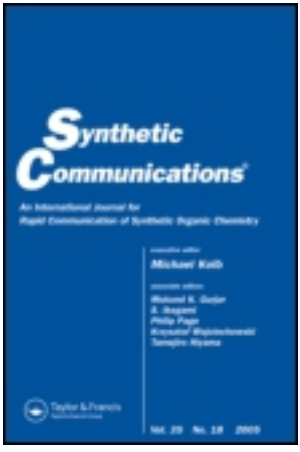

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Chemoselective Oxidation of Sulfides to Sulfones with Magnesium Monoperoxyphthalate (MMPP) On Silica Gel Support in Methylene Chloride Solvent

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CHEMOSELECTIVE OXIDATION OF SULFIDES TO SULFONES WITH MAGNESIUM MONOPEROXYPHTHALATE (MMPP) ON SILICA GEL SUPPORT IN METHYLENE CHLORIDE SOLVENT.

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A simple, efficient and chemoselective, non-aqueous procedure for oxidation of sulfides to the corresponding sulfones with magnesium monoperoxyphthalate on hydrated silica gel has been developed.

Sulfones are important intermediates in organic synthesis.[1] The most widely used method for sulfone synthesis is the oxidation of the corresponding sulfide. A number of methods have been developed for such conversion.[2] Most of these methods work well for simple alkyl or aryl sulfides, however, presence of functionalities on the substrate often complicate the oxidation of sulfides to sulfones due to the competing reactions of the functional groups.[2] Additional disadvantages such as laborious preparation of the oxidizing reagent, employment of heavy metal based reagents, or requirements of aqueous media make them synthetically unattractive. Few of these procedures can be used to selectively oxidize sulfides to sulfoxides or sulfides to sulfones.[2] In this

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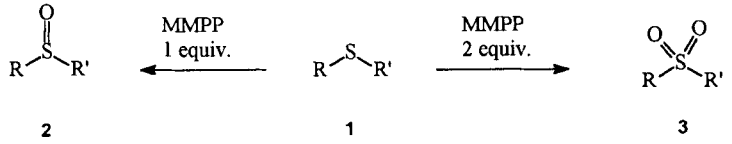
paper, we report a simple, mild, and highly chemoselective oxidation procedure that can be used to oxidize a wide range of sulfides to the corresponding sulfones in excellent yields.

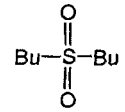
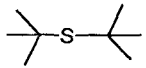
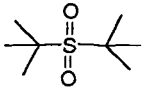
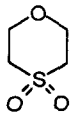
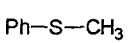
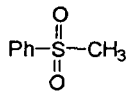
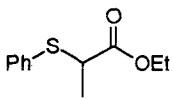
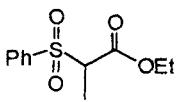
We have recently demonstrated that MMPP can oxidize a variety sulfides to sulfoxides in excellent yields on hydrated silica gel support in methylene chloride solvent.[3] We report herein an extension of this method to include oxidation of sulfides to sulfones. As reported elsewhere when one mole equivalent of MMPP is used the sulfide is oxidized to the corresponding sulfoxide[3], however, if two mole equivalents or excess MMPP is employed sulfones are produced, equation-1.



2 1 3 (1)

Oxidation procedures employing MMPP reagent are generally carried out in protic solvents such as water or alcohol due to the limited solubility of MMPP in aprotic solvents. However, the present method employs methylene chloride, an aprotic solvent, as the reaction media. In this procedure, a mixture of hydrated silica gel, MMPP and solution of a sulfide in methylene chloride is stirred at 40°C (at room temperature in one case) for the duration listed in the Table. Under these reaction conditions, sulfides containing functional groups such as alkene, ether, ester, ketone, and nitro groups are oxidized to the corresponding sulfones

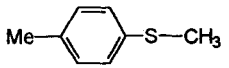
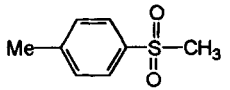
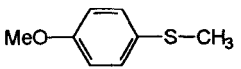
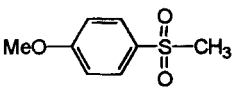
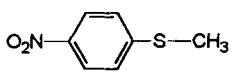
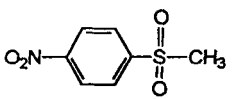
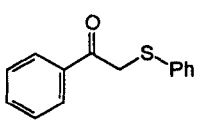
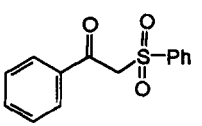
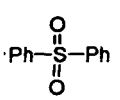
Table : Oxidation of sulfides to sulfones

	Sulfide (1)	Sulfone (3)	Yield%[a]	Rxn. time min.	mp/bp °C	(reported)[4]
a.			90	40	43	44
b.			95	40	128-129	130
c.			100	50	283-284	284-285
d.			100	50	130-132	132
e.			100	60	85-86	88
f.			80[b] 92[c]	120 12 hr	yellow oil	yellow oil

a. Isolated yield. **b**. Remaining intermediate sulfoxide isolated. **c**. Reaction performed at room temperature.

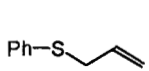
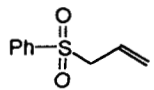
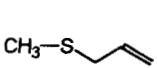
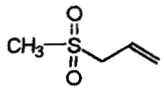
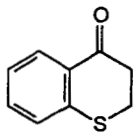
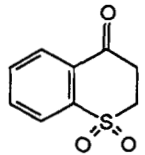
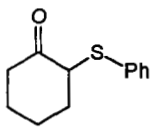
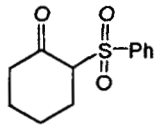
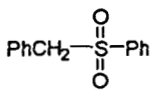
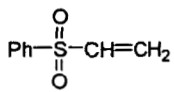
(*continued*)

Table (Contd.) : Oxidation of sulfides to sulfones

	Sulfide (1)	Sulfone (3)	Yield%[a]	Rxn. time min.	mp/bp °C	(reported)[4]
g.			100	70	84-86	86
h.			95	20	120-122	121
i.			92	180	139-141	142
j.			74[b]	5 hr	93-94	93-95
k.	Ph—S—Ph		93	10 hr	120-122	123

a. Isolated yield. b. Remaining intermediate sulfoxide isolated.

Table (Contd.): Oxidation of sulfides to sulfones

	Sulfide (1)	Sulfone (3)	Yield%[a]	Rxn. time min.	mp/bp °C	(reported)[4]
l.			70[b]	60	109-111 (0.5 torr)	110-113 (0.5 torr)
m.			100	50	oil	oil
n.			84	85	130-132	130-131
o.			90	120	84-86	87
p.	$PhCH_2SPh$		94	75	40-42	39-42
q.	$Ph-S-CH=CH_2$		91	60	65-67	67-69

a. Isolated yield. b. Remaining intermediate sulfoxide isolated.

in high yields, and without any interference from these groups. The oxidation procedure described here is easy to carry out and does not require any aqueous work-up. A simple filtration removes the solid which include the by-product of the MMPP reagent and any excess MMPP, if present, from the reaction mixture. In most cases, pure, or nearly pure, products were obtained when the solvent was removed from the filtrate by rotary evaporation. Radial chromatography was employed to purify the impure products.

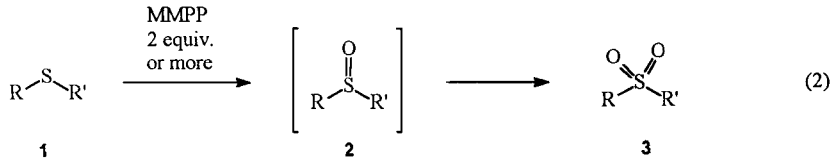
The synthetic utility of this method is clearly demonstrated by its ability to oxidize sulfides containing various functional groups under mild conditions. The oxidation reactions are facile at 40°C. The reactions also proceed at room temperature at a slower rate. For example, the oxidation of ethyl α-phenylthio propionate **1f** to the corresponding α-phenylsulfonyl propionate **3f** at 40°C was complete in 2 hours, whereas at room temperature it took 12 hours. Sulfides containing an alkene moiety such as allyl phenyl sulfide **1l**, allyl methyl sulfide **1m**, phenyl vinyl sulfide **1q**, or sulfides bearing carbonyl functional group such as ethyl α-phenylthio propionate **1f**, α-phenylthio acetophenone **1j**, thiochroman-1-one **1n**, and α-phenylthio cyclohexanone **1o** were each oxidized to the corresponding sulfones in excellent yields. This result is particularly notable since alkene and carbonyl functional groups are vulnerable to attack by peroxy reagents.[5] Trost[6] and Maikap[7] have reported oxidation procedures for the

conversion of sulfides to the sulfones that tolerate the presence of alkene and carbonyl functional groups, however, these procedures are slow, require aqueous media or employ special reagents which require laborious preparation. As a result those methods are not synthetically useful. Until now, simple method to selectively oxidize sulfide to sulfone in the presence of a wide range of functional groups was rare. The ability of this newly developed method to selectively produce either sulfoxides[3] or sulfones by controlling the amount of MMPP used in the reaction is also remarkable. Only a few reported sulfide oxidation procedures have demonstrated such chemoselectivity.[8]

The quantitative conversion of *tert*-butylsulfide **1b** to the *tert*-butylsulfone **3b** in only 40 minutes indicates that Steric hindrance has no detrimental effect on the oxidation procedure. However, a strong electronic effect by groups at the para position of substituted-aryl alkyl sulfide on the rate of oxidation reaction has been observed. For example, oxidation of methyl *p*-methoxyphenyl sulfide **1h** took only 20 minutes whereas methyl *p*-nitrophenyl sulfide **1i** took 3 hours. This observation is consistent with the reports in the literature regarding oxidation of sulfides with electrophilic oxidizing agents.[9]

Our previous investigation found that during oxidation of sulfides to the corresponding sulfoxides no significant amount of sulfone was detected in the reaction mixture at any time.[3] However, when oxidation

reactions employing two or more equivalents of MMP are stopped by removing MMPP by filtration before the sulfide is completely oxidized to the sulfone, the reactions yield a mixture of sulfoxide and sulfone. These observations indicate that under the reaction conditions presented in this paper the oxidation of sulfides to sulfones proceeds through the formation of sulfoxides, equation-2. Oxidation of a sulfide to the corresponding sulfoxide is apparently faster than oxidation of a sulfoxide to the corresponding sulfones. The later observation was expected from the electrophilic reagent MMPP.[10]



(2)

In conclusion, the method presented in this paper offers a simple, mild, efficient, and highly chemoselective procedure for conversion of sulfides to sulfones in reasonably short time.

Experimental

All reaction mixtures were magnetically stirred. Methylene chloride was used as received from the supplier without further purification. Sulfides **1a-e**, **1g-i**, **1k**, **1n**, and **1q** were purchased from Aldrich Chemical Company, U. S. A. The above sulfides used as they were received without further purification. Sulfides **1f**, **1j**, **1o**, and **1p** were prepared according to the procedure discussed in reference 3. Reactions reported in the Table-1 employed 3.0 - 4.0 mole equivalents of MMPP. All

products are known compounds and were identified by comparison of the NMR, IR and melting point data with those reported in the literature or of authentic commercial products. Magnesium monoperoxyphthalate (MMPP) was purchased from Aldrich Chemical Company, U. S. A. The silica gel used in the oxidation reactions as solid support was MN-Kieselgel 60 (0.04-0.063 mm mesh) supplied by Fisher Scientific. ^{1}H NMR spectra were recorded on a Hitachi-Perkin Elmer R-24A 60 MHz NMR instrument. Samples for NMR were dissolved in $CDCl_3$. ^{1}H chemical shifts are expressed as ppm relative to tetramethylsilane. IR spectra were recorded on an Analect RFX-30 FT-IR instrument and are reported in wavenumbers (cm^{-1}). Chromatographic separations were carried out by preparative centrifugal thin-layer chromatography with silica gel (Merck #7749) on a Chromatotron Model 7924T. Analytical thin-layer chromatography was done on precoated silica gel plates with 254 nm fluorescent indicator (Merck # 5715) and developed in the indicated solvent systems. Compounds were visualized under a UV lamp and/or by staining either with a *p*-anisaldehyde/sulfuric acid or phosphomolybdic acid.

Oxidation of dibutyl sulfide to the dibutyl sulfone: a general procedure for sulfides (1a-q) oxidation.

The following oxidation procedure for butyl sulfide is representative of all sulfides presented in the Table-1:

Dry silica gel (10 g) was placed in a 100 mL round bottom flask containing a magnetic stirring bar and fitted with a condenser. Water (5.0 g) was added slowly from a syringe to the vigorously stirred silica gel. After complete addition of the water, stirring continued until a free flowing powder was obtained (5 min). Magnesium monoperoxyphthalate (2.3 g, 4.65 mmol) was added to the above flask and the solids were mixed by stirring. Methylene chloride (25 mL) was added to the flask. A solution of butyl sulfide **1a** (368 mg, 2.52 mmol) in methylene chloride (5 mL) was added slowly to the stirred heterogeneous mixture. The reaction mixture was stirred at 40°C (refluxed) for 40 minutes. During this period complete disappearance of the butyl sulfide was evident by thin-layer chromatography which utilized ethyl acetate:hexane (1:1) as the developing solvent and *p*-anisaldehyde/sulfuric acid as the staining agent. The reaction mixture was then filtered through a sintered glass funnel, the solid residue was washed with methylene chloride (75 mL) and the washings were added to the filtrate. Removal of solvent from the filtrate under vacuum produced a colorless thick oil. Radial chromatography of the crude product using ethyl acetate:hexane (1:1) as the eluent produced butyl sulfone **3a** as a colorless thick oil (404 mg, 90% yield).

Spectral data for Compounds 3a-q:

Products 3a-q are known compounds and their identities were established by comparison of their NMR and IR data with the data

reported in the literature.

Dibutyl Sulfone 3a[11]

^{1}H NMR 0.95 (t, 6H, *J*=7.0 Hz), 1.20-2.00 (m, 8H), 3.01 (t, *J*=7.0 Hz, 4H). IR 787, 918, 1000, 1105, 1141, 1275, 1401, 2876, 2945, 2979.

***Ditert*-Butyl sulfone 3b**[11]

^{1}H NMR 1.50 (s). IR 700, 809, 1098, 1185, 1273, 1490, 2870, 2940, 2983.

Tetrahydrothiophene dioxide 3c[11]

^{1}H NMR 2.00-2.50 (m, 4H), 2.75-3.2.0 (m, 4H). IR 890, 1095, 1145, 1265, 1470, 2870, 2910.

1,4-Oxathiane 4,4-dioxide 3d[12]

^{1}H NMR 3.00-3.25 (m, 4H), 4.00-4.25 (m, 4H). IR 733, 852, 994, 1114, 1201, 1300, 1380, 1406, 2891, 2936, 2990.

Methyl phenyl sulfone 3e[13]

^{1}H NMR 3.05 (s, 3H), 7.70 (m, 2H), 8.00 (m, 2H). IR 780, 840, 1160, 1330, 1230, 1370, 2930, 3010.

Ethyα-phenylsulfonylpropionate 3f[14]

^{1}H NMR 1.15 (t, *j*=7.0 Hz, 3H), 1.55 (d, *j*=7.4 Hz, 3H), 4.05 (q, *j*=7.5 Hz, 1H), 4.10 (q, *j*=7.5 Hz, 2H), 7.35-7.90 (m, 5H). IR 754, 1027, 1082, 1191, 1220, 1380, 1444, 1747, 2873, 2947, 2990, 3076.

Methyl 4-methylphenyl sulfone 3g[11]

^{1}H NMR 2.42 (s, 3H), 3.00 (s, 3H), 7.30 (d, *j*=8.5 Hz, 2H), 7.75 (d, *j*=8.5 Hz, 2H); IR 765, 831, 973, 1098, 1153, 1307, 2931, 3018.

4-Methoxyphenyl methyl sulfone 3h[11]

^{1}H NMR 3.00 (s, 3H), 3.80 (s, 3H), 7.00 (d, *j*=9 Hz, 2H), 7.80 (d, *j*=9 Hz, 2H). IR 776, 842, 984, 1038, 1158, 1307, 1470, 1510, 1600, 2854, 2930, 2972, 2990, 3070, 3100.

Methyl 4-nitrophenyl sulfone 3i[12]

^{1}H NMR 3.10 (s, 3H), 8.10 (d, *j*=9 Hz, 2H), 8.40 (d, *j*=9 Hz, 2H). IR 683, 749, 793, 869, 977, 1080, 1205, 1360, 1545, 2942, 3028, 3110.

2-(Phenylsulfonyl)- acetophenone 3j[13]

^{1}H NMR 4.75 (s, 2H), 7.20-7.90 (m, 10H). IR 682, 765, 1005, 1092, 1160, 1321, 1410, 1463, 1587, 1605, 1681, 1677, 2947, 3012.

Diphenyl sulfone 3k[11]

^{1}H NMR 7.20-7.40 (m, 6H), 7.70-7.85 (m, 4H) IR 708, 744, 776, 1081, 1114, 1168, 1328, 1458, 3094.

Allyl phenyl sulfone 3l[13]

^{1}H NMR 3.80 (d, 2H), 4.90-5.40 (m, 2H), 5.45-6.00 (m, 1H), 7.30-7.70 (m, 3H), 7.75-7.90 (m, 2H). IR 885, 951, 1005, 1092, 1158, 1322, 1463, 1580, 2925, 2990, 3078, 3100.

Allyl methyl sulfone 3m[15]

^{1}H NMR 2.90 (s, 3H), 3.75 (d, 2H), 5.25-5.80 (m, 3H). IR 951, 1147, 1321, 1400, 2936, 2975, 3034.

Thiochroman-4-one s,s-dioxide 3n[16]

^{1}H NMR 3.50 (symmetric m, 4H), 7.60-8.01 (m, 4H). IR 721, 918, 1119, 1141, 1179, 1207, 1262, 1480, 1698, 2960, 3094.

α-Phenylsulfonyl cyclohexanone 3o[17]

^{1}H NMR 1.70-2.85 (m, 8H), 4.10 (t, 1H), 7.50-8.10 (m, 5H). IR 765, 1147, 1338, 1484, 1585, 1686, 1742, 2876, 2955, 3078.

Benzyl phenyl sulfone 3p[13]

^{1}H NMR 4.35 (s, 2H), 6.90-8.00 (m, 10H). IR 705, 771, 804, 1087, 1131, 1164, 1305, 1458, 2930, 2960, 3065.

Phenyl vinyl sulfone 3q[11]

^{1}H NMR 5.80-6.90 (m, 3H), 7.30-7.90 (m, 5H). IR 918, 1158, 1316, 1458, 2941, 3072.

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