Oxaziridine-Mediated Oxidation Reaction of Thiolates To Give Sulfenates: The First One-Pot Synthesis of Sulfoxides from Thiols

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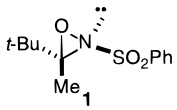
The oxidation of thiolates (RS^-) to sulfenates (RSO^-) is not a common reaction in organic chemistry[1] and has been reported in only three papers[2] to date. Furthermore, the examples described are too specific for this reaction to be generally applicable in synthesis.[3] This lack of examples stems from the following reasons: (i) sulfenate anions are of limited stability,[4] (ii) a competitive oxidative pathway leading to symmetrical disulfides may occur,[1,5] (iii) the oxidizing agents employed up to now, *m*-CPBA and hydrogen peroxide,[2,3] were not particularly well suited to this task. Because of this, we reasoned that a switch to a totally different type of oxidant might bring about significant improvements. *N*-Sulfonyloxaziridines are known to convert thiols into sulfenic acids.[6] Since thiolate anions have somewhat greater nucleophilicity, we thought we might achieve some interesting results with this class of oxidant. Initial attempts using the classical Davis oxaziridine[7] derived from benzalhehyde were unsuccessful. We then turned to the novel ketone-derived oxaziridine **1**,[8] in which the oxaziridine carbon atom is now a quaternary center with methyl and *tert*-butyl substituents. In this paper we wish to report the results obtained using this oxidant, which have led to the development of an elegant method for the generation and subsequent synthetic application of sulfenate anions.



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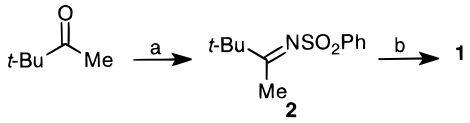
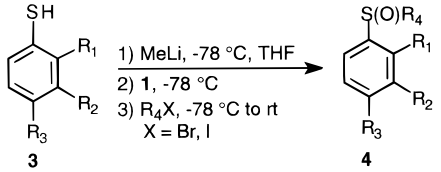
The *N*-sulfonyloxaziridine **1** was prepared in two steps as follows (Scheme 1). Equimolar amounts of pinacolone, benzenesulfonamide, and titanium tetrachloride were heated to reflux in 1,1,2-trichloroethane for 14 h, affording the *N*-sulfonylimine **2** in 73% crude yield. The crude material was sufficiently pure to be used subsequently without further purification. Imine **2** was then converted into the corresponding oxaziridine **1** with pure *m*-CPBA[9] in a CH_2Cl_2/H_2O biphasic system buffered with K_2CO_3. The oxaziridine **1** was isolated in 84% yield after recrystallization from hexane and was obtained as a single geometric isomer, as indicated by the presence, in the ^1H and ^{13}C NMR spectra, of a single set of signals for both the methyl and *tert*-butyl substituents. A trans geometry was unambiguously assigned after analysis of these spectra and comparison with those of known oxaziridines[10] previously obtained as a mixture of cis/trans diastereoisomers.

Scheme 1[a]



[a] Reagents and conditions: (a) $PhSO_2NH_2$, $TiCl_4$, $ClCH_2CHCl_2$, reflux, 14 h, 73%; (b) *m*-CPBA (100%), $CH_2Cl_2/H_2O/K_2CO_3$, rt, 1.5 h, 84%.

Table 1



entry	thiol	R_1	R_2	R_3	R_4	sulfoxide[a]	isolated yield (%)
1	**3a**	H	H	H	Me	**4a$_1$**	89[14a]
2	**3a**	H	H	H	Et	**4a$_2$**	83[14b]
3	**3a**	H	H	H	*i*-Pr	**4a$_3$**	66[14b]
4	**3a**	H	H	H	Bn	**4a$_4$**	79[14c]
5	**3b**	*t*-Bu	H	H	Me	**4b$_1$**	70
6	**3c**	F	H	H	Me	**4c$_1$**	85[14d]
7	**3d**	OMe	H	H	Me	**4d$_1$**	89[14e]
8	**3e**	H	CF_3	H	Me	**4e$_1$**	75[14f]
9	**3f**	H	H	SEt	Me	**4f$_1$**	71

[a] The electrophiles employed to introduce the R_4 substituent were MeI (1.1 equiv), EtI (5 equiv), *i*-PrI (5 equiv), and $PhCH_2Br$ (1.1 equiv).

The protocol we have developed involves three consecutive reactions carried out in one pot (Table 1): deprotonation of the thiol **3** to generate the corresponding thiolate, oxidation with oxaziridine **1**, and finally reaction with an alkyl halide to trap the intermediate sulfenate anion. Although sulfenate ions can act as ambident

(1) *The Chemistry of Sulfenic Acids and their Derivatives-The Chemistry of Functional Groups*; Patai, S., Ed.; Wiley: Chichester, 1990.

(2) (a) Heckel, A.; Pfleiderer, W. *Tetrahedron Lett.* **1983**, *24*, 5047−5050. (b) Hogg, D. R.; Rashid, M. A. M. *J. Chem. Res. (S)* **1988**, 160−161. (c) Ishii, A.; Komiya, K.; Nakayama, J. *J. Am. Chem. Soc.* **1996**, *118*, 12836−12837.

(3) The oxidation of silver 1,3,6-trimethyllumazine-7-thiolate to the corresponding silver sulfenate with 1 equiv of H_2O_2 has been reported without description of the conditions and the yield.[2a] A sodium sulfenate was identified by ^{19}F NMR spectroscopy in the products from the reaction of sodium 2-nitro-4-(trifluoromethyl)benzenethiolate with 0.5 equiv of H_2O_2.[2b] More recently a stable thiophenetriptycene-8-sulfenic acid has been prepared in 70% yield by oxidation of the corresponding sodium thiolate with *m*-CPBA.[2c]

(4) Weigand, W.; Wünsch, R. *Chem. Ber.* **1996**, *129*, 1409−1419.

(5) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS Monograph 186, American Chemical Society: Washington, DC, 1990.

(6) (a) Davis, F. A.; Billmers R. L. *J. Am. Chem. Soc.* **1981**, *103*, 7016−7018. (b) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703−5742. In a recent paper a stable sulfenic acid was synthesized by direct oxidation of a thiol with PhIO, and its X-ray structure and unique reactivities were revealed: (c) Goto, K.; Holler, M.; Okazaki, R. *J. Am. Chem. Soc.* **1997**, *119*, 1460−1461.

(7) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203-210.

(8) The use of oxaziridine **1** for the hydroxylation of a β-lactam is reported in a single paper. Its preparation is not, however, described, and the reasons for choosing this unusual oxaziridine are not given; Shimizu, M.; Ishida, T.; Fujisawa, T. *Chem. Lett.* **1994**, 1403−1406.

(9) Derbesy, G.; Harpp, D. N. *Sulfur Lett.* **1995**, *19*, 1−10.

(10) (a) Jennings, W. B.; Watson, S. P.; Boyd, D. R. *J. Chem. Soc., Chem. Commun.* **1988**, 931−932. (b) Jordan, G. J.; Crist, D. R. *Org. Magn. Reson.* **1977**, *9*, 322−324. Additional details about the assignment of stereochemistry to the oxaziridine **1** are provided as Supporting Information.

(11) (a) Crumbie, R. L.; Ridley, D. D. *Aust. J. Chem.* **1981**, *34*, 1017−1026. (b) Bonini, B. F.; Maccagnani, G.; Mazzanti, G.; Zani, P. *Gazz. Chim. Ital.* **1990**, *120*, 115−121. (c) Hogg, D. R.; Robertson, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1125−1128. (d) Jones, D. N.; Kogan, T. P.; Newton, R. F.; Smith, S. *J. Chem. Soc., Chem. Commun.* **1982**, 589−591. (e) Refvik, M. D.; Froese, R. D. J.; Goddard, J. D.; Pham, H. H.; Pippert, M. F.; Schwan, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 184−192.

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nucleophiles by reaction either at sulfur to give sulfoxides or at oxygen to form sulfenic esters, the sulfoxide **4** should still be the main, if not sole, product.[11] The selective *S*-alkylation generally observed is in accordance with the accepted concepts of hard and soft acids and bases.[12]

We began by subjecting thiophenol **3a** to the deprotonation/oxidation/alkylation sequence (Table 1, entries 1−4). Thiophenol **3a** was deprotonated at low temperature with MeLi (1 equiv) in THF to give the corresponding lithium thiolate. Dropwise addition of oxaziridine **1** (1 equiv) at −78 °C resulted in an immediate reaction in which all the oxidant was consumed according to TLC. Treatment of the resulting solution with an alkyl halide followed by hydrolysis with aqueous ammonium chloride solution gave an extremely clean crude product on workup, consisting of only two species, the anticipated sulfoxide **4a** and benzenesulfonamide (the imine **2** formed from the oxidation reaction is cleaved to benzenesulfonamide and the volatile pinacolone during hydrolysis). Benzenesulfonamide was then easily removed by precipitation from dichloromethane:pentane. The sulfoxides **4a** were further purified by column chromatography and were obtained in good to excellent isolated yields.

A few points relating to the sequence overall are worthy of note. The oxidation of the thiolate proceeded smoothly without any evidence of diphenyl disulfide formation. The requisite temperature is much lower compared with oxaziridine-mediated oxidations of other sulfur-containing functional groups, i.e., sulfides or sulfoxides.[6b] The transient sulfenate anion was captured exclusively at sulfur, with no contamination from the sulfenic ester that is the product of the competing *O*-alkylation.[13] A single molar equivalent of methyl iodide or benzyl bromide traps the sulfenate efficiently, whereas an excess is required with less reactive electrophiles, e.g. ethyl iodide or isopropyl iodide. It should also be noted that alkylation could not be achieved with isopropyl bromide.

The present reaction has been further extended to a range of substituted aromatic thiols. The results obtained are summarized in Table 1. In all cases, the desired sulfoxides **4** were formed and isolated in good to excellent yield, thus demonstrating compatibility with a variety of different substituents.

Oxidation of thiol **3f**, with an ethylsulfenyl substituent, led to the isolation in 71% yield of a single sulfoxide **4f$_1$**, via a completely chemoselective oxidation reaction (Table 1, entry 9) in which the oxaziridine oxidized the thiolate sulfur center without affecting the sulfide group at all. In contrast, oxidation of the bis-sulfide **5** with the same oxaziridine gave a complex mixture.[15] The major components, formed in a 1:1 ratio, were identified as the two mono-sulfoxides **4f$_1$** and **6**.

Summarizing, we have introduced the first efficient and fairly general method for the oxidation of aromatic thiolates[16] to the corresponding sulfenates. The oxidant employed is an unusual oxaziridine. This oxidation reaction, combined with in situ trapping of the sulfenate that is formed, shows exceptional promise as a convenient approach to the synthesis of sulfoxides. This methodology is highly competitive with the existing repertoire.[17] Its advantages include its good to excellent yields, ease of purification, tolerance of a wide range of substrates, and high chemoselectivity. Above all it is able to be performed in one pot from thiols. The classical preparation of sulfoxides from thiols is carried out in two steps with the initial formation of the sulfide followed by oxidation, isolation of the sulfide being necessary to avoid overoxidation.[17] The application of the above methodology to the synthesis of optically pure sulfoxides is currently under investigation along with the reactivity of the sulfenates toward other electrophiles.

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Supporting Information Available: Experimental procedures and spectral data of compounds **1**, **2**, **4b$_1$**, **4f$_1$**, and **6** reported herein (12 pages).

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(12) Pearson, R. G. *Hard and Soft Acids and Bases*; Sisler, H. H., Ed.; Dowden, Hutchinson and Ross: Stroudsburg, 1973.

(13) A dramatic influence of the solvent was observed. For example, mixtures of *S*- and *O*-alkylation products were isolated when the alkylation reaction was carried out in the presence of DMF.

(14) (a) Weber, J. V.; Schneider, M.; Salami, B.; Paquer, D. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 99−102. (b) Hojo, M.; Masuda, R.; Saeki, T.; Fujimori, K., Tsutsumi, S. *Synthesis* **1977**, 789−791. (c) Kakarla, R.; Dulina, R. G.; Hatzenbuhler, N. T.; Hui, Y. W.; Sofia, M. J. *J. Org. Chem.* **1996**, *61*, 8347−8349. (d) Benassi, R.; Folli, U.; Iarossi, D.; Mucci, A.; Schenetti, L.; Taddei, F. *J. Chem. Soc., Perkin Trans. 2* **1989**, 517−522. (e) Pérez-Encabo, A.; Perrio, S.; Slawin, A. M. Z.; Thomas, S. E.; Wierzchleyski, A. T.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 629−642. (f) Andersen, K. K.; Edmonds, W. H.; Biasotti, J. B.; Strecker, R. A. *J. Org. Chem.* **1966**, *31*, 2859−2861.

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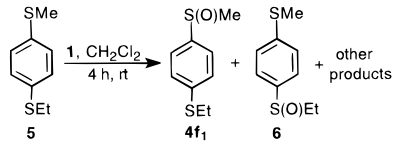

5 4f$_1$ 6

(16) Starting with aliphatic thiolates, the expected sulfoxides were not formed. Investigations on this reaction are currently in progress.

(17) Madesclaire, M. *Tetrahedron* **1986**, *42*, 5459−5495.