A Facile and Selective Procedure for Oxidation of Sulfides to Sulfoxides with Molecular Bromine on Hydrated Silica Gel in Dichloromethane

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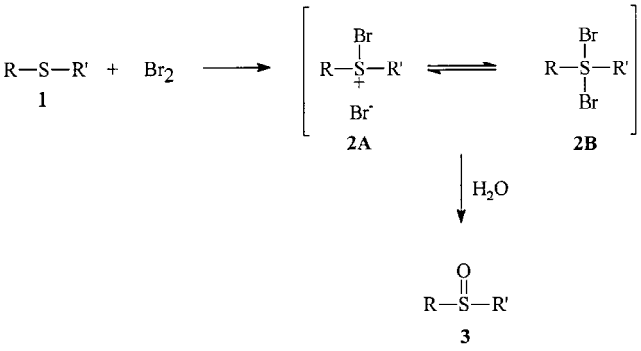
Abstract: A new method for oxidation of sulfides to sulfoxides with molecular bromine on a solid silica gel support has been developed. This procedure cleanly oxidizes sulfides to the corresponding sulfoxides in excellent yields. To our knowledge, this is the first example of oxidation of sulfides by molecular bromine in dichloromethane that does not require the presence of a base or another reagent to scavenge the byproduct hydrogen bromide in order to prevent side reactions. The reported procedure is simple, fast, product isolation is trivial, and it produces excellent yields.

Key words: sulfides, sulfoxides, bromine, hydrated silica gel support, solid, support

The biggest disadvantage of the utilization of bromine in the oxidation of sulfides was undesired side reactions that often predominated over sulfoxide formation.[1] Cleavage of the C–S bond and bromination of the sulfide substrate at various positions are two unwanted reactions observed in this oxidation process. Hydrogen bromide is considered responsible for these unwanted side reactions. Procedures that produced limited success in preventing these side reactions utilized either a complex of bromine and an amine in aqueous acetic acid media, or are carried out in a biphasic medium (CH_2Cl_2/H_2O) using potassium hydrogen carbonate or pyridine as the hydrogen bromide acceptor.[2] Another procedure involved treatment of the reaction mixture with hexabutyldistannoxane in order to suppress the formation of sulfones.[3] Although these reactions have some success in preventing undesired side reactions, they are less attractive because they require additional steps in the preparation of the bromine–amine complexes or utilize a toxic reagent. In addition, reactions in aqueous media produce low product yields. This demonstrates the need for a simple and efficient method for conversion of sulfides to the corresponding sulfoxides with molecular bromine.

We have recently demonstrated that sulfides can be oxidized to sulfoxides or sulfones on hydrated silica gel employing magnesium monoperoxyphthalate (MMPP) as the oxidant in dichloromethane solvent.[4] In this paper, we demonstrate that bromine can also be utilized as the oxidant for conversion of sulfides to the corresponding sulfoxides on hydrated silica gel utilizing dichloromethane as the solvent. Use of hydrated silica gel as solid support for this oxidation reaction offers many advantages. These include: (1) dichloromethane can be utilized as the reaction media instead of water which was traditionally employed in the oxidation reactions with bromine; (2) hydrated silica gel activates the oxidation reaction by dispersing the oxidant, which is reflected in the very short reaction time for oxidation of sulfides with bromine supported on silica gel compared to the longer reaction time for non-silica gel supported reactions;[3] and (3) hydrated silica gel support eliminates laborious aqueous workup of the reaction, as the solid support, and the byproduct of the oxidant are all easily removed by filtration. In addition, bromine is an inexpensive and readily available reagent. In this procedure, a dichloromethane solution of bromine (5–10 mole percent excess) is added to a heterogeneous mixture of a sulfide and hydrated silica gel (see the general procedure) in dichloromethane. The reaction mixture is stirred at room temperature for five minutes or until the reaction is complete (reaction time for various sulfides listed in the Table). The reaction mixture is then filtered and the solid is washed with dichloromethane. Removal of solvent from the filtrate yields product. Impure products were purified by radial chromatography utilizing chromatotron.

We believe this oxidation process follows the mechanism previously proposed in the literature.[1]

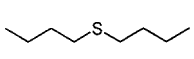
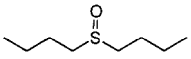
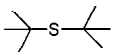
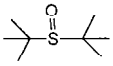
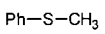
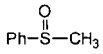
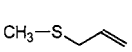
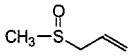
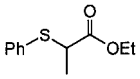
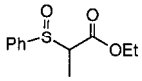
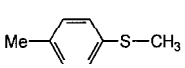
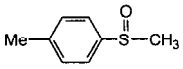
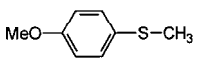
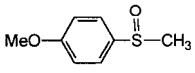
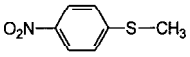
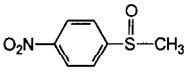
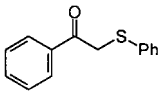
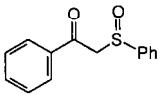
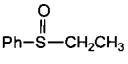
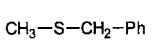
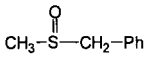


In this reaction, hydrated silica gel also plays the following two very important roles. (i) The water present in the hydrated silica gel affects the hydrolysis of the sulfonium bromide **2A** and/or sulfurane **2B** intermediate to the sulfoxide. (ii) Silica gel acts as a hydrogen bromide acceptor. Hydrogen bromide is absorbed on the silica gel and as a result side reactions, which are believed to be initiated by free hydrogen bromide, are minimized.

This new method provides a convenient, fast, and economic way to oxidize sulfides to the corresponding sulfoxides. The most important feature of this procedure, unlike others, is that the presence of a base or another reagent is not required to prevent side reactions. Overoxidation of sulfides to sulfones can easily be prevented by not employing a large excess of bromine in the reaction.[5]

The selectivity of this procedure is excellent. Oxidation of sulfides to the corresponding sulfoxides can tolerate the

Table. Oxidation of Sulfides to Sulfoxides

1–3	Sulfide **1**	Sulfoxide **3**	Time (min.)[a]	Yield (%)[b]
a			10	100
b			40	100
c			50	100
d			50	100
e			60	100
f			5[c]	87
g			120	80
h			15	95
i			10	100
j			40	97
k			40	90
l			15	98
m			5	100
n			120	60[d]

[a] All reaction mixtures stirred at r.t. for at least 5 min.
[b] Isolated yield.
[c] Reaction temperature 0 °C.
[d] Remaining unreacted phenyl sulfide recovered.

presence of alkene, ketone, ester, nitro, and ether groups. Oxidation of ethyl 2-(phenylthio)propanoate **(1g)**, methyl 4-methylphenyl sulfide **(1h)**, 2-(phenylthio)acetophenone **(1k)** and benzyl methyl sulfide **(1m)** to the corresponding sulfoxides without any complication from bromination at the α-position is also notable. Until now, undesired α-bromination was the biggest disadvantage for employment of molecular bromine in the oxidation of sulfides.[1] Steric bulkiness of the sulfide has no detrimental effects on the efficacy of this procedure except, that as expected, oxidation of sterically hindered sulfides proceeds somewhat slowly compared to unhindered sulfides. For example, diphenyl sulfide **(1n)** requires a longer reaction time and produces yields which are lower than the other sulfides studied. This is not surprising since the reported oxidation of diphenyl sulfide with a complex of molecular bromine and hexabutyldistannoxane gave poor results.[3]

The results of oxidation of methyl 4-methylphenyl sulfide **(1h)**, 4-methoxyphenyl methyl sulfide **(1i)**, and methyl 4-nitrophenyl sulfide **(1j)**, clearly demonstrate that a deactivating group at the 4-position of the aromatic ring makes the sulfides less reactive whereas an activating group at this position makes it more reactive towards the oxidation reaction. This observation is consistent with the reported results on oxidation reactions of sulfides with electrophilic reagents.[6]

All reaction mixtures were magnetically stirred. CH_2Cl_2 was used as received from the supplier without any further purification. Sulfides **1a–f**, **1h–j** and **1n** were purchased from Aldrich Chemical Company, USA. and sulfides **1l,m** were purchased from Lancaster Synthesis Inc. The above sulfides were used as they were received without further purification. Sulfides **1g**, and **1k** were prepared according to the procedure described in ref 7. Reactions reported in the Table employed a slight excess of Br_2 (~10 mol% excess). All products are known compounds and were identified by comparison of the NMR and IR data with those reported in the literature or of authentic commercial products. Br_2 was purchased from Aldrich Chemical Company, USA. The silica gel used in the oxidation reactions as solid support was MN-Kieselgel 60 (0.04–0.063 mm mesh size) supplied by Fisher Scientific. ^{1}H NMR spectra were recorded on a Hitachi–Perkin Elmer R24A 60 MHz NMR instrument. Samples for NMR were dissolved in $CDCl_3$. ^{1}H chemical shifts are expressed as ppm relative to TMS. 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 TLC with silica gel (Merck #7749) on a Chromatotron Model 7924T. Analytical TLC 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 *p*-anisaldehyde/H_2SO_4 or phosphomolybdic acid.

Oxidation of Dibutyl Sulfide (1a) to Dibutyl Sulfoxide (3a); Typical Procedure:

Dry silica gel (5 g) was placed in a 100-mL round bottom flask containing a magnetic stirring bar and a loosely fitted rubber septum. Water (2.5 g) was added to the vigorously stirred silica gel. After complete addition of the water, stirring continued until a free flowing powder was obtained (5 min). CH_2Cl_2 (25 mL) was added to the flask. A solution of dibutyl sulfide **(1a)** (384 mg, 2.62 mmol) in CH_2Cl_2 (5 mL) was added to the stirred heterogeneous mixture. A solution of Br_2 (0.14 mL, 2.72 mmol) in CH_2Cl_2 (2 mL) was added dropwise from a syringe to the mixture. The color of the Br_2 disappeared instantly. The mixture was stirred at r.t. for 10 min. During this period complete disappearance of the dibutyl sulfide was confirmed by TLC (EtOAc/hexane 1:1, *p*-anisaldehyde/H_2SO_4). The mixture was then filtered through a sintered glass funnel, the solid residue was washed with CH_2Cl_2 (75 mL) and the washings were added to the filtrate. Removal of solvent from the CH_2Cl_2 solution under vacuum produced a colorless thick oil. Radial chromatography (EtOAc/hexane 1:1) of the crude product produced dibutyl sulfoxide **(3a)** as a colorless thick oil (426 mg, 100%).

Dibutyl Sulfoxide **(3a)**:[8]
^{1}H NMR: δ = 0.974 (t, 6H, J = 7.0 Hz), 1.20–1.8 (m, 8H), 2.70 (t, J = 7.0 Hz, 4H).
IR: ν = 1027, 1280, 1406, 1425, 1469, 2887, 2942, 2964 cm^{-1}.

Di-tert-*butyl Sulfoxide* **(3b)**:[9]
^{1}H NMR: δ = 1.35 (s).
IR: ν = 816, 1027, 1035, 1180, 1236, 1376, 1485, 2876, 2931, 2963 cm^{-1}.

1-Oxotetrahydrothiophene **(3c)**:[8]
^{1}H NMR: δ = 1.80–2.50 (m, 4H), 2.55–2.90 (m, 4H).
IR: ν = 1025, 1215, 1235, 1616, 1771, 1725, 2887, 2952 cm^{-1}.

4-Oxo-1,4-thioxane **(3d)**:[10]
^{1}H NMR: δ = 2.40–3.10 (m, 4H), 3.50–4.50 (m, 4H).
IR: ν = 1005, 1028, 1071, 1114, 1224, 1289, 1398, 1409, 1475, 1660, 2871, 2936, 2980 cm^{-1}.

Methyl Phenyl Sulfoxide **(3e)**:[8]
^{1}H NMR: δ = 2.68 (s, 3H), 7.40–7.70 (m, 5H).
IR: ν = 692, 754, 954, 1046, 1092, 1415, 1446, 1477, 2915, 3000, 3062 cm^{-1}.

Allyl Methyl Sulfoxide **(3f)**:[11]
^{1}H NMR: δ = 2.05 (s, 3H), 3.48 (d, 2H), 5.10–6.20 (m, 3H).
IR: ν = 743, 951, 1049, 1431, 1649, 2925, 3001, 3088 cm^{-1}.

Ethyl 2-(Phenylsulfinyl)propanoate **(3g)**:[12]
^{1}H NMR: δ = 1.00–1.50 (m, 6H), 3.40– 4.50 (m, 3H), 7.45 (m, 5H).
IR: ν = 701, 759, 1060, 1094, 1180, 1232, 1325, 1385, 1464, 1741, 2873, 2920, 2954, 2988, 3070 cm^{-1}.

Methyl 4-Methylphenyl Sulfoxide **(3h)**:[13]
^{1}H NMR: δ = 2.40 (s, 3H), 2.70 (s, 3H), 7.30 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H).
IR: ν = 820, 962, 1049, 1093, 1420, 1507, 1605, 2882, 2936, 3000, 3056 cm^{-1}.

4-Methoxyphenyl Methyl Sulfoxide **(3i)**:[13]
^{1}H NMR: δ = 2.60 (s, 3H), 3.80 (s, 3H), 7.00 (d, J = 9 Hz, 2H), 7.50 (d, J = 9 Hz, 2H).
IR: ν = 820, 957, 986, 1016, 1103, 1180, 1267, 1311, 1474, 1507, 1605, 2860, 2915, 2969, 2990, 3078, 3100 cm^{-1}.

Methyl 4-Nitrophenyl Sulfoxide **(3j)**:[14]
^{1}H NMR: δ = 2.80 (s, 3H), 7.75 (d, J = 9 Hz, 2H), 8.30 (d, J = 9 Hz, 2H).
IR: ν = 748, 863, 967, 1048, 1094, 1348, 1533, 2868, 2925, 3029, 3110 cm^{-1}.

2-(Phenylsulfinyl)acetophenone **(3k)**:[15]
^{1}H NMR: δ = 4.10–4.60 (m, 2H), 7.20–7.90 (m, 10H).
IR: ν = 692, 754, 1000, 1046, 1092, 1200, 1277, 1446, 1468, 1587, 1600, 1677, 2908, 2954, 3000, 3062 cm^{-1}.

Ethyl Phenyl Sulfoxide **(3l)**:[16]
^{1}H NMR: δ = 1.10 (t, J = 8 Hz, 3H), 2.80 (dq, J = 8 Hz, 2H), 7.50 (m, 5H).
IR: ν = 692, 749, 965, 1022, 1040, 1078, 1412, 1446, 1488, 2954, 2976, 3056 cm^{-1}.

Benzyl Methyl Sulfoxide **(3m)**:[13]
^{1}H NMR: δ = 2.46 (s, 3H), 4.00 (s, 2H), 7.10–7.50 (m, 5H).
IR: ν = 1010, 1286, 1370, 1455, 1500, 3050 cm^{-1}.

Diphenyl Sulfoxide **(3n)**:[12]
^{1}H NMR: δ = 7.40–7.64 (m).
IR: ν = 708, 766, 1049, 1104, 1453, 1485, 3067 cm^{-1}.

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(5) We have found that in the presence of two or more mole equivalents of bromine, sulfides are oxidized to the sulfones in excellent yields. A study to explore this route to produce sulfones is in progress.
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(7) A mixture of PhSH, Et_3N, an appropriate chloro- or bromo-compound and Et_2O was stirred at r.t. overnight. The mixture, which produces copious amount of Et_3NHX (X = Cl or Br), was then filtered. The filtrate was washed with water and brine successively, and then dried (anhyd $MgSO_4$). The drying agent was removed by filtration, filtrate was concentrated under vacuum and the residue was purified by recrystallization or by flash chromatography as appropriate.
(8) This product was identified by comparing the NMR and IR data with those of the commercially available authentic sample.
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