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

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-sulfonyloxaziridine² 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 advantage³ of being executable in one pot.

In this Letter are described the different results obtained with our initial investigations using classical (±)-trans-2-(phenylsulfonyl)-3-phenyloxaziridine⁴ ¹, commonly known as the Davis reagent.⁵

A preliminary experiment starting from disubstituted thiophenol ²· quickly established that the reaction of the corresponding lithium thiolate with 1 equiv of the Davis oxaziridine⁶ ¹ under the previously used conditions, followed by addition of ethyl iodide, did not result in the formation

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³ Hall, N. Science 1994, 266, 32—34.
particularly intriguing, since TLC analysis of the reaction mixture immediately after addition of the oxaziridine revealed complete consumption of the oxidant, 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 (ArSO2O−) and unreacted thiolate (ArS−)10 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-butane thiol was preferentially oxidized by oxaziridine 1 to the corresponding sulfenic 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” nucleophile14 which is much more nucleophilic than the thiol. Similarly, treatment of trialkylphenylthio-silanes PhSSiR3 with 1 equiv of oxaziridine 1 or m-CPBA afforded a 50% yield of the corresponding trialkylsilyl benzenesulfonates Ph(SO2)SiR3.13b,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,16–f superoxide anion,16g iodine,16h and hydrogen peroxide16o). Following the same procedure as above, but using 2 equiv of oxidant 1, an 80% yield of sulfone 4 was obtained.


(15) 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.; Penrhon, 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. J. Am. Chem. Soc. 2008, 130, 6430–6431.

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. 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. Furthermore, potential side products arising from addition of the sulfinate anion to the liberated imine were not formed.

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=NSO₂Ph. Optimization of the conditions was far from trivial and was not helped by the relative lack of literature information on the alkylation of lithium arenesulfimates, most examples having focused on the sodium analogues, and especially the commercially available sodium benzene- and p-toluensulfinate. 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 H₂O, the lithium sulfinate was quantitatively isolated in high purity as stable white crystals. The salt was then reacted in a 3:3:4 toluene/acetone/water mixture 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 6a₁ 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 Ar(S)=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 with an ethylthio substituent selectively furnished sulfone 6f, which is otherwise difficult to prepare (Table 1, entry 10). Oxidation took place at the anionic sulfur center, without affecting the sulfide

<table>
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<th>R₁</th>
<th>R₂</th>
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<td>Et</td>
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<td>25b</td>
</tr>
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(20) By comparison, the oxidation of benzenethiol afforded a very complex mixture, from which was isolated adduct PhCH(SO₂Ph)NH₂SO₂Ph, resulting from addition of the intermediate sulfonic acid to the imine. See ref 13a.
(23) The sulfinate salts may be contaminated with up to 5% benzene-sulfonamide. Copies of 1H and 13C NMR spectra are provided as Supporting Information.

(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.
A remarkable chemoselectivity was also observed when an equimolar mixture of benzenethiolate and dibenzyl sulfide was treated with 2 equiv of oxaziridine 1. 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. 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 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. 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 labeled sulfones for biological studies using positron emission tomography is also underway.

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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.