A FACILE AND SELECTIVE OXIDATION OF SULFIDES TO SULFONES

Waldemar Priebe* and Grzegorz Grynkiewicz¹ The University of Texas M. D. Anderson Cancer Center Houston, Texas 77030, USA

Abstract: Sulfides undergo a facile and selective oxidation to sulfones under mild conditions using a catalytic amount of osmium tetroxide and tertiary amine N-oxides (N-methylmorpholine N-oxide or trimethylamine N-oxide). Both N-oxides are equally effective. The observed yields ranged between 60%-95%.

An important synthetic aspect of sulfone chemistry² is the possibility to generate α -sulfonylcarbanions as well as nucleophilic addition to the electron-deficient double-bond of α , β -unsaturated sulfones. The numerous applications of the Ramberg-Backlund reaction further demonstrate the synthetic usefulness of sulfone group.² In carbohydrate chemistry, aryl glycosyl sulfones have been successfully used for the synthesis of 1,6-anhydromono- and disaccharides³ and the synthesis of 1-sulfonyl glycals.⁴

The most common method for the preparation of sulfones is the oxidation of sulfides. A variety of oxidizing reagents have been described in the literature, including hydrogen peroxide, peracids, oxygen, ozone, organic peroxides, potassium and zinc permanganate, potassium persulfate, sodium hypochlorite.⁵ They seemed to be effective when a substrate is a simple sulfide; however, other functionalities often are not compatible with the above mentioned oxidizing agents. Therefore, there was a need for a reagent that would selectively oxidize sulfides to sulfones in a high yield under mild conditions.



More than ten years ago, in an initial study involving functionalization of a double bond of unsaturated thioglycosides, we discovered that the combination of a tertiary amine *N*-oxide and a catalytic amount of osmium tetroxide can act as an effective reagent for oxidizing sulfides to sulfones.^{6,7} Here we present the extension of these studies and examples demonstrating the oxidation of sulfides to sulfones under mild conditions in the presence of *N*-methylmorpholine *N*-oxide (NMMO), as well as a less expensive tertiary *N*-oxide, trimethylamine *N*-oxide (TMNO).

No	Product	Yield (isolated) ^a	m.p.	[α] ²⁸ D (c=1.0, CH ₂ Cl ₂)
1		92 %	143°C	+ 137.2°
2		93 %	185 -186°C (lit. 189°C) ¹²	- 23.6° (lit 26.9°, CHCl3)
3		95 % 94% (TMNO) ^b	136-137°C	- 26.0°
4		87 %	126-128°C	-16.0°
5		88 %	112-113°C	+12.5°
6	CH2OAC ACO-CHO SO2Me	94 % 94% (TMNO) ^b	87°C	+ 44.0°
7		83 %	118-119°C	(d,l)
8		85 %	167 °C (dec.)	(d,l)
9		83 % Ref.7	134-135 °C	+ 315.3° (c=1.2, EtOAc)
10	NH OMe	60 %	211°C	-

 Table 1. Oxidation of Sulfides to Sulfones Using Catalytic Amount of OsO4 and Tertiary Amine N-Oxide

^aThe yields of isolated products are for reactions conducted with 4-methylmorpholine *N*-oxide and a catalytic amount of osmium tetroxide. All products gave satisfactory elemental analysis ($\pm 0.3\%$). ¹H NMR and ¹³C NMR spectra were in full agreement with proposed structures. ^bReported yields are for reactions with trimethylamine *N*-oxide (TMNO).

Earlier reports indicated that sulfides are not oxidized by osmium tetroxide^{8,9,10}; however, there is one example showing that osmium tetroxide can oxidize thiacyclohexane to the related sulfone in 58% yield, even though at the same time authors demonstrated that other tested sulfides remained unchanged.⁹ Oxidation by *N*-oxides can occur solely for sulfoxides and under extreme conditions. Dimethyl sulfoxide was oxidized by amine-*N*-oxides only when heated at 195°C for 20 hr in H_2SO_4 .¹¹

In our system both components, N-methylmorpholine N-oxide and osmium tetroxide, when used separately, were not able to oxidize sulfides. Reactions monitored by TLC showed that substrates remained unchanged. These observations indicate that the tertiary amine N-oxide plays a double role; it oxidizes osmium in its lower valence forms to the tetroxide and at the same time actively participates in the formation or oxidative breakdown of the OsO_4 / sulfur complex.



Oxidation of sulfides to sulfones. Typical procedure.

Ethyl 2,3,4,6-tetra-O-acetyl-1-thio- α -D-glucopyranoside (1S, 330 mg, 0.84 mmol) was dissolved in tetrahydrofuran/tbutanol 4:1 mixture (5 mL). Then the monohydrate of N-methylmorpholine N-oxide (351 mg, 2.56 mmol) and osmium tetroxide (10 mg, 0.0393 mmol; added as 0.5 mL of 20 mg/mL stock solution of OsO₄ in t-butanol) were added and the mixture was stirred at r.t. overnight. After 24 hr the TLC showed one product (Rf 0.43, hexane-ethyl acetate 1 : 1) more polar than the substrate 1S (Rf 0.65). The reaction mixture was treated with sodium hydrogen sulfite and water and then extracted with ethyl acetate. The organic solution was dried with anhydrous sodium sulfate, filtered, and evaporated under diminished pressure to give a crystalline residue of 3,4,6-tetra-O-acetyl- α -D-glucopyranoside ethyl sulfone (1), which was purified by trituration with hexane-ethyl acetate 9 : 1 mixture. Yield: 328 mg (92 %).

Oxidation reactions were carried out in various mixtures of tetrahydrofuran and t-butanol containing none or 5% of added H₂O. At all ratios, as judged by TLC, results were similar. Other solvents used in a typical *cis*-hydroxylation reaction like acetone/t-butanol/water mixtures were also suitable for this oxidation process. A 3- to 4-fold excess of amine N-oxide was used. Osmium tetroxide was handled as a t-butanol solution (20 mg/mL) and was used in catalytic amounts ranging from 1 to 5 mole percent. Two tertiary Noxides were tested: N-methylmorpholine N-oxide and trimethylamine N-oxide. They were used as monohydrate or dihydrate, respectively.

Trimethylamine N-oxide was used for comparison studies in two reactions with methyl 2,3,5,6-tetra-Oacetyl-1-thio-β-D-glucofuranoside (6S) and n-octyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (3S) as substrates. The yields and the reaction times for both the N-methylmorpholine and trimethylamine N-oxides were similar (Table 1).

All reactions were carefully monitored by TLC in order to check for the presence of possible intermediate sulfoxides. In all cases only formation of a single product (sulfone) was observed. This fact could be explained by a significantly lower rate of the oxidation by OsO₄/NMMO of sulfides to sulfoxides than of sulfoxides to sulfones. Support for this explanation can be found in Henbest's and Khan's work.⁹ They observed a drastic difference in the ability of OsO₄ itself to oxidize sulfoxides and sulfides. Sulfoxides, in contrast to unreactive sulfides, were easily oxidized by OsO₄ to corresponding sulfones.⁹

High degree of chemoselectivity was observed for compounds **7S**, **8S**, and **9S**. All of these sulfides were oxidized to sulfones in high yield without noticeable hydroxylation of the double bond. However, the increase of the reaction time, as it was shown before,6.7 might lead to *cis*-hydroxylated products.

This study proved that $OsO_4/NMMO$ is a highly efficient, mild, and selective reagent for the oxidation of sulfides to sulfones. It also established that the other less-expensive *N*-oxides like trimethylamine *N*-oxide can be as effective reagent as NMMO.

Acknowledgements: This work was supported, in part, by National Institutes of Health grant No. RR5511-25 and by Argus Pharmaceuticals, Inc.

References and Notes

- 1. Current address: Pharmaceutical Research Institute, Warsaw, Poland.
- K. Tanaka and A. Kaji, "Synthetic Uses of Sulfones" in *The Chemistry of Sulphones and Sulphoxides* ;S. Patai, Z. Rappoport and C. J. M. Stirling, Eds.; John Wiley & Sons, Ltd.: 1988; pp 759-821.
- a) A. L. Clingman and N. K. Richtmyer. J. Org. Chem., 11, 363 (1969); b) A. L. Clingman and N. K. Richtmyer. J. Org. Chem., 12, 297 (1970); c) M. Funabashi and H Nagashima, Chem. Lett., 2065 (1987).
- a) J. F. Cassidy and J. M. Williams, *Tetrahedron Lett.*, 27, 4355 (1986); b) D. Qiu and R. R. Schmidt, Synthesis 1990, 875.
- a) K. Schank, "Synthesis of Open-chain Sulfones" in *The Chemistry of Sulphones and Sulphoxides*; S. Patai, Z. Rappoport and C. J. M. Stirling, Eds.; John Wiley & Sons, Ltd.: 1988; pp 165-231; b) A. V. Mashkina, *Sulfur Reports*, 10, 279 (1991).
- W. Priebe, Ph.D. Thesis, Polish Academy of Sciences, Institute of Organic Chemistry, Warsaw, Poland, 1978.
- 7. W. Priebe and A. Zamojski, Polish J. Chem., 54, 731 (1980).
- 8. C. Djerassi and R. R. Engle, J. Am. Chem. Soc., 75, 3838 (1953).
- 9. H. B. Henbest and S. A. Khan, Chem. Commun., 1968, 1036.
- 10. D. M. Vyas and C. W. Hay, Can. J. Chem., 53, 1362 (1975).
- 11. M. E. C. Biffin, J. Miller and D. B. Paul, Tetrahedron Lett., 13, 1015 (1969).
- 12. W. A. Bonner and R. W. Drisko, J. Am. Chem. Soc., 70, 2435 (1948).

(Received in USA 16 September 1991)