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A New Reaction of 2-(Phenylsulfonyl)-3-phenyloxaziridine (Davis Reagent): Oxidation of Thiolates to Sulfinates. Application to the Synthesis of Sulfones

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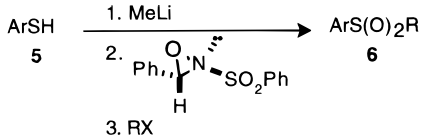
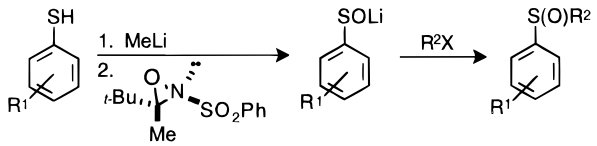
ABSTRACT



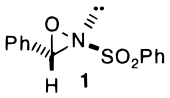
The first efficient and general method for the generation of sulfinate anions by oxidation of the corresponding thiolates is described. The oxidizing agent employed is the classical 2-(phenylsulfonyl)-3-phenyloxaziridine, commonly known as the Davis reagent. Subsequent *S*-alkylation of the sulfinates under phase-transfer catalysis affords sulfones 6 in 71–91% isolated yields (10 examples).

We have recently reported the first efficient procedure for the oxidation of aromatic thiolates (ArS^-) into the corresponding sulfenates ($ArSO^-$).[1] The oxidant employed was an unusual racemic *N*-sulfonyloxaziridine[2] derived from pinacolone. In situ *S*-alkylation of the sulfenate anion with aliphatic halides led to sulfoxides in good to excellent yields (Scheme 1). The overall sequence allowed a new and convenient synthesis of sulfoxides from thiols, with the major advantage[3] of being executable in one pot.

Scheme 1



In this Letter are described the different results obtained with our initial investigations using classical (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine[4] **1**, commonly known as the Davis reagent.[5]



A preliminary experiment starting from disubstituted thiophenol **2**[6] quickly established that the reaction of the corresponding lithium thiolate with 1 equiv of the Davis oxaziridine[7] **1** under the previously used conditions, followed by addition of ethyl iodide, did not result in the formation

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(1) Sandrinelli, F.; Perrio, S.; Beslin, P. *J. Org. Chem.* **1997**, *62*, 8626−8627.

(2) Shimizu, M.; Ishida, T.; Fujisawa, T. *Chem. Lett.* **1994**, 1403−1406.

(3) Hall, N. *Science* **1994**, *266*, 32−34.

(4) (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703−5742. (b) Davis, F. A.; Haque, M. S. Oxygen-Transfer Reactions of Oxaziridines. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI Press INC.: Greenwich, 1990; Vol. 2, pp 61−116. (c) Chen, B.-C.; Davis, F. A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 6, pp 4054−4057.

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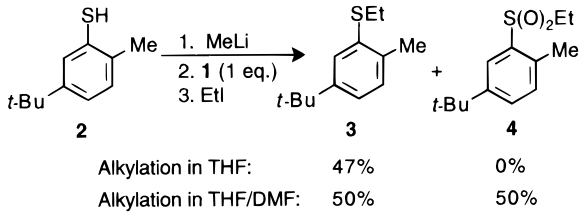
of the expected sulfoxide. Instead, sulfide **3** was produced and isolated in 47% yield (Scheme 2).[8] This result was

Scheme 2



particularly intriguing, since TLC analysis of the reaction mixture immediately after addition of the oxaziridine revealed complete consumption of the oxidant, but without detection in the crude mixture of any oxidation products. We finally reasoned that (i) the Davis reagent had oxidized the thiolate twice to afford a 1:1 mixture of the sulfinate salt ($ArSO_2^-$) and unreacted thiolate (ArS^-)[9] and that (ii) the alkylation step had failed to trap the sulfinate salt,[10,11] which had then undergone extraction into the aqueous layer on workup.[12] Sulfide **3** was also isolated as the sole product when the reaction was repeated with either a large excess of electrophile (10 equiv) or an extended reaction time of up to 3 days. However, on addition of an equal volume of DMF to the THF solution,[11] alkylation of both presumed sulfur species occurred and we were able to isolate an equimolecular mixture of sulfide **3** and sulfone **4** (Scheme 2). Analogies can be drawn with various literature observations.[13] Davis' group showed that *tert*-butanethiol was preferentially oxidized by oxaziridine **1** to the corresponding sulfinic acid even in the presence of a large excess of thiol.[13a] The reason for this is that the intermediate sulfenic acid is an "α-effect" nucleophile[14] which is much more nucleophilic than the thiol. Similarly, treatment of trialkyl(phenylthio)-silanes $PhSSiR_3$ with 1 equiv of oxaziridine **1** or *m*-CPBA afforded a 50% yield of the corresponding trialkylsilyl benzenesulfinates $PhS(O)OSiR_3$.[13b,c]

On the basis of these results, we reasoned that by using 2 equiv of oxaziridine **1** we might effect complete conversion into the sulfinate, thereby providing straightforward access to these species and thence to sulfones.[15] Particularly noteworthy is that despite some inspired efforts directed at this oxidative transformation, there is still no practical and efficient general procedure available.[16−18] A major reason for this is probably the lack of suitability of the few oxidants so far investigated (molecular oxygen,[16a−f] superoxide anion,[16g] iodine,[16h] and hydrogen peroxide[16i]). Following the same procedure as above, but using 2 equiv of oxidant **1**, an 80% yield of sulfone **4** was obtained.

(5) See, for example: (a) Pearson, A. J.; Chang, K. *J. Org. Chem.* **1993**, *58*, 1228−1237. (b) Mithani, S.; Drew, D. M.; Rydberg, E. H.; Taylor, N. J.; Mooibroek, S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1997**, *119*, 1159−1160.

(6) This aromatic thiol was used for much of the initial work owing to its ease of handling (not malodorous, relatively high molecular weight).

(7) The oxaziridine is readily prepared by literature procedures from benzaldehyde via an *N*-sulfonylimine: (a) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203−210. (b) Davis F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy T. *J. Org. Chem.* **1988**, *53*, 2087−2089.

(8) The imine $PhCH{=}NSO_2Ph$ derived from the oxaziridine was present in the crude product. Small amounts of benzaldehyde and benzenesulfonamide, resulting from partial hydrolysis of the imine on workup, were also detected.

(9) Similar results involving a selective double oxidation have also been observed in transition metal chemistry with ruthenium[9a] and tungsten[9b] thiolates. The oxidants employed were respectively dimethyldioxirane and *m*-CPBA: (a) Schenk, W. A.; Frisch, J.; Adam, W.; Prechtl, F. *Inorg. Chem.* **1992**, *31*, 3329−3331. (b) Weinmann, D. J.; Abrahamson, H. B. *Inorg. Chem.* **1987**, *26*, 3034−3040.

(10) Sulfinates are ambident nucleophiles. With soft electrophiles such as alkyl halides, the alkylation occurs predominantly at sulfur to give sulfones: Simpkins N. S. *Sulphones in Organic Synthesis*; Baldwin, J. E., Magnus P. D., Eds.; Pergamon Press: Oxford, 1993; Vol. 10, pp 11−15.

(11) The failure of the alkylation reaction of lithium alkenylsulfinate salts with THF as solvent has already been reported: Dishington, A. P.; Douthwaite, R. E.; Mortlock, A.; Muccioli, A. B.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 323−337.

(12) (a) For a recent example of sulfinate salt extraction from an organic phase on aqueous workup, see: (a) Fleming, I.; Frackenpohl, J.; Ila, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1229−1235. Sulfinate salts are not protonated by simple workup; for example, the pK_a value of benzenesulfinic acid is 1.29: (b) Veltwisch, D.; Janata, E.; Asmus, K. D. *J. Chem. Soc., Perkin Trans. 2* **1980**, 146−153.

(13) (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.

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

(15) For a mild and simple preparation of sulfinates, sulfonyl chlorides, and sulfonamides from thioanisoles, see: De Vleeschauwer, M.; Gauthier, J. Y. *Synlett* **1997**, 375−377.

(16) Reported oxidation reactions with oxygen or superoxide anion suffer from at least one of the following drawbacks: lack of selectivity with formation of other unwanted oxidation products alongside the anticipated sulfinate or requirement of unusual conditions (for example, electrochemical generation of thiolates or use of resin-supported arenethiolates): (a) Claessen, P. *J. Prakt. Chem.* **1877**, *15*, 193−222. (b) Young, M. B.; Young, H. A.; Kleiber, M. *J. Am. Chem. Soc.* **1941**, *63*, 1488. (c) Berger, H. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 773−789. (d) Shell Internationale Research Maatschappij Neth. Patent Appl. 287, 952, 1963; *Chem. Abstr* **1965**, *63*, 9815f. (e) Degrand, C.; Lund, H. *Acta Chem. Scand. Ser. B* **1979**, *33*, 512−514. (f) Weber, J. V.; Schneider, M.; Paquer, D.; Faller, P. *Sulfur Lett.* **1985**, *3*, 45−50. (g) Oae, S.; Takata, T.; Kim, Y. H. *Tetrahedron* **1981**, *37*, 37−44. (h) Doerr, I. L.; Wempen, I.; Clarke, D. A.; Fox, J. J. *J. Org. Chem.* **1961**, *26*, 3401−3409. The report involving hydrogen peroxide was much more attractive. However, the yields were highly structure dependent and formation of over-oxidation products, i.e., sulfonic acids, could not be avoided: (i) Kamiyama, T.; Enomoto, S.; Inoue, M. *Chem. Pharm. Bull.* **1988**, *36*, 2652−2653.

(17) The analogous reaction, in nonbasic conditions, has been investigated with considerable success. Direct oxidation of aliphatic and aromatic thiols with 2 equiv of *m*-CPBA afforded the corresponding sulfinic acids in high purity and good yield: (a) Filby, W. G.; Günther, K.; Penzhorn, R. D. *J. Org. Chem.* **1973**, *38*, 4070−4071. More recently, dimethyldioxirane was found to be a very effective oxidant for aliphatic thiols, though a variety of other oxidation products were isolated when using benzylic or aromatic substrates: (b) Gu, D.; Harpp, D. N. *Tetrahedron Lett.* **1993**, *34*, 67−70.

(18) This reaction is somewhat more commonplace with thiolates coordinated to transition elements. See, for example: (a) Kumar, M.; Colpas, G. J.; Day, R. O.; Maroney, M. J. *J. Am. Chem. Soc.* **1989**, *111*, 8323−8325. (b) Schrauzer, G. N.; Zhang, C.; Chadha, R. *Inorg. Chem.* **1990**, *29*, 4104−4107. (c) Grapperhaus, C. A.; Darensbourg, M. Y. *Acc. Chem. Res.* **1998**, *31*, 451−459. (d) Cocker, T. M.; Bachman, R. E. *J. Chem. Soc., Chem. Commun.* **1999**, 875−876. (e) Sloan, C. P.; Krueger, J. H. *Inorg. Chem.* **1975**, *14*, 1481−1485. (f) Adzamli, I. K.; Libson, K.; Lydon, J. D.; Elder, R. C.; Deutsch, E. *Inorg. Chem.* **1979**, *18*, 303−311. (g) Yamanari, K.; Kawamoto, T.; Kushi, Y.; Komorita, T.; Fuyuhiro, A. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2635−2643. (h) Murata, M.; Kojima, M.; Hioki, A.; Miyagawa, M.; Hirotsu, M.; Nakajima, K.; Kita, M.; Kashino, S.; Yoshikawa, Y. *Coord. Chem. Rev.* **1998**, *174*, 109−131. (i) Connick, W. B.; Gray, H. B. *J. Am. Chem. Soc.* **1997**, *119*, 11620−11627. (j) Miyashita, Y.; Sakagami, N.; Yamada, Y.; Konno, T.; Okamoto, K.-I. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2153−2160. (k) Pin, C.-W.; Peng, J.-J.; Shiu, C.-W.; Chi, Y.; Peng, S.-M.; Lee, G.-H. *Organometallics* **1998**, *17*, 438−445. (l) Lee, M.-T.; Hsueh, C.-C.; Freund, M. S.; Ferguson, G. S. *Langmuir* **1998**, *14*, 6419−6423.

An important feature of this sequence is the impressive rapidity of the *double oxidation reaction*, which on TLC evidence was almost immediate at very low temperatures, in contrast, e.g., with oxaziridine-mediated oxidations of sulfides to sulfones.[19] By way of comparison, oxidation of methyl phenyl sulfide with 2.5 equiv of the same oxaziridine took more than 3 days to go to completion at room temperature.[19] Furthermore, potential side products arising from addition of the sulfinate anion to the liberated imine were not formed.[20]

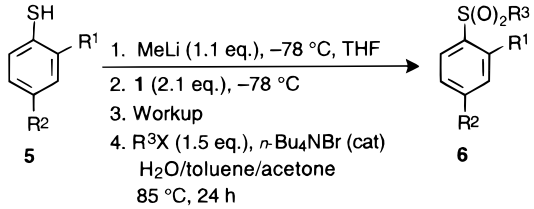
The alkylation conditions described above (1:1 THF/DMF mixture) were, however, none too satisfactory in terms of efficiency and ease of purification of the products, lengthy reaction times, and a large excess of electrophiles being required. An additional problem was the presence in the crude product of the *N*-sulfonylimine PhCH=NSO_2Ph. Optimization of the conditions was far from trivial and was not helped by the relative lack of literature information on the alkylation of lithium arenesulfinates,[21] most examples having focused on the sodium analogues, and especially the commercially available sodium benzene- and *p*-toluenesulfinate.[21,22] Investigation of various conditions suitable for sodium salts showed the lithiated derivatives to be insufficiently reactive.

Of all the conditions we investigated, using thiophenol **5a** for optimization of the sequence, the best results were obtained by *isolation* of the intermediate *sulfinate* and subsequent *alkylation* under *phase-transfer catalysis*. After the oxidation step, the reaction mixture was poured onto a mixture of ethyl acetate and distilled water. The liberated imine remained dissolved in the organic layer whereas the sulfinate was extracted into the aqueous phase. After evaporation of H_2O, the lithium sulfinate was quantitatively isolated in high purity as stable white crystals.[23] The salt was then reacted in a 3:3:4 toluene/acetone/water mixture[24] in the presence of a catalytic amount of tetra-*N*-butylammonium bromide with one of five electrophiles (1.5 equiv). The yields of the resulting sulfones were uniformly high (75−91%), as shown in Table 1 (entries 1−5). To assess the practical utility of this method, the reaction with allyl bromide as the electrophile (entry 3) was scaled up. Starting from 1 g of thiophenol **5a** (9 mmol) and 4.9 g of oxaziridine **1** (18.9 mmol), no drop in efficiency was observed and the anticipated sulfone **6a$_3$** was isolated in 94% yield.

Having established these suitable conditions, the range of substrates was extended to thiols **5b**−**f** containing common substituents or functional groups (Table 1, entries 6−10). In all cases, the intermediate sulfinates were isolated in quantitative yield and were then subjected to the alkylation conditions. Once again, the anticipated sulfones **6b**−**f** were formed in good to excellent yield. Sulfinic esters ArS(O)-OR resulting from the competing *O*-alkylation were not detected, except when ethyl iodide was used (less than 10%).

Application of the sequence to thiol **5f**[26] with an ethylthio substituent selectively furnished sulfone **6f**, which is otherwise difficult to prepare[27] (Table 1, entry 10). Oxidation took place at the anionic sulfur center, without affecting the sulfide

Table 1



entry	thiol	R^1	R^2	R^3	sulfone[a]	isolated yield (%)[b,c]	ref
1	**5a**	H	H	Me	**6a$_1$**	75	25a
2	**5a**	H	H	Et	**6a$_2$**	75	25b
3	**5a**	H	H	Allyl	**6a$_3$**	91	25a
4	**5a**	H	H	Bn	**6a$_4$**	85	25a
5	**5a**	H	H	$CH_2C{\equiv}CMe$	**6a$_5$**	79	25c
6	**5b**	CO_2Me	H	Me	**6b**	77	25d
7	**5c**	Me	H	Et	**6c**	74	25e
8	**5d**	OMe	H	Et	**6d**	80	25f
9	**5e**	H	F	Et	**6e**	76	25g
10	**5f**	H	SEt	Me	**6f**	71	

[a] The electrophiles used to introduce the R^3 substituent were MeI, EtI, $CH_2{=}CHCH_2Br$, $PhCH_2Br$, and $MeC{\equiv}CCH_2Br$. [b] The reaction time for the alkylation reaction, arbitrarily set at 24 h, could be shortened considerably. For example, the yield of sulfone **6a$_1$** had already reached 70% after 1 h (compare with entry 1). [c] Yield calculated from starting thiol.

(19) Davis, F. A.; Jenkins, R., Jr.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, *19*, 5171−5174.

(20) By comparison, the oxidation of benzenethiol afforded a very complex mixture, from which was isolated adduct $PhCH(SO_2Ph)NHSO_2$-Ph, resulting from addition of the intermediate sulfinic acid to the imine. See ref 13a.

(21) *The Chemistry of Sulfinic Acids and their Derivatives−The Chemistry of Functional Groups*; Patai, S., Ed.; John Wiley & Sons: Chichester, 1990.

(22) Macke, J. D. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 7, pp 4512−4515.

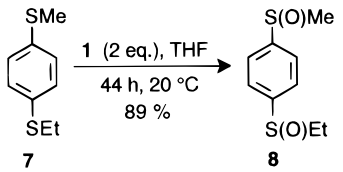
(23) The sulfinate salts may be contaminated with up to 5% benzenesulfonamide. Copies of ^1H and ^{13}C NMR spectra are provided as Supporting Information.

(24) We preferred to use toluene instead of benzene: Crandall, J. K.; Pradat, C. *J. Org. Chem.* **1985**, *50*, 1327−1329.

(25) (a) Ali, M. H.; Bohnert, G. J. *Synth. Commun.* **1998**, *28*, 2983−2998. (b) Ishida, M.; Minami, T.; Agawa, T. *J. Org. Chem.* **1979**, *44*, 2067−2073. (c) Padwa, A.; Filipkowski, M. A.; Kline, D. N.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1993**, *58*, 2061−2067. (d) Bowden, K.; Rehman, S. *J. Chem. Res., Synop.* **1997**, 406−407. (e) Jones, I. W.; Tebby, J. C. *Phosphorus Sulfur* **1978**, *5*, 57−60. (f) Dabrowska, U.; Stachura, R.; Dabrowski, J. *Rocz. Chem.* **1970**, *44*, 1751−1755. (g) Dumont, J.-M.; Rumpf, P. *Bull. Soc. Chim. Fr.* **1962**, 1213−1218.

(26) Thiol **5f** was prepared by heating 1,4-dichorobenzene with an excess of sodium ethanethiolate in refluxing DMF followed by acidification. See: Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis* **1983**, 751−755.

(27) The oxidation of bis-sulfide **7** with 2 equiv of oxaziridine **1** led to a different result, with the formation of the bis-sulfoxide **8** in 89% yield.



(28) No dibenzyl sulfoxide or dibenzyl sulfone, even as trace amounts, was detected; the starting sulfide was recovered quantitatively after column chromatography.

group. A remarkable chemoselectivity was also observed when an equimolar mixture of benzenethiolate and dibenzyl sulfide was treated with 2 equiv of oxaziridine **1**.[28] In the presence of octyl methyl sulfide, oxidation was slightly less selective, with the aliphatic sulfoxide detected and isolated in 7% yield.

In summary, we have succeeded in developing the first high-yield procedure for converting aromatic thiolates into the corresponding sulfinates. The oxidant is the classical oxaziridine derived from benzaldehyde (Davis reagent). Subsequent alkylation of these sulfinates with alkyl halides affords the corresponding sulfones in high yield. We believe the overall sequence holds much promise in synthesis on account of its high efficiency, compatibility with a large variety of substrates, chemoselectivity, technical simplicity, and convenient workup. The lithium sulfinates thus formed can also be used as precursors for the synthesis of sulfonyl chlorides or sulfonamides.[21] The only limitation of which we are aware is the availability of the starting thiols. Furthermore, this study extends still further the already impressive synthetic utility of oxaziridines[4a,b] and illustrates clearly how a slight modification in the oxaziridine structure can dramatically alter its reactivity. Thus, with the Davis oxaziridine possessing a phenyl substituent on the carbon atom of the three-membered ring, products arising from a double oxidation were formed, with no evidence of mono-oxidation, even if a single equivalent of this oxidant was used. In contrast, with the oxaziridine recently introduced by us, which has *tert*-butyl and methyl substituents, it was possible to stop at the mono-oxidation stage.[1] Future work will seek to identify the origin of this difference in behavior by screening a wider range of oxaziridines (does this result from steric effects, electronic factors, or a difference in oxidizing power?). Application to the rapid synthesis of ^{11}C-labeled sulfones for biological studies using positron emission tomography is also underway.

Acknowledgment. We gratefully acknowledge financial support from the Ministère de l'Education Nationale de l'Enseignement Supérieur et de la Recherche (F. Sandrinelli). We also thank Marco Greb of the University of Würzburg (Germany) for a technical contribution to this work.

Supporting Information Available: Experimental procedures and spectroscopic data for the lithium sulfinates prepared from thiols **5a**−**b**, **5e**−**f**, and compounds **3/4/6f/8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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