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Oxidation of Prochiral Sulfides with Chiral Dioxirane

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Abstract—Dioxirane generated *in situ* by reaction of chiral 1,2:4,5-di-*O*-isopropylidene-D-*erythro*-hexo-2,4-diulo-2,6-pyranose with Oxone oxidizes prochiral sulfides to the corresponding sulfoxides with an enantiomeric excess of 2 to 25%.

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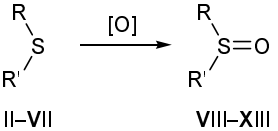
Nonracemic sulfoxides are widely used in modern enantioselective synthesis due to their versatile reactivity and high configurational stability of the sulfur atom as chiral center. This follows from numerous review articles published in the past decade [1–3]. Search for new methods for the synthesis of scalemic sulfoxides and improvement of the existing ones are also extensively performed (for reviews, see [3–6]). Setting aside methods for the preparation of nonracemic sulfoxides from nonracemic initial compounds and noting (with some remarks) striking advances in biotechnology [6], we can conclude that all known chemical methods are not free from essential disadvantages and that their results strongly depend on the substrate, although some chiral sulfoxides can be obtained with excellent yields and high enantioselectivity by purely chemical procedures. Therefore, development of new methods for enantioselective synthesis of sulfoxides remains an important problem.

Taking into account the above stated, in the present work we tried to effect enantioselective oxidation of prochiral sulfides with a nonracemic dioxirane derivative generated *in situ*. In doing so, the following aspects were considered. First, chiral dioxiranes have not been used previously for oxidation of sulfides; only successful enantioselective oxidation of alkyl aryl sulfides with achiral dioxiranes in the presence of bovine serum albumin (as chiral inductor) was reported in early publication by Colonna and Gaggero [7]. However, it was shown later that other oxidants (such as hydrogen peroxide or *tert*-butyl hydroperoxide) are also capable of oxidizing sulfides with high enantioselectivity in the presence of bovine serum albumin [8]. Presumably, achiral dioxiranes in the above procedure played an auxiliary role. Second, a number of oxidants capable of enantioselectively epoxidating double C=C bond were found to act similarly on a sulfide fragment either directly or after a slight modification. For example, Kagan [9] and Modena [10] independently showed that treatment of the system hydroxyperoxide–titanium(IV)alkoxide–tartaric acid ester (which was proposed by Sharpless for enantioselective epoxidation of allyl alcohols) with one equivalent of water makes it suitable for enantioselective oxidation of sulfides to sulfoxides. Chiral metal salen complexes used to oxidize unsaturated systems are also effective in enantioselective oxidation of sulfides [5]. According to the recently published data, conjugated dienes [11], α,β-unsaturated ethers [12], and some other *trans*-disubstituted and trisubstituted olefins [13, 14] undergo enantioselective epoxidation with dioxirane **A** derived from a chiral ketone, 1,2:4,5-di-*O*-isopropylidene-D-*erythro*-hexo-2,3-diulo-2,6-pyranose (**I**). Therefore, we examined the oxidation of prochiral sulfides **II**–**VII** with dioxirane **A** (Scheme 1).

The simplest dioxiranes, in particular dimethyldioxirane, can be isolated as individual substances and

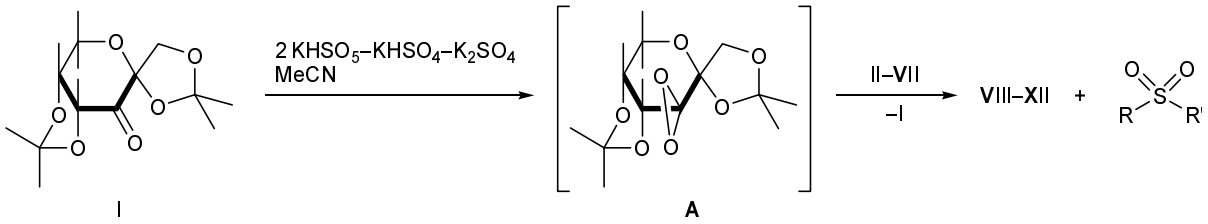
Scheme 1.



II–VII VIII–XIII

II, **VIII**, R = Ph, R' = Me; **III**, **IX**, R = Ph, R' = Pr; **IV**, **X**, R = Ph, R' = *i*-Pr); **V**, **XI**, R = Me, R' = *p*-MeC_6H_4; **VI**, **XII**, R = Me, R' = *p*-$NO_2C_6H_4$; **VII**, **XIII**, R = Me, R' = $PhCH_2$.

Scheme 2.



I A

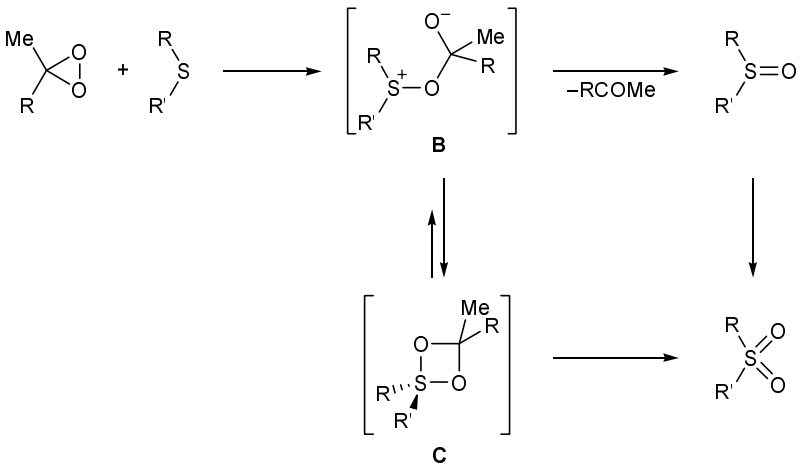
stored for a short time in solution at reduced temperature [15]. Our attempts to isolate dioxirane **A** from a solution in methylene chloride were unsuccessful, and it was generated *in situ* by oxidation of ketone **I** with Oxone ($2KHSO_5$–$KHSO_4$–K_2SO_4) (Scheme 2).

Wang *et al*. [13] studied in detail the effect of pH on asymmetric epoxidation with dioxirane **A** and showed that its concentration in the reaction mixture increases while the probability for side Baeyer–Villiger reaction decreases as pH rises. Details of the mechanism of sulfide oxidation with dioxiranes are unknown. The most thorough study of this process was performed by Gonzalez-Nunez *et al*. [16] with the use of simplest 3,3-dimethyl- and 3-methyl-3-trifluoromethyl-1,2-dioxiranes. It was shown that the first stage is electrophilic attack by cyclic peroxide on the sulfur atom to form an S–O bond. The subsequent intramolecular oxidation of zwitterionic species **B** leads to four-coordinate sulfur intermediate **C** which decomposes to give the corresponding sulfone, while decomposition of zwitterion **B** yields sulfoxide. Also, the formation of sulfone via oxidation of sulfoxide cannot be ruled out (Scheme 3).

Thus the formation of sulfone is implied by the dual character of the oxidation process, and it cannot always be avoided even by increasing the sulfide-to-dioxirane ratio tenfold [16]. Our experiments showed that twofold increase of the ratio sulfide–ketone (i.e., dioxirane) only slightly increased the yield of sulfoxide and that the corresponding sulfone was always formed as by-product. According to [16], the direction of oxidation of sulfides strongly depends on the solvent and the presence of protic or aprotic substances. Polar solvents (CH_3CN, CH_2Cl_2, CH_3COCH_3) favor formation of sulfoxides, while nonpolar (e.g., CCl_4) increase the fraction of sulfones. In addition, the reaction system should be homogeneous to ensure successful oxidation.

Taking into account published data, the oxidation of sulfides was performed in acetonitrile at –5 to –10°C in the presence of 0.05 mol of $Na_2B_2O_7 \cdot 10H_2O$ in a 4×10^{-4} M aqueous solution of Trilone B (pH 9), the ratio ketone **I**–Oxone–sulfide being 1:1:1. To avoid prolonged contact of the substrate with Oxone, an aqueous solution of the latter was gradually added to the reaction mixture. The temperature range was selected on the basis of the following considerations: (1) the probability for direct oxidation of sulfides with peroxodisulfate ion (Oxone) decreases at low temperature [17] and (2) strongly reduced temperature (below –14°C) induces thickening of the reaction mixture. The results are summarized in table.

Scheme 3.



B C

Oxidation of sulfides **II**–**VI** to sulfoxides **VIII**–**XII** with chiral dioxirane **A**

Compound no.	Yield, %	Specific rotation $[\alpha]_D^{20}$ (concentration, %, solvent)		Optical purity, %
		experiment	reference data	
VIII	60.0	14.7 (1, acetone)	135 (1, acetone), *ee* = 99.2% [18]	10.8
IX	55.0	27.1 (1, $CHCl_3$)	192 (1, $CHCl_3$), *ee* = 100% [19]	14.1
X	51.2	3.7 (1, $CHCl_3$)	145 (1, $CHCl_3$), *ee* = 83% [19]	2.1
XI	48.0	37.5 (1, acetone)	145 (2, acetone), *ee* = 99.5% [18]	25.7
XII	46.7	10.1 (1, $CHCl_3$)	156.9 (0.75, $CHCl_3$), *ee* = 99.3% [18]	6.4

According to the GC–MS data, the major oxidation product obtained from benzyl methyl sulfide (**VII**) under standard conditions was the corresponding sulfone, and we failed to isolate benzyl methyl sulfoxide (**XIII**) as individual substance. The composition of the reaction mixtures was monitored by mass spectrometry and GC–MS. The mass spectra of **VIII**, **IX**, and **XI**–**XIII** are available from MS libraries; therefore, we had no difficulties in identification of these compounds. In most cases, the corresponding sulfones were detected among the products in addition to sulfoxides, and in some cases the former were the major products (e.g., in the oxidation of **VII**). Sulfoxide **X** was identified by the GC–MS data (the corresponding reference data were lacking). The mass spectrum of **X** contained the molecular ion peak with *m*/*z* 168, indicating addition of one oxygen atom. Fragmentation of such compounds typically includes elimination of propylene molecule, *m*/*z* 42 $[C_3H_6]^+$, from the molecular ion $[M]^+$. In fact, we observed a fragment ion peak with *m*/*z* 126 $[M - C_3H_6]^+$ in the mass spectrum. The most abundant ion (I_{rel} 100%) was $[C_6H_6]^+$ with *m*/*z* 78; its formation is typical of the corresponding sulfone. We can conclude that this process requires the presence of one or two oxygen atoms attached to sulfur, for initial sulfide does not produce ion with *m*/*z* 78. Among the oxidation products of methyl phenyl sulfide, we detected a small amount of diphenyl disulfide (*m*/*z* 218) in addition to methyl phenyl sulfoxide and methyl phenyl sulfone.

Despite a poor enantiomeric purity of the resulting sulfoxides, we can state with certainty that dioxirane **A** participates in the oxidation of sulfides. The examined procedure is not free from disadvantages intrinsic to many (unless all) chemical methods for enantioselective oxidation of sulfides, specifically from strong dependence of the results on particular substrate and undesirable formation of extra oxidation product (sulfone). Presumably, the reason is participation of free peroxodisulfate ion in the process. Further improvement of the proposed procedure may include separation of the stages involving generation of chiral dioxiranes and enantioselective oxidation, as well as search for more volatile chiral dioxiranes which could be isolated (in this case, the use of other achiral oxidants could be avoided).

EXPERIMENTAL

The NMR spectra were recorded on Bruker MSL-400 and Bruker Avance-600 spectrometers using $CDCl_3$ as solvent and reference. The optical rotations were measured on a Perkin–Elmer 341 polarimeter. The IR spectra were obtained on a UR-20 instrument and a Bruker Vektor-22 Fourier spectrometer from neat substances or samples dispersed in mineral oil. The mass spectra (electron impact, 60 eV) were run on a MAT-212 mass spectrometer with direct sample admission into the ion source (electron emission current 0.1 mA, ion source temperature 120°C, batch inlet temperature 60°C). The GC–MS data were acquired using a 50-m SE-54 column, injector temperature 220°C, oven temperature programming from 100°C (6 min) at 6 deg/min to 220°C (20 min); recording of the mass spectra was started in 4 min after injection. The purity of the products was checked by TLC on Silufol plates (development with iodine vapor). Ketone **I** was synthesized by the procedure reported in [13]. Sulfides **II**–**IV** were prepared as described in [20]. Sulfides **V**–**VII** and Oxone were commercial products (Lancaster).

Oxidation of alkyl aryl sulfides II–V (*general procedure***).** A mixture of 2.58 g (10 mmol) of ketone **I** in 133 ml of acetonitrile, 100 ml of a solution of 0.05 mol of $Na_2B_4O_7 \cdot 10H_2O$ in 4×10^{-4} M aqueous Trilone B, 9.28 g (67.3 mmol) of K_2CO_3 in 65 ml of water, and 10 mmol of sulfide **II**–**V** in 65 ml of aceto-

nitrile was cooled to –5 to –10°C, and a solution of 6.14 g (10 mmol) of Oxone in 65 ml of 4×10^{-4} M aqueous Trilone B was added dropwise over a period of 8 h, maintaining the temperature within the above range. The mixture was stirred for an additional 1 h, diluted with 300 ml of water, and extracted with methylene chloride (3×100 ml). The extracts were combined, washed with a saturated solution of NaCl, and dried over Na_2SO_4. The solvent was removed, and the product was purified by column chromatography on silica gel L (40–100 μm) using petroleum ether–diethyl ether (3:1) as eluent.

(*R*)-Methyl phenyl sulfoxide (VIII). IR spectrum, ν, cm^{-1}: 3450, 1655, 1347, 1445, 1415, 1090, 1048, 958, 749, 692, 502. ^{1}H NMR spectrum, δ, ppm: 2.73 s (3H), 7.49–7.54 m (3H), 7.64 d (2H, *J* = 5.08 Hz).

(*R*)-Phenyl propyl sulfoxide (IX). IR spectrum, ν, cm^{-1}: 3060, 1585, 1450, 1300, 1110, 1050, 1030, 1000, 760, 695, 600, 570, 540. ^{1}H NMR spectrum, δ, ppm: 0.80 t (3H), 1.23–1.81 m (2H), 2.62 t (2H), 7.48–7.53 m (3H), 7.63 d (2H, *J* = 5.08 Hz).

(*R*)-Isopropyl phenyl sulfoxide (X). IR spectrum, ν, cm^{-1}: 3060, 1585, 1445, 1310, 1095, 1055, 1030, 1005, 760, 700, 580, 545, 510. ^{1}H NMR spectrum, δ, ppm: 1.10 d (3H, *J* = 6.84 Hz), 1.19 d (3H, *J* = 7.02 Hz), 2.84–2.76 m (1H), 7.49–7.46 m (3H), 7.56 d (2H, *J* = 7.56 Hz).

(*R*)-Methyl *p*-tolyl sulfoxide (XI). IR spectrum, ν, cm^{-1}: 3040, 1590, 1450, 1060, 1030, 815, 760, 690, 540. ^{1}H NMR spectrum, δ, ppm: 2.47 s (3H), 3.04 s (3H), 7.38 d (2H, *J* = 7.86 Hz), 7.70 d (2H, *J* = 8.1 Hz).

Oxidation of methyl *p*-nitrophenyl sulfide (VI). A mixture of 2.58 g (10 mmol) of ketone **I** in 133 ml of acetonitrile, 100 ml of a solution of 0.05 mol of $Na_2B_4O_7\cdot10H_2O$ in 4×10^{-4} M aqueous Trilone B, 9.28 g (67.3 mmol) of K_2CO_3 in 65 ml of water, and 1.69 g (10 mmol) of methyl *p*-nitrophenyl sulfide in 65 ml of diethyl ether was cooled to –7 to –10°C. A solution of 6.14 g (10 mmol) of Oxone in 65 ml of 4×10^{-4} M aqueous Trilone B was added dropwise to the above mixture over a period of 8 h at –7 to –10°C. The mixture was stirred for 1 h, diluted with 300 ml of water, and extracted with diethyl ether (3×100 ml). The extracts were combined, washed with a solution of NaCl, and dried over Na_2SO_4. The solvent was removed, and the product was purified by column chromatography on silica gel L (40–100 μm) using petroleum ether–diethyl ether (15:1) as eluent.

(*R*)-Methyl *p*-nitrophenyl sulfoxide (XII). IR spectrum, ν, cm^{-1}: 3099, 2990, 2925, 1601, 1579, 1519, 1462, 1344, 1153, 1086, 962, 852, 775, 739, 721, 682, 560, 527. ^{1}H NMR spectrum, δ, ppm: 2.79 s (3H), 7.83 d (2H, *J* = 8.76 Hz), 8.39 d (2H, *J* = 8.44 Hz).

The yields and optical purities of compounds **VIII**–**XII** are given in table.

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