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Graphical Abstract

Selective synthesis of sulfoxides and sulfones from sulfides by silica bromide as heterogeneous promoter and hydrogen peroxide as the terminal oxidant

Behrooz Maleki, Hojat Veisi, Alireza Sedrpoushan, Saba Hemmati, Samaneh Sedigh Ashrafi

✓ Chemoselective oxidation of sulfides to sulfoxides and sulfones
✓ Heterogeneous promoter
✓ Synthesis of sulfoxides and sulfones at room temperature
Selective synthesis of sulfoxides and sulfones from sulfides by silica bromide as heterogeneous promoter and hydrogen peroxide as the terminal oxidant

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Abstract

Silica bromide as heterogeneous promoter and reagent is prepared from reaction of silica gel with PBr₃ as a non-hydroscopic, filterable, cheap, and stable yellowish powder that can be stored for months. The results show that the silica bromide is suitable and efficient promoter for the chemoselective oxidation of sulfides to the corresponding sulfoxides or sulfones in the presence of 30% H₂O₂ in acetonitrile. The excellent yields, heterogeneous conditions, simplicity, compatibility with a variety of functionalities, and ease of isolation of the products make our procedure a practical alternative.

Key words: Silica bromide; Sulfides; Sulfoxides; Sulfones; Hydrogen peroxide
Introduction

In order to perform chemical reactions in heterogeneous media rather than homogeneous, deliberately a number of ideas was suggested by R. B. Merrifield\textsuperscript{1} for use in polypeptide synthesis and by R. L. Letsinger\textsuperscript{2} for polynucleotide synthesis. It was demonstrated that the classical idea that chemical reactions should be performed in a completely homogeneous medium was not necessarily correct and that reactions can be accomplished even if one of the substrates was insoluble in the reaction media. Uncatalyzed reactions of neat reactants are of elemental importance in chemistry and one of the most preferred transformations. The methodology of some organic synthesis has been revolutionized by this idea in that the normal procedures associated with the workup of a chemical reaction are obviated and replaced by a simple filtration step\textsuperscript{1,2}. This general advantage of solid-phase synthesis has been particularly exploited in polypeptide synthesis\textsuperscript{3} where a polypeptide is synthesized in a repetitive sequential manner on the solid phase and the final products are only liberated from the polymer in a final cleavage reaction. Another approach to using polymer supports in organic synthesis was outlined by Fridkin, Patchornik, and Katchalski,\textsuperscript{4} who showed that a polymer-bound reagent could be used in heterogeneous reaction in such a way that excess reagents or by-products remain attached to the insoluble resin. These unwanted materials are then removed by filtration and the pure product is isolated from the filtration\textsuperscript{5-11}.

Many specific advantages of using insoluble resins as supports, reagents, or catalysts have been reviewed,\textsuperscript{12,13} these include the simulation of high-dilution\textsuperscript{14,15} or pseudodilution\textsuperscript{16} conditions, the fishhook and concentration principle,\textsuperscript{17} selective intrapolymeric reactions,\textsuperscript{18} bulk and steric effects of the polymer backbone in asymmetric
synthesis,\textsuperscript{19} the stabilization of reactive substances,\textsuperscript{20,21} and the elimination of volatile malodorous reagents.\textsuperscript{22,23}

Oxidation of sulfides is the most straightforward method for the synthesis of sulfoxides and sulfones. Sulfones are valuable synthetic intermediates for the construction of various chemically and biologically significant molecules in particular.\textsuperscript{24,25} Sulfones represent an important course group of compounds due to their properties and reactivity. The direct oxidation of sulfides is an important and widely studied reaction for the preparation of sulfoxides and sulfones. However, the oxidation of sulfides to sulfones has been much less investigated as compared to the oxidation of sulfides to sulfoxides. For the selective oxidation of sulfides to sulfoxides and sulfones, a range of oxidants have been studied. In addition, $\text{H}_2\text{O}_2$ was frequently utilized in combination with different catalysts such as $\text{MoO}_3$,\textsuperscript{26} $\text{CH}_3\text{ReO}_3$,\textsuperscript{27} dioxo-molybdenum(VI) complex,\textsuperscript{28} $\text{NH}_4\text{Cl}$,\textsuperscript{29} polyoxometalate-cored dendrimers,\textsuperscript{30} silica-vanadia catalyst,\textsuperscript{31} silica sulfuric acid,\textsuperscript{32} heterogeneous $\text{TiO}_2$,\textsuperscript{33} tetra-(tetraalkylammonium)octamolybdate,\textsuperscript{34} immobilized molybdenum heteropolyacid,\textsuperscript{35} $\text{TaC}$ and $\text{NbC}$,\textsuperscript{36} sodium tungstate/PTC/phenylphosphonic acid,\textsuperscript{37} $\text{MoO}_2\text{Cl}_2$,\textsuperscript{38} $\text{Cp'Mo(CO)}_3\text{Cl}$,\textsuperscript{39} cerium (IV) triflate,\textsuperscript{40} cyanuric chloride,\textsuperscript{41} $[\text{SeO}_4\{\text{WO(O}_2\}_2]_2$,\textsuperscript{42} composite oxide catalyst LiNbMoO$_6$,\textsuperscript{43} carbon-based solid acid,\textsuperscript{44} 1,3,4-triazaz-2,4,6-triphosphorine-2,2,4,4,6,6-tetrachloride,\textsuperscript{45} $\text{H}_3\text{BO}_3$,\textsuperscript{46} $\text{H}_5\text{IO}_6$,\textsuperscript{47,49} ozone,\textsuperscript{50} an aqueous $\text{NaOCl}$,\textsuperscript{51} $\text{HOF-CH}_3\text{CN}$,\textsuperscript{52} oxygen/2-methylpropanal,\textsuperscript{53} $\text{NaIO}_4$,\textsuperscript{54} Oxone,\textsuperscript{55} $\text{ZnCl}_2$/DBU,\textsuperscript{56} $[(\text{C}_{18}\text{H}_{37})_2(\text{CH}_3)_2\text{N}][\text{SiO}_4\text{H(WO}_5\_3]$,\textsuperscript{57} $\text{TsOH/PhI(OAc)}_2$,\textsuperscript{58} $\text{PyHBr}_3$/TBN,\textsuperscript{59} $(\text{C}_{19}\text{H}_{32}\text{N})_2[\text{MoO(O}_2\_2(\text{C}_2\text{O}_4)]\text{.H}_2\text{O}$,\textsuperscript{60} poly(N-vinylpyrrolidone) and poly(4-vinylpyridine),\textsuperscript{61} silica-based tungstate interphase,\textsuperscript{62} and 30% $\text{H}_2\text{O}_2$.\textsuperscript{63}
Besides extended reaction times, some of these processes suffer from drawbacks, such as elevated temperatures, undesired side reactions occurring on other functional groups, the use of hazardous peracids, and toxic metallic compounds that generate waste streams. However, a promoter was still required in those processes. Therefore, simple, convenient and environmentally benign methods for the oxidation of sulfides to sulfoxides or to sulfones are still highly desired.

**Result and Discussions**

In continuation of our research on new synthetic methods in organic synthesis, herein, we report the application of silica bromide as a selective and efficient heterogeneous promoter for the oxidation of sulfides into sulfoxides and sulfones using H$_2$O$_2$ in acetonitrile at room temperature (Scheme 1).

![Scheme 1](image-url)

**Scheme 1** Conversion of sulfides into sulfoxides and sulfones.

Heterogeneous reagents have gained significant attraction due to economic and environmental considerations. They can be handled conveniently and removed from the reaction mixture, thus making experimental procedures simple.
Silica bromide as heterogeneous promoter and reagent is prepared from reaction of silica gel with PBr$_3$ as a non-hygroscopic, filterable, cheap, and stable yellowish powder that can be stored for months.$^{78-81}$

A preliminary study with benzyl phenyl sulfide (2 mmol), 30% H$_2$O$_2$ (2 mmol), and silica bromide (2 mmole Br/ g silica ) as a model reaction quickly established that this oxidation protocol produced the anticipated sulfoxide in excellent yield (98%) and in a short reaction time (5 min) in CH$_3$CN at room temperature. Then, the influence of different reaction parameters (amount of reagents, temperature and solvent) on the efficiency of the oxidation process was evaluated in this model reaction. The oxidation was investigated in various solvents such as toluene, THF, CH$_3$CN, CH$_3$NO$_2$, CH$_3$OH, C$_2$H$_5$OH, CH$_3$COOH, CH$_2$Cl$_2$ and CCl$_4$ using 30% H$_2$O$_2$ (2 mmol), and silica bromide (2 mmole Br/ g silica ) at room temperature. After screening different solvents, it was found that CH$_3$CN is proved to be the optimum solvent and was used in subsequent optimization studies. At lower concentration of hydrogen peroxide (1 mmol), the reaction took a long time (10 min) and low yield (86%). The increasing of the hydrogen peroxide (3 mmol), loading did not significantly affect the yield and time. The reaction was also monitored with different silica bromide loading, at a lower silica bromide loading (1 mmol) the reaction took longer time (8 min) and lower yield (91%). Further increase in amount of silica bromide (3 mmol) in the mentioned reaction did not has significant effect on the product time and yield. It was also found that without H$_2$O$_2$, and silica bromide alone cannot oxidize sulfides to sulfoxides. Therefore, A ratio of (sulfide/H$_2$O$_2$/SB;2:2:2) was found to be optimum for the complete conversion of sulfides to sulfoxides in CH$_3$CN at room temperature.
In order to generalize the scope of the reaction, a series of structurally diverse sulfides were subjected to oxidation under the optimized reaction conditions, and the results are presented in Table 1. Oxidation of allyl phenyl, alkyl aryl, aryl benzyl, dialkyl, diaryl, cyclic, and heterocyclic sulfides produced excellent yields of the corresponding sulfoxides. It is notable that the sulfides were chemoselectively oxidized in the presence of oxidation-prone functional groups, such as OH and C≡C.

Table 1 Conversion of sulfides to sulfoxides or sulfones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time(^a) (min)</th>
<th>Yield(^b) (%)</th>
<th>Time(^a) (min)</th>
<th>Yield(^b) (%)</th>
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<td></td>
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<td>No.</td>
<td>Structure</td>
<td>Yield (°C)</td>
<td>Isolated Pure Sulfide (%)</td>
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*The course of reaction was checked by TLC or GC. \(^b\)Yield of isolated pure sulfide.

Encouraged by these results, we studied the complete conversion of sulfides (via sulfoxides) into sulfones. Initially, we optimized amount of silica bromide and hydrogen peroxide for oxidation of benzyl phenyl sulfide (2 mmol) to corresponding sulfone. The best result was obtained with a ratio of (benzyl phenyl sulfide /H_2O_2/SB;2:2:2) in CH_3OH at 40^\circ C. To investigate the versatility of the system, the reaction of oxidation sulfides (via sulfoxides) into sulfones was carried out in CH_3OH at 40^\circ C (Table 2). All reactions
proceeded efficiently within 25-100 minutes at 40°C to provide the corresponding sulfones derivatives in excellent yields ranging from 84-95%.

A possible mechanism for oxidation of the sulfide into the corresponding sulfoxides and sulfones using H$_2$O$_2$ in the presence of silica bromide is shown in Scheme 2. Nucleophilic attack of H$_2$O$_2$ on silica bromide leads to intermediate 1 in which the oxygen atom is more electrophilic. Next, nucleophilic attack of sulfide 2 on this intermediate gives intermediate 3 followed by the abstraction of hydrogen to yield the corresponding sulfoxide 4. Sulfoxide 4 reacts with the intermediate 1 to form 5, which follows the abstraction of hydrogen produces sulfone 6.

![Scheme 2 Proposed mechanism.](image)

**Experimental**

Chemicals were obtained from Merck and Fluka chemical companies. Nuclear magnetic resonance spectra were recorded on a Brucker Advanced DPX-250 MHz spectrometer using tetramethylsilane as internal standard. Infrared spectra were recorded
on a Perkin-Elmer 781 spectrometer. The plate silica gel used for the preparation of silica bromide was type 60 (15-40 µm).

**Procedure for preparation of silica bromide**

To silica gel (40 g) and dry toluene (80 mL) in a round bottomed flask equipped with a condenser and a drying tube, was added phosphorus tribromide (75 g, 0.21 mol) and refluxed for 18 h. After cooling, the product was filtered and washed, first, with dry 1,4-dioxane (2 x 20 mL) and then with dichloromethane (2 x 20 mL). The yellowish product was kept in dessicator. The amount of bromosilyl group (2.2 mmole of Br/ g silica) is determined by a standard method.\(^\text{78}\)

**General procedure for the preparation of sulfoxides**

To a mixture of sulfide (2 mmol) and yellowish silica bromide (2 mmole) in acetonitrile (5 mL) was added 30% H\(_2\)O\(_2\) (2 mmol). The mixture was stirred at room temperature for the appropriate period of time until complete consumption of the starting material as observed by TLC. After completion of the reaction, the reaction mixture was filtered to separate the white SiO\(_2\). Then, the filtrate was extracted with EtOAc (10 ml) and washed with Na\(_2\)CO\(_3\) (20%, 10 ml). The organic layer was dried over anhydrous Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure to afford the desired product without further purification (Table 1).

**General procedure for the preparation of sulfones**

To a mixture of sulfide (2 mmol) and yellowish silica bromide (2 mmole) in methanol (5 mL) was added 30% H\(_2\)O\(_2\) (2 mmol) at 40ºC. The mixture was stirred at 40ºC for the appropriate period of time until complete consumption of the starting material as
observed by TLC. After completion of the reaction, the reaction mixture was filtered to separate the white solid SiO$_2$. Then, the filtrate was extracted with EtOAc (10 ml) and washed with Na$_2$CO$_3$ (20%, 10 ml). The organic layer was dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure to afford the desired product without further purification (Table 1).

**Conclusion**

In conclusion, we have shown that silica bromide (SB) as heterogeneous reagent can promote the selective oxidation of a variety of sulfides into the corresponding sulfoxides and sulfones in the presence of H$_2$O$_2$ as the terminal oxidant. This reagent is prepared from reaction of silica gel with PBr$_3$ as a non-hygroscopic, filterable, cheap, and stable yellowish powder that can be stored for months. Although the literature reports a number of procedures for the oxidation of sulfides, the excellent yields, heterogeneous conditions, simplicity, good availability of starting materials, compatibility with a variety of functionalities, and ease of isolation of the products make our procedure a practical alternative.

**Acknowledgements**

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