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A Mild, Osmium Tetraoxide-Catalyzed Method for the Oxidation of Sulfides to Sulfones

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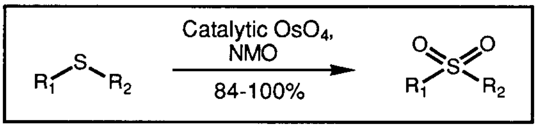
Abstract: Osmium tetraoxide has been demonstrated to be a highly efficient catalyst for the chemoselective oxidation of a variety of sulfides to the corresponding sulfones. Tertiary amine catalysis appears to play a key role in the reaction.

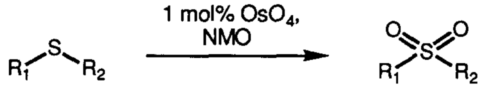
Although considerable effort has been expended on the development of methods for the oxidation of sulfides to sulfones,[1] mild, chemoselective procedures for effecting this transformation are relatively scarce. We now wish to report that osmium tetraoxide is a selective and highly efficient catalyst for performing this oxidation. In the presence of the co-oxidant *N*-methylmorpholine-*N*-oxide (NMO), one mole percent of catalyst is sufficient to oxidize a variety of sulfides to the corresponding sulfones in nearly quantitative yields. This room temperature oxidation method is tolerant of a number of other functional groups: chemoselective oxidation of a sulfide in the presence of an olefin is even possible in some instances.



In contrast to the hierarchy of reactivity exhibited by sulfides and sulfoxides toward peracid and periodate oxidants, sulfoxides are frequently more reactive than sulfides towards transition-metal oxidants.[2,3] Several researchers have observed that sulfides are generally inert to oxidation by osmium tetraoxide under stoichiometric conditions.[4] For example, in a seminal paper in 1965 Henbest demonstrated that although oxidation of sulfoxides to the corresponding sulfones with OsO_4 is a facile process at room temperature, treatment of dibenzyl or diphenyl sulfide with stoichiometric osmium tetraoxide in refluxing ether for 48 h resulted in complete recovery of starting sulfide.[3]

In light of this literature precedent, we were startled to discover that dibenzyl sulfide was quantitatively oxidized to dibenzyl sulfone at room temperature when treated with *N*-methylmorpholine-*N*-oxide in the presence of one mole percent of osmium tetraoxide (Table, entry F).[5] A representative series of sulfides was then examined to determine the scope of this catalytic oxidation method (Table). All oxidations we have attempted to date have proceeded smoothly and in excellent yield. Despite the known susceptibility of osmium tetraoxide to rate retardation in sterically encumbered substrates (e.g. tri- and tetrasubstituted olefins),[6] oxidation of both branched and straight chain alkyl sulfides proceeds with equal facility (Entries B-D). Significant attenuation of reaction rate was noted only for the oxidation of diphenyl sulfide (Entry G); 10 mol% of OsO_4 was employed to speed this reaction to completion overnight. In accord with the observations of Henbest,[3] sulfoxide intermediates appear to have only a fleeting existence in the reaction medium; only traces of sulfoxide were observed by tlc at various time points during the reaction. Catalyst turnover is clearly quite efficient in some instances: complete and quantitative oxidation of thioanisole was possible in a 24-hour period employing only 0.1 mol% osmium tetraoxide.

Table. Osmium Tetraoxide-Catalyzed Oxidation of Sulfides to Sulfones



(1)

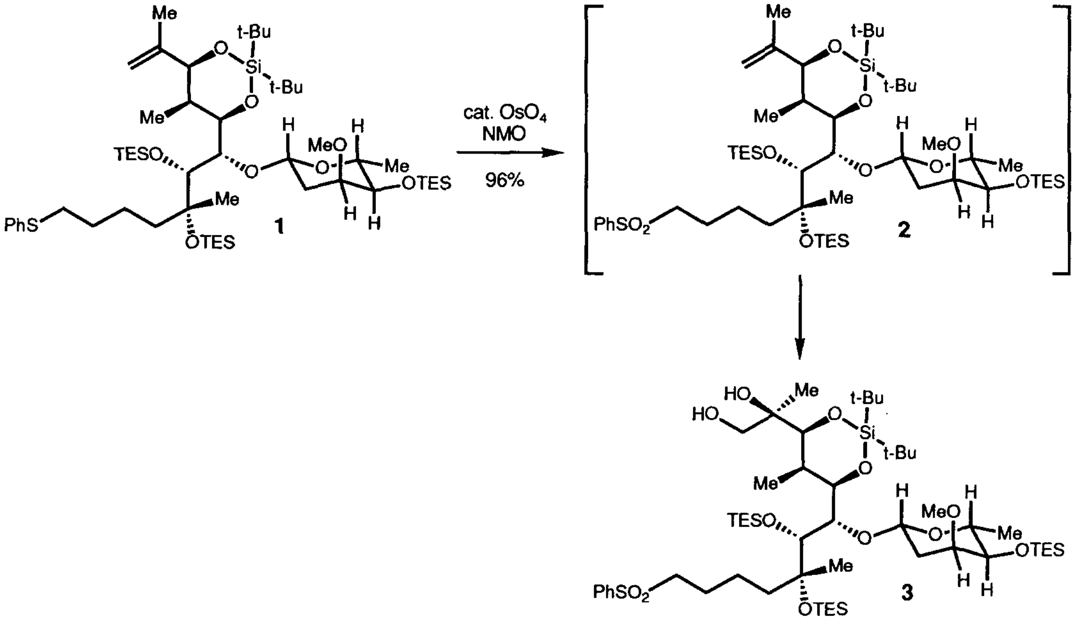
Entry	R_1	R_2	Yield (%)[a,b]	mp (°C)[c]
A	Ph	Me	99	84.5 (88)[7a]
B	*n*-Bu	*n*-Bu	91	44-45 (44)[7b]
C	*i*-Pr	*i*-Pr	99	32 (36)[7c]
D	*t*-Bu	Me	95	82-83 (84.5)[7d]
E	Bn	Et	91	83-84 (84)[7e]
F	Bn	Bn	99	149.5 (151)[7f]
G	Ph	Ph	84[d]	123-124 (123)[7g]
H	$-CH_2CH_2CH_2CH_2-$		84	oil[7h]

[a] reactions performed according to the sample procedure (*vide infra*); [b]isolated, unoptimized yields of analytically pure material (satisfactory ^1H NMR, IR, MS and elemental analysis); [c]literature mp given in parentheses; [d]10 mol% OsO_4 employed

In a representative experiment, a 50 mL round-bottom flask equipped with a nitrogen inlet was charged with 1.00 mL of thioanisole (0.95 g, 7.61 mmol), 3.09 g of NMO (22.8 mmol), 15 mL of acetone and 7 mL of water. To the stirred solution was added 423 μL of 0.18 M aqueous OsO_4 solution (0.076 mmol, 1 mol%), producing a mild exotherm. The reaction was allowed to stir at room temperature overnight (12 h), and was subsequently quenched by addition of 5 mL of saturated aqueous sodium bisulfite. After extraction of the quenched reaction mixture with two 10 mL portions of CH_2Cl_2, the combined organic layers were washed successively with 2 x 10 mL of 1 N aqueous sodium bisulfate and 10 mL of brine. The CH_2Cl_2 layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash silica gel chromatography of the residue with 9:1 CH_2Cl_2/EtOAc provided a quantitative yield (1.34 g) of the sulfone as a colorless solid. Recrystallization of 1.29 g of the sulfone from hexanes/EtOAc afforded 1.08 g (91%) of the sulfone as colorless needles, mp 84.5 °C (lit mp 88 °C).[7a]

Application of this process to more complicated substrates has also proven successful. In the course of the synthesis of the macrolide antibiotic cytovaricin, the need arose for the oxidation of sulfide olefin **1** to the corresponding sulfone diol **3**.[8] Attempts to effect the desired transformation by a two-step protocol involving sulfide oxidation followed by olefin osmylation were thwarted by competitive desilylation and epoxidation on treatment of **1** with either *m*-CPBA or oxone ($KHSO_5$)[9] under a variety of conditions.[10] However, osmium tetraoxide-mediated oxidation of **1** resulted in clean bis-oxidation to the desired sulfone diol **3** in a one-step process (Scheme). Interestingly, sulfone olefin **2** could be isolated from the reaction mixture in 93% yield if the reaction was terminated after 20 minutes. Although chemoselective oxidation of a sulfide in the presence of an olefin was possible in this instance, attempted oxidation of thioanisole in the presence of one equivalent of allyl benzoate resulted in competitive oxidation of both olefin and sulfide.

Scheme



The seeming dichotomy between our results and those of previous researchers[3,4] has prompted us to perform several control experiments. Treatment of either dibenzyl sulfide or thioanisole with excess *N*-methylmorpholine-*N*-oxide in the absence of OsO_4 gave no reaction after 14 h at 25 °C, thus confirming the need for osmium catalysis. These results complement those of Biffen et al., who observed that *N*-oxides oxidize sulfoxides to sulfones only under relatively drastic conditions (sulfuric acid, 195 °C).[11] In accord with the observations of Henbest,[3] treatment of dibenzyl sulfide with two equivalents of osmium tetraoxide (diethyl ether, 25 °C, 14 h) gave no reaction. However, subsequent addition of either *N*-methylmorpholine or *N*-methylmorpholine-*N*-oxide to the reaction mixture resulted in rapid oxidation to dibenzyl sulfone. We therefore conclude that tertiary amine catalysis is critical to the success of our osmium tetraoxide-catalyzed sulfide oxidation procedure.[12]

In summary, we have demonstrated that osmium tetraoxide is an effective and general catalyst for the oxidation of sulfides to sulfones. The mild conditions and highly catalytic nature of the method suggest it as a viable alternative to other existing oxidation procedures.

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2. (a) See Trocha-Grimshaw, J.; Henbest, H. B. *J. Chem. Soc.; Chem. Commun.* **1968**, 1035-1036 and references cited therein. (b) Ref. 1b. (c) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press; NY, **1981**; pp. 392-395.

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5. (a) To the best of our knowledge, the only literature precedent for this OsO_4-catalyzed process is found in a footnote to a sulfoxide-directed olefin osmylation paper by Hauser: Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458-2459. For related sulfoxide oxidations, see: Solladie, G.; Frechou, C.; Demailly, G. *Tetrahedron Lett.* **1986**, *27*, 2867-2870. (c) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973-1976.

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9. Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287-1290.

10. (a) Buffered reaction conditions led to no significant suppression of competing side reactions (*m*-CPBA/ powdered $NaHCO_3$, oxone/Na_2HPO_4). (b) Oxone is known to efficiently epoxidize olefins: Bloch, R.; Abecassis, J.; Hassan, D. *J. Org. Chem.* **1985**, *50*, 1544-1545.

11. Biffin, M. E.; Miller, J.; Paul, D. B. *Tetrahedron Lett.* **1969**, 1015-1018.

12. (a) Interestingly, in a separate oxidation experiment pyridine was demonstrated to be a relatively poor catalyst for the oxidation of thioanisole to the corresponding sulfone in the presence of excess OsO_4 (2 equiv OsO_4, 3 equiv pyridine, ether, 25 °C, 72 h, greater than 85% recovered sulfide). (b) Tertiary amine catalysis is a well-documented phenomenon in the osmylation of alkenes (See Ref. 6, p. 121).

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