

## Chemoselective Catalytic Oxidation of Sulfides to Sulfones With Tetrapropylammonium Perruthenate (TPAP)

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*Abstract: Tetrapropylammonium perruthenate has been found to be an efficient catalyst for the conversion of sulfides to sulfones. The method is highly chemoselective and isolated double bonds are generally unaffected.*

As the use of sulfones in organic synthesis has continued to grow,<sup>1</sup> so has the need for mild chemoselective methods of their preparation. To date, numerous methods for the oxidation of sulfides to sulfones have been reported,<sup>1,2</sup> but very few are mild and chemoselective. The conventional methods of carrying out this transformation include oxidation of the sulfide with peracid (i.e., *m*-CPBA or H<sub>2</sub>O<sub>2</sub>/Acetic acid), or Oxone<sup>®</sup>.<sup>3</sup> Hydrogen peroxide with a variety of metal catalysts<sup>4a</sup> as well as KMnO<sub>4</sub><sup>4b</sup> and Zn(MnO<sub>4</sub>)<sub>2</sub><sup>4c</sup> have also been used for this purpose. One important limitation of these methods is that isolated double bonds are frequently oxidized under the experimental conditions.<sup>5</sup> More recently, Kaldor and co-workers<sup>6</sup> reported a mild, osmium tetroxide-catalysed method for the oxidation of sulfides to sulfones. Although it was demonstrated that chemoselective oxidation of a sulfide in the presence of a disubstituted olefin could be achieved in one particular case, competitive experiments revealed that olefin hydroxylation can be a significant problem.

In 1987, Ley and co-workers first reported the use of tetrapropylammonium perruthenate (TPAP) for the oxidation of a variety of alcohols to their corresponding carbonyl compounds.<sup>7</sup> The reagent was found to be tolerant of a number of functional groups such as silyl ethers, double and triple bonds, esters, acetals, epoxides, lactones and halides.<sup>8</sup> We now report that TPAP is a highly efficient and chemoselective catalyst for the oxidation of sulfides to sulfones (Eq. 1). Indeed, in the presence of the co-oxidant *N*-methylmorpholine-*N*-oxide (NMO), five mole percent of the catalyst smoothly oxidizes a variety of sulfides to the corresponding sulfones in high chemical yield (Table 1).

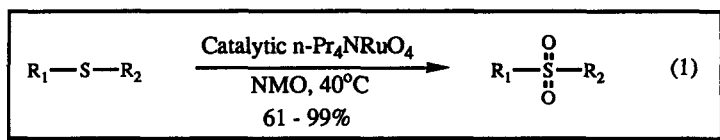



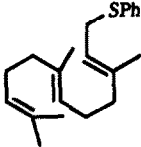
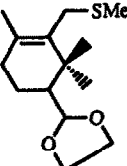


Table 1: Chemoselective Catalytic Oxidation of Sulfides to Sulfones with TPAP.<sup>a</sup>

| Entry | Sulfide   | Reaction Time (h) | % Yield <sup>b</sup> sulfone | mp (°C) <sup>c</sup> | Lit. mp (°C)      |
|-------|---|-------------------|------------------------------|----------------------|-------------------|
| 1     | PhSMe   | 3.0               | 97 <sup>d</sup>              | 84-86                | 88 <sup>9a</sup>  |
| 2     | PhSMe   | 2.5               | 95 <sup>d,e</sup>            |                      |                   |
| 3     | PhSPh   | 23                | 61(87) <sup>d,f</sup>        | 121-122              | 123 <sup>9b</sup> |
| 4     | PhCH <sub>2</sub> SCH <sub>2</sub> Ph   | 3.0               | 90 <sup>d</sup>              | 150-151              | 151 <sup>9c</sup> |
| 5     |    | 2.0               | 92 <sup>d</sup>              | oil                  | --                |
| 6     |    | 17.5              | 99 <sup>d</sup>              | 130-131              | 132 <sup>9d</sup> |
| 7     |    | 3.5               | 83 <sup>g</sup>              | oil                  | --                |
| 8     |   | 1.5               | 77 <sup>h,i</sup>            | oil                  | --                |
| 9     |  | 3.0               | 80 <sup>j</sup>              | 81-83                | --                |

<sup>a</sup> Unless otherwise noted, reactions were carried out on a 1 mmol scale in CH<sub>3</sub>CN at 40 °C with 3 equiv. of NMO, 5 mole % TPAP, and powdered 4Å molecular sieves. <sup>b</sup> Refers to isolated yield (after chromatography). <sup>c</sup> After recrystallization from ethyl acetate / hexane. <sup>d</sup> The identity of the product was confirmed by tlc and <sup>1</sup>H NMR comparison with an authentic commercial sample. <sup>e</sup> The reaction was performed on an 8 mmol scale. <sup>f</sup> Yield based on recovered sulfide in parentheses. <sup>g</sup> See ref. 10. <sup>h</sup> Spectral data are given in ref. 11. <sup>i</sup> 6 equiv. of NMO were used. <sup>j</sup> Spectral data are given in ref. 12.

In particular, sulfides bearing isolated double bonds (Table 1, entries 7, 8 and 9) undergo clean oxidation without complication. In sharp contrast, attempted oxidation of the *trans,trans*-farnesyl derivative (entry 8) with *m*-CPBA (0 °C or 0 °C to room temp.) resulted in a complex mixture of products, and the desired sulfone was isolated in only 7-10 % yield. Furthermore, when oxidation was attempted with Oxone<sup>®</sup> in methanol, a complicated mixture ensued and none of the sulfone could be detected by tlc.

A similar scenario was observed for the oxidation of an allyl sulfide bearing a tetrasubstituted olefin (entry 9). Exposure of this sulfide to Oxone<sup>®</sup> in methanol provided an exceedingly complex mixture of products, and none of the expected sulfone could be detected. In turn, standard peracid oxidation (*m*-CPBA, 0 °C to r.t.) afforded a ca. 70:30 mixture of the desired sulfone and epoxide-containing products, which could not be separated by flash chromatography.

A number of general observations concerning this new oxidation reaction are in order. (1) Although most of the oxidations were carried out on a small scale (1 mmol), preparative scale reactions are also possible (entry 2). (2) Acetonitrile is the solvent of choice for this reaction. If the reactions are carried out in other less polar solvents such as CH<sub>2</sub>Cl<sub>2</sub> or THF, they become quite sluggish and usually do not reach completion. (3) The use of molecular sieves is not crucial to the success of this reaction, but is recommended for moisture sensitive compounds. (4) The workup procedure is remarkably simple. The solvent (CH<sub>3</sub>CN) is simply removed *in vacuo*, the residue redissolved in an appropriate solvent and filtered through a bed of silica gel (to remove the molecular sieves as well as residual TPAP). After evaporation of the filtrate, the residue may be chromatographed to provide the pure sulfone.

In a representative experiment, powdered molecular sieves (4Å, 100 mg) followed by NMO (352 mg; 3.0 mmol) were added to a stirred solution of thioanisole (124 mg; 1.0 mmol) in CH<sub>3</sub>CN (5.0 mL) under nitrogen at room temperature. After 5 min. TPAP (Aldrich, 18 mg; 0.05 mmol) was added and the mixture warmed to 40°C. After 3h, tlc revealed that all of the thioanisole had been consumed and only PhSO<sub>2</sub>Me could be observed. The mixture was then allowed to cool to room temperature and the solvent removed *in vacuo*. The residue was filtered through a bed of silica gel (eluent: ethyl acetate) and the filtrate concentrated *in vacuo*. The resulting oily residue was chromatographed (eluent: 40% ethyl acetate / hexane) to give 151 mg (97%) of phenyl methyl sulfone.

In contrast to the osmium tetroxide-catalysed method,<sup>6</sup> considerable amounts of sulfoxide were observed by tlc at various time points during our reactions. This would suggest that the transformations of sulfide to sulfoxide and sulfoxide to sulfone proceed at comparable rates. It is possible to use less than 5 mole % of the catalyst for these oxidations. For example, thioanisole can be completely converted to its corresponding sulfone in 4h with 2 mole % TPAP, provided that 6 equivalents of the co-oxidant (NMO) is used.

In conclusion, we have demonstrated that tetrapropylammonium perruthenate is an effective catalyst for the chemoselective oxidation of sulfides to sulfones. The highly tolerant nature of the catalyst towards isolated double bonds, as well as a number of other functionalities, suggests that this method will find wide application in organic synthesis.<sup>13</sup>

## References and Notes

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10. Sulfone Entry 7: Spectral data were in accord with the literature values; see Dharanipragada, R. and Fodor, G. *J. Chem. Soc. Perkin Trans. 1* 1986, 4, 545.
11. Sulfone Entry 8: <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ): 7.88 (d, J = 7.6 Hz, 2H), 7.51 - 7.65 (m, 3H), 5.20 (t, J = 8.0 Hz, 1H), 5.11 - 5.06 (m, 2H), 3.82 (d, J = 8.0 Hz, 2H), 1.98 - 2.10 (m, 8H), 1.69 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.32 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ): 146.3, 138.7, 135.6, 133.4, 131.2, 128.9, 128.7, 128.5, 124.2, 123.3, 110.3, 56.1, 39.6, 26.7, 26.1, 25.6, 17.6, 16.1, 15.9.
12. Sulfone Entry 9: <sup>1</sup>H NMR (CDCl<sub>3</sub>, δ): 4.94 (d, J = 2.9 Hz, 1H), 3.99 (s, 2H), 3.97 - 3.83 (m, 4H), 2.95 (s, 3H), 2.11 - 2.17 (m, 2H), 1.82 (s, 3H), 1.62 - 1.79 (m, 3H), 1.22 (s, 3H), 1.09 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, δ): 139.0, 126.6, 104.5, 64.9, 64.5, 56.3, 48.2, 42.2, 36.7, 32.3, 27.8, 23.4, 22.1, 18.5.
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