all the oxidant was consumed. Treatment of the resulting colorless solution with methyl iodide (1 equiv) at −78 °C, followed by warming to room temperature and hydrolysis with ammonium chloride solution, gave an extremely clean crude product, consisting of the anticipated dithioacetal *S*-oxide $\mathbf{3a_1}$ and benzenesulfonamide.[20] The latter was easily removed by precipitation from dichloromethane/pentane and the sulfoxide $\mathbf{3a_1}$ purified by column chromatography and isolated in 79% yield (Table 1, entry 1). Using benzyl bromide as an alternative electrophile, the analogous benzylic sulfoxide $\mathbf{3a_2}$ was produced in 56% yield (entry 2). An important point to note is that hydroxy and methylsulfinyl products were not detected, thus revealing complete chemoselectivity in favor of the negatively charged sulfur center. Furthermore, alkylation with the soft alkyl halide took place at the soft sulfur center of the sulfenate.

With these results in hand, the procedure was next applied to dithioester **2b** (R^1 = Me). Treatment of the intermediate sulfenate with methyl iodide at −78 °C (conditions B) led to the formation of ketene dithioacetal *S*-oxide $\mathbf{3b_1}$ in 61% yield as a 76:24 mixture of the (*Z*) and (*E*) isomers, which reflected perfectly the stereoselectivity of the initial deprotonation (entry 3).[21] This configuration was assigned on the basis of literature data[22] and further confirmed by NMR spectra in the presence of europium[23] shift reagents. The reaction was then repeated on the same substrate, but this time the temperature of the sulfenate solution was allowed to rise slowly to −15 °C before exposure to the electrophile (conditions C). This afforded sulfoxide $\mathbf{3b_1}$ in 80% yield, but with an almost completely inverted isomeric ratio (13:87, entry 4). An intermediate situation with a 54:46 mixture of isomers was obtained when removing the cold bath at −78 °C immediately after introduction of the electrophile (entry 5, conditions D). A similar switch in favor of the (*E*) isomer was likewise observed when using benzyl bromide and ethyl iodide as alternative electrophiles under conditions C (entries 6 and 7).[24] The resulting diastereoisomeric sulfoxides of $\mathbf{3b_1}$, $\mathbf{3b_2}$, and $\mathbf{3b_3}$ were

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(16) Metzner, P. *Synthesis* **1992**, 1185−1199.

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(20) The imine byproduct of the oxidation reaction undergoes hydrolytic cleavage to benzenesulfonamide and the volatile pinacolone.

(21) The cis:trans ratio of the enethiolates obtained by deprotonation of dithioesters **2** with methyllithium was determined by conversion into the corresponding ketene dithioacetals with an ethyl iodide quench and ^{1}H NMR analysis of the crude product, based on the vinyl hydrogen and the SCH_2 protons (see the Supporting Information).

(22) Remarkable differences are observed in the ^{1}H NMR data of the pair of (*Z*) and (*E*) isomers. The vinylic proton in the (*Z*) series occurs at approximately δ 6.3 ppm but is substantially deshielded at around 6.8 ppm in the corresponding (*E*) isomer. (a) Cazes, B.; Huynh, C.; Julia, S.; Ratovelomanana, V.; Ruel, O. *J. Chem. Res.* (*M*) **1978**, 957−968. (b) Seebach, D.; Bürstinghaus, R.; Gröbel, B.-T.; Kolb, M. *Liebigs. Ann. Chem.* **1977**, 830−845.

(23) The sulfinyl functional group is known to bind strongly to lanthanide shift reagents, as a result of which any vinyl hydrogens cis to this moiety are shifted noticeably downfield. $Eu(fod)_3$ was used for the spectra recorded with compounds $\mathbf{3b_1}$ and $\mathbf{3b_2}$. See the Supporting Information. (a) Dannhardt, G.; Kiefer, W. *Arch. Pharm.* (*Weinheim, Ger.*) **1994**, *327*, 509−514. (b) Mazzanti, G.; van Helvoirt, E.; van Vliet, L. A.; Ruinaard, R.; Masiero, S.; Bonini, B. F.; Zwanenburg, B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3299−3304. (c) Schwan, A. L.; Roche, M. R.; Gallagher, J. F.; Ferguson, G. *Can. J. Chem.* **1994**, *72*, 312−324.

TABLE 1. Ketene Dithioacetal *S*-Oxides 3 from Dithioesters 2 According to Scheme 2

entry	dithioester	R^1	R^2	sulfoxide	alkylation conditions[a]	yield (%)	(*Z*):(*E*)[b]	deprotonation cis:trans[c]
1	**2a**	H	Me	**3a$_1$**	A	79		
2	**2a**	H	Bn	**3a$_2$**	A	56		
3	**2b**	Me	Me	**3b$_1$**	B	61	76:24	75:25
4	**2b**	Me	Me	**3b$_1$**	C	80	13:87	75:25
5	**2b**	Me	Me	**3b$_1$**	D	76	54:46	75:25
6	**2b**	Me	Bn	**3b$_2$**	C	66	22:78	75:25
7	**2b**	Me	Et	**3b$_3$**	C	76	15:85	75:25
8	**2c**	*n*-Pr	Me	**3c$_1$**	B	58	79:21	81:19
9	**2d**	*n*-Oct	Me	**3d$_1$**	B	85	74:26	76:24
10	**2d**	*n*-Oct	Me	**3d$_1$**	C	62	42:58	76:24
11	**2e**	Ph	Me	**3e$_1$**	B	26	58:42	63:37

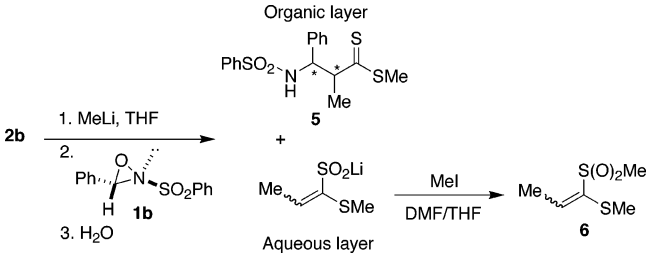
[a] Conditions A: Slow warming from −78 °C to rt in the presence of the electrophile (1.1 equiv). Conditions B: −78 °C/5 h in the presence of the electrophile (5 equiv). Conditions C: Slow warming from −78 to −15 °C, followed by addition of the electrophile (1.1−2 equiv). Conditions D: Rapid warming from −78 °C to rt in the presence of the electrophile (1. equiv). [b] Determined by ^{1}H NMR of the crude product. [c] Determined by reaction of the enethiolate with ethyl iodide.

easily separated by column chromatography on silica gel. Enethiolates and the final sulfoxides being configurationally stable,[16] these observations suggest that the intermediate sulfenates, which initially have a cis geometry, can undergo isomerization into the thermodynamically stable trans anion. The reaction temperature is therefore of critical importance to the product diastereoselectivity (alkylation is rather slow at low temperature), though the initial configuration remains stable for as long as the low temperature is maintained.

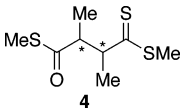
The reaction has been further extended to three other dithioesters **2c**−**e** with iodomethane in each case employed as the electrophile. A series of ketene dithioacetal monoxides **3** was thus prepared and, with performance of the entire sequence at −78 °C (conditions B), the diastereomeric ratios were identical with those of the enethiolate precursors[21] (entries 8, 9, and 11). In all cases, both double bond isomers were separable by purification on silica gel and the stereochemistry was assigned on the basis of NMR data.[22,25] Isomerization of the intermediate sulfenate under conditions C was once again observed in the case of dithioester **2d** (entry 10).

The oxidation was also investigated by using the classical benzaldehyde-derived *N*-sulfonyloxaziridine **1b** (Scheme 3).[26] Upon addition of the oxidizing solution, an obvious difference was apparent, with the reaction mixture immediately developing a bright orange color characteristic of a dithioester function. After treatment with an alkyl halide and workup, no sulfoxide was produced and instead amino dithioester **5** was isolated in 43% yield as a single diastereoisomer.[27] Rationalizing this finding by comparison with the results previously obtained by us with the same reagent in the thiophenol series,[28] it is likely that (i) oxidation of the enethiolate selectively afforded the corresponding sulfinate salt (i.e. the double oxidation product) with (ii) nucleophilic addition of the enethiolate on the liberated *N*-sulfonylimine PhCH=NSO_2Ph resulting in adduct **5** as a sideproduct and that (iii) the absence of any significant alkylation in the THF solution led to extraction of the sulfinate into the aqueous layer. Thus, with a modification of the original reaction conditions, concentration of the aqueous layer followed by treatment with methyl iodide in THF/DMF led to vinyl sulfone **6** in 21% yield.[29] Both diastereoisomers were produced in a 56:44 ratio, but separation by column chromatography on silica gel was unsuccessful. The origin of this difference in behavior between **1a** and **1b** is unclear: it might be a consequence of steric effects or electronic factors or it may simply reflect a difference in oxidizing power. A noteworthy observation that should be pointed out is that sulfenate anions, whose structure contains an unshared electron pair adjacent to the sulfur center, are considered to be α-nucleophiles[30] with heightened reactivity, therefore the double oxidation reaction leading to the sulfinate ought to be preferred.[31]

SCHEME 3. Oxidation with Oxaziridine 1b



(24) The sulfenate formed from dithioester **2b** was also subjected to a simple aqueous workup, resulting in the isolation of thiolester **4** in 25% yield as a 83:17 mixture of two diastereoisomers. Its formation can be interpreted by the following pathway: protonation of the oxidized anion to give the sulfenic acid, dimerization into the corresponding thiosulfinate with elimination of H_2O, Claisen rearrangement into a sulfine, and finally rearrangement, via an oxathiirane, with loss of elemental sulfur (see the Supporting Information).



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(25) In the case of compound **3e$_1$**, which has a phenyl substituent, a 0.7 ppm downfield shift is observed for the vinylic proton, but the singlet for the (*Z*) isomer again occurs at higher field (δ 7.00 against 7.63 ppm).

(26) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703−5742.

(27) The relative configuration was not determined.

(28) Sandrinelli, F.; Perrio, S.; Beslin, P. *Org. Lett.* **1999**, *1*, 1177−1180.

(29) The yield is calculated from the dithioester based on an optimum value of 50%, as a single equivalent of oxidant is used.

(30) Kice, J. L.; Cleveland, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 104−109.

(31) (a) Davis, F. A.; Billmers, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 7016−7018. (b) Davis, F. A.; Rizvi, S. Q. A.; Ardecky, R.; Gosciniak, D. J.; Friedman, A. J.; Yocklovich, S. G. *J. Org. Chem.* **1980**, *45*, 1650−1653. (c) Refvik, M. D.; Schwan, A. L. *Can. J. Chem.* **1998**, *76*, 213−220.

In conclusion, we have shown that our methodology for the oxidation of anionic sulfur centers using the pinacolone-derived *N*-sulfonyloxaziridine **1a** can be successfully extended to enethiolates from dithioesters as substrates. *S*-alkylation of the resulting vinyl sulfenates with an alkyl halide affords ketene dithioacetal *S*-oxides in good yield. The overall sequence provides an original and straightforward route to these compounds, the major advantage of being carried out in one pot starting from the thiocarbonyl precursor. Despite the sulfenate, which has an initial cis geometry, being prone to isomerization, complete retention of configuration is achieved if the reaction temperature is maintained at −78 °C. The (*Z*) geometry of the sulfoxide thus available is the opposite of that observed with the more conventional routes involving, for example, oxidation of the ketene dithioacetal. By contrast, using the classical oxaziridine **1b** derived from benzaldehyde, a competing double oxidation produces a vinyl sulfinate, with isolation of a sulfone as the alkylation product. Future work will seek to broaden to other substrates the unique reactivity of oxaziridine **1a** and to develop further applications of sulfenate chemistry in organic synthesis.

Experimental Section

General Procedure for the Synthesis of Ketene Dithioacetal *S*-Oxides 3. A solution of dithioester **2** (1.00 mmol) in anhydrous THF (5 mL) was cooled to −78 °C and MeLi (0.69 mL of a 1.6 M solution in Et_2O, 1.1 mmol) was added dropwise. Discoloration of the orange reaction mixture was immediately observed. After being stirred at −78 °C for 15 min, a solution of oxaziridine **1a** (267 mg, 1.05 mmol) in anhydrous THF (2 mL) was slowly added dropwise (exothermic reaction). The reaction mixture was stirred at this temperature for 20 min and treated with the alkyl halide (1−5 equiv). The solution was stirred at −78 °C for 5 h and then hydrolyzed at this temperature with saturated aqueous NaCl (3 mL). The product was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were dried over magnesium sulfate, filtered, and evaporated to dryness. A 7:1 pentane:dichloromethane mixture was added to precipitate the benzenesulfonamide byproduct from the crude mixture. After filtration and concentration under reduced pressure the resulting yellow oil was analyzed by ^1H NMR to determine the diastereoisomeric ratio and purified by column chromatography (silica gel, petroleum ether/ethyl acetate mixtures) to give the anticipated sulfoxides **3**. The individual diastereoisomers were separated and isolated in the same proportions as were observed in the crude material.

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Supporting Information Available: General experimental methods, stereoselectivity for deprotonation of dithioesters **2**, summary of lanthanide shift experiments with sulfoxides $\mathbf{3b_1}$ and $\mathbf{3b_2}$, full spectroscopic data for **3**−**6**, experimental procedures for **5** and **6**, mechanism for the generation of **4**, and $^1H-^{12}C$ COSY of sulfone **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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