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Oxidation of sulfides to sulfoxides with 1, 3-dibromo-5, 5-dimethylhydantoin in the presence of hydrated silica gel

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Oxidation of sulfides to sulfoxides with 1, 3-dibromo-5, 5-dimethylhydantoin in the presence of hydrated silica gel

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Chemo selective oxidation of sulfides to sulfoxides with 1,3-dibromo-5,5-dimethylhydantoin in dichloromethane in the presence of hydrated silica gel has been developed. Decomposition of the bromosulfonium salt intermediate produced in this reaction to the product is facilitated by the water present in hydrated silica gel. Hydrated silica gel, as the source of necessary water, expanded the scope of oxidation reactions of sulfides to sulfoxides with N-halogenated reagents by allowing a wider range of protic and aprotic solvents. Also, the heterogeneous nature of this oxidation procedure made the product isolation easy. The procedure presented here is very simple, fast, and oxidizes a wide variety of sulfides that were difficult to achieve by many N-halo reagents in the past.

Keywords: silica gel; 3, 3-dibromo-5,5-dimethylhydantoin; sulfides; sulfoxides; DBDMH

1. Introduction

A wide variety of halogen reagents have been reported in the literature for oxidation of sulfides to sulfoxides (*1–13*). Generally, an aqueous or aqueous-organic mixed solvent system is employed in these reactions. Aqueous media is necessary for decomposition of halosulfonium intermediates to the products.

We have reported the use of hydrated silica gel as a source of water to decompose intermediates to the desired products in a number of reactions (*13–16*). Since in these reactions the necessary water was supplied by the silica gel, we were able to replace traditionally used aqueous or aqueous-organic biphasic reaction media with aprotic reaction media. Moreover, the heterogeneous nature of these procedures offered a number of additional advantages that included shorter reaction time, cleaner product, higher yields, waste reduction, and non-aqueous work up.

The success of our previous procedures led us to explore the oxidation of sulfides with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) to the corresponding sulfoxides in the presence of hydrated silica gel in dichloromethane.

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2. Results and discussion

Our attempt to develop a procedure for oxidation of sulfides to sulfoxides utilizing DBDMH in the presence of hydrated silica gel in dichloromethane was successful. The presence of hydrated silica gel is essential for the success of this oxidation procedure. Water bound to the silica gel promotes decomposition of the bromosulfonium intermediate to the sulfoxide product. In addition, hydrated silica gel allows us to avoid aqueous work-up, uses a simple filtration for products isolation, prevents potential acid-promoted side reactions by removing the hydrogen bromide by-products produced in this reaction, and eliminates the necessity to monitor the reaction temperature by acting as a heat sink in this exothermic reaction. This procedure rapidly and efficiently oxidizes various sulfides to sulfoxides without producing over-oxidized sulfone products.

We have successfully oxidized a number of sulfides to sulfoxides using the procedure outlined in this communication. Oxidation of sulfides with DBDMH showed high selectivity toward formation of sulfoxides. Most of the sulfides utilized in this study produced the corresponding sulfoxides in excellent yields.

Generally, over-oxidation, alkyl C–S bond cleavage, and HBr-promoted side reactions complicate oxidation of sulfide with N-halo reagents. Also, electrophilic halogenation of the aromatic ring is also a potential complicating factor for aryl sulfides. It has been found that the DBDMH-promoted oxidation of sulfides described here does not suffer from any of these side reactions. Oxidation of sulfides with DBDMH produced results that are comparable with the oxidation of sulfides with N-bromosuccinimide (NBS) we reported earlier (*13*). Results from the oxidation of sulfides with DBDMH study are presented in Table 1.

Deactivated thioanisoles **1i–j** and sterically hindered sulfides **1c**, **1e**, **1k–m** reacted sluggishly compared with unactivated or activated thioanisoles **1f–h** and unhindered sulfides **1a**, **1b**, **1d**. These observations are similar to the observations we reported in the literature for sulfide oxidations with N-bromosuccinimide (*13*).

DBDMH and N-bromosuccinimide both produce similar results but DBDMH is less expensive (7.2¢ per gram, Aldrich Chemical, 2007-08 Catalog) than N-bromosuccinimide (10.6¢, Aldrich Chemical, 2007-08 Catalog). Moreover, one-half equivalent of DBDMH compared with one equivalent of NBS is necessary to achieve complete oxidation of sulfides since each DBDMH supplies two bromonium ion (Br^+), whereas each NBS supplies only one 'Br^+' ion. Therefore, the new procedure reporting in this communication is less expensive than the NBS procedure. Another advantage is that the by-product 5,5-dimethylhydantoin can easily be removed from the sulfoxide product by washing the crude product with water. Generally, washing the crude product with water gave us analytically pure sulfoxide product. We have also utilized a chromatographic separation technique to remove 5,5-dimethylhydantoin. Washing with water is a convenient alternative to chromatographic purification of crude products. However, the chromatographic separation procedure will be advantageous for sulfoxides that are unstable in aqueous media.

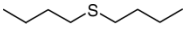
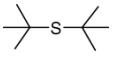
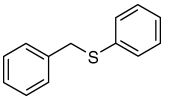
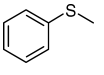
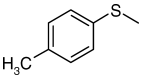
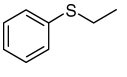
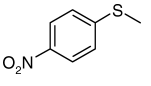
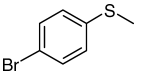
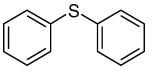
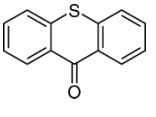
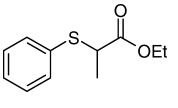
Non-halogenated aprotic solvents such as ethyl acetate (EtOAc) and dimethyl carbonate (DMC) can also be used in this reaction. This conclusion is based on our results from oxidation of a limited number of sulfides with DBDMH in EtOAc and DMC (Table 2). We plan to explore oxidation of a wide range of sulfides in various non-halogenated solvents in the future.

We suggest the following mechanism for oxidation of sulfides with DBDMH **2** in the presence of hydrated silica gel (Scheme 1).

An initial reaction between sulfide **1** and DBDMH **2** may produce bromosulfonium intermediate **3**. Intermediate **3** is likely to decompose to the corresponding sulfoxide **4** by the water present in hydrated silica gel.

The newly developed procedure presented in this communication is a simple, convenient, fast, and efficient procedure for oxidation of dialkyl, aryl-alkyl, and diaryl sulfides to the corresponding

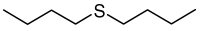
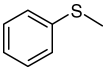
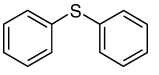
Table 1. Oxidation of sulfides **1** to sulfoxides **4**.

Entry	Sulfides (1)	Rxn. time (min)	Yield (%)
a.		10	98
b.		25	93
c.		120	[a]
d.		10	96
e.		45	86
f.		10	99
g.		10	96
h.		12	91
i.		45	92
j.		35	88
k.		6 hours	62
l.		27	78
m.		190	89

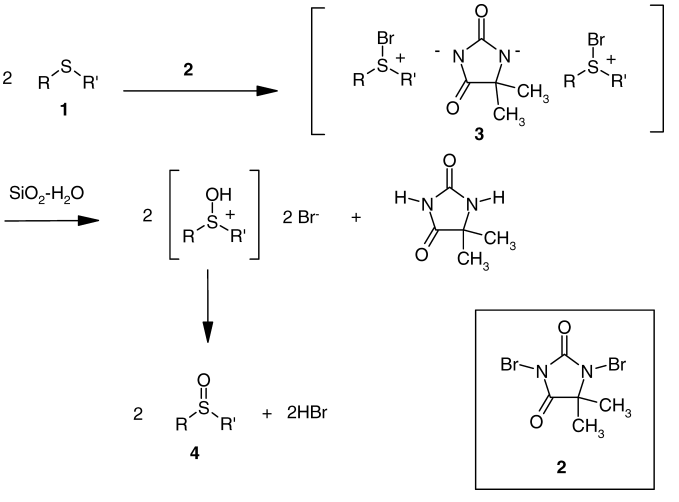
Note: [a]Produced a mixture of unidentified products.

sulfoxides. This procedure allows for the oxidation of dialkyl and aryl-alkyl sulfides without any complication from side reactions reported by others. This procedure expands the scope of oxidation reactions with halogen reagents by allowing a wide variety of solvents, both protic and aprotic in nature.

Table 2. Oxidation of sulfides **1** to sulfoxides **4** in EtOAc and DMC.

Entry	Sulfides (1)	Rxn. time (min)	Yield (%)
a.		10 10	96[a] 84[b]
f.		15 10	86[a] 89[b]
k.		Overnight Overnight	79[a] 76[b]

Notes: [a]Ethyl acetate (EtOAc) reaction media.
[b]Dimethyl carbonate (DMC) reaction media.



Scheme 1. Proposed mechanism for oxidation of sulfides with DBDMH.

3. Experimental

3.1. *General procedure*

Distilled water, 2.00 mL, was added drop by drop to 5.0 g of silica gel (40–64 μm mesh size) placed in a 100 mL round-bottom flask. The mixture was stirred using a magnetic stirrer until a free flowing solid was obtained (less than 5 min). CH_2Cl_2 (15 mL; or EtOAc or DMC) was added to the flask followed by the addition of a solution of 2.0 mmol of the sulfide under investigation. While stirring, 1.1 mmol of solid DBDMH (which gives identical result when added as a solution in CH_2Cl_2) was added in small portions to the reaction flask. A transient orange-yellow color was observed when DBDMH hit the reaction mixture. Once all the DBDMH was added, the color of the reaction mixture remained light yellow-orange. Progress of the reaction was monitored by TLC. Once the reaction was complete, the reaction mixture was filtered using a fritted glass funnel and the solid residue was washed with 70–75 mL of CH_2Cl_2 or EtOAC when the reaction was carried out in EtOAc or DMC. Sulfoxide products were isolated from the solution by two different procedures (Procedure A and B), described below. Both of these procedures produced similar yields.

3.1.1. *Procedure A*

Aqueous work-up: Water soluble by-product 5,5-dimethylhydantoin was removed from the crude product by washing with aqueous $NaHCO_3$ as follows. The combined dichloromethane solution was transferred into a separatory funnel and extracted with three 20 mL portions of 5% aqueous $NaHCO_3$ solution and finally with a 20 mL saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate. After removing the drying agent by filtration, the solvent was removed using a rotary evaporator. The products were characterized by NMR (proton and carbon) and IR. No further purification of the products was necessary.

3.1.2. *Procedure B*

Non-aqueous work-up: The CH_2Cl_2 solution was concentrated under vacuum and the crude product was purified by utilizing radial chromatography using a mixture of EtOAc and hexane (1:9 and then 2:8) as the eluent.

3.2. *Spectral data*

3.2.1. *Dibutyl sulfoxide* ***4a*** (*17*)

δ_H 0.92 (t, $J = 7.2$ Hz, 6H), 1.28–1.70 (m, 4H), 1.68–1.78 (m, 4H), 2.60 (t, $J = 7.62$ Hz, 4H); δ_C 13.7, 22.0, 24.6, 52.1. IR (Film) 1026, 1272, 1408, 1465, 2872, 2930, 2958 cm^{-1}.

3.2.2. *2-(Methylsulfinyl)butane* ***4b*** (*about 1:1 diastereomeric mixture*)

δ_H 1.04 (2t, $J = 7.3$ Hz, 3H), 1.07 (t, $J = 7.4$ Hz, 3H), 1.21 (d, $J = 6.84$ Hz, 3H), 1.27 (d, $J = 6.84$ Hz, 3H), 1.45 (m, 2H), 1.84–1.87 (m, 2H), 2.42 (m, 1H), 2.53 (2s, 6H), 2.69–2.71 (m, 1H); δ_C 10.7, 10.9, 11.3, 11.4, 22.6, 23.2, 33.9, 34.4, 57.7, 58.3. IR (Film) 943, 1023, 1152, 1214, 1383, 1404, 1460, 2879, 2935, 2973 cm^{-1} (produced identical NMR data as compared with commercially available product).

3.2.3. *Di-tert-butyl sulfoxide* ***4c*** (*16*)

δ_H 1.35 (s). IR (Film) 816, 1027, 1038, 1184, 1234, 1374, 1488, 2881, 2932, 2967 cm^{-1}; δ_C 25.39, 57.01.

3.2.4. *Tetrahydrothiophene oxide* ***4d*** (*18*)

δ_H 2.01–2.10 (m, 2H), 2.40–2.45 (m, 2H), 2.85–2.92 (m, 4H, ($2CH_2$)); δ_C 25.2, 54.5. IR (Film) 768, 995, 1096, 1212, 1284, 1408, 2877, 2974 cm^{-1}.

3.2.5. *Benzyl phenyl sulfoxide* ***4e*** (*17*)

δ_H 3.97 (d, $J = 12.5$ Hz, 1H), 4.10 (d, $J = 12.5$ Hz, 1H), 6.90–6.98 (m, 2H), 7.21–7.28 (m, 3H), 7.38–7.48 (m, 5H); δ_C 63.4, 124.4, 128.2, 128.4, 128.8, 129.0, 130.3, 131.2, 142.5; IR (Film) 690, 742, 925, 1026, 1283, 1441, 1516, 2924, 2976, 3060 cm^{-1}.

3.2.6. *Methyl phenyl sulfoxide* ***4f*** (*17*)

δ_H 2.73 (s, 3H), 7.50–7.54 (m, 3H), 7.62–7.70 (m, 2H); δ_C 43.8, 123.4, 129.3, 131.0, 145.5. IR (Film) 690, 746, 955, 1034, 1088, 1415, 1443, 1477, 2912, 2997, 3056 cm^{-1}.

3.2.7. *Methyl* p-*tolyl sulfoxide* ***4g*** (*17*)

δ_H 2.41 (s, 3H), 2.72 (s, 3H), 7.32 (d, $J = 8.5$ Hz, 2H), 7.54 (d, $J = 8.5$ Hz, 2H); δ_C 21.3, 43.8, 123.5, 130.0, 141.5, 142.3. IR (Film) 812, 956, 1039, 1087, 1294, 1407, 1495, 1597, 2736, 2921, 2993, 3045 cm^{-1}.

3.2.8. *Ethyl phenyl sulfoxide* ***4h*** (*17*)

δ_H 1.20 (t, $j = 7.8$ Hz, 3H), 2.75–2.96 (m, 2H), 7.50–7.64 (m, 5H). IR 693, 750, 969, 1042, 1085, 1276, 1403, 1442, 2933, 2978, 3057 cm^{-1}. δ_C 5.85, 50.20, 124.01, 128.99, 130.79, 143.10.

3.2.9. *Methyl* p-*nitrophenyl sulfoxide* ***4i*** (*17*)

δ_H 2.80 (s, 3H), 7.86 (d, $J = 8.8$ Hz, 2H), 8.41 (d, $J = 8.8$, 2H); δ_C 44.8, 124.5, 124.64 149.5, 153.3. IR (Film) 740, 849, 958, 1045, 1344, 1518, 2838, 2936, 3036 cm^{-1}.

3.2.10. *4-Bromophenyl methyl sulfoxide* ***4j*** (*17*)

δ_H 2.74 (s, 3H), 7.53 (d $J = 8.7$ Hz, 2H), 7.68 (d, $J = 8.7$ Hz, 2H); δ_C 43.83, 125.16, 125.40, 132.46, 144.60. IR (Film) 722, 816, 960, 1007, 1045, 1085, 1386, 1420, 1472, 2910, 2995, 3044 cm^{-1}.

3.2.11. *Diphenyl sulfoxide* ***4k*** (*17*)

δ_H 7.30–7.60 (m, 10H). ^{13}C ($CDCl_3$) NMR 125.78, 129.14, 130.97, 145.74. IR 708, 766, 1049, 1104, 1453, 1485, 3067 cm^{-1}.

3.2.12. *Thioxanthanone S-oxide* ***4l***

δ_H 7.46–7.52 (m, 2H), 7.57–7.64 (m, 2H), 8.61–8.64 (m, 2H); δ_C 126.0, 126.3, 129.4, 130.0, 132.3, 137.3, 180.0. IR (Film) 1058, 1164, 1334, 1459, 1562, 1661, 3060 cm^{-1}. MP 199–202 °C (reported 200–202 °C) (*19*).

3.2.13. *Ethyl-α̃-sulfinylphenylpropionate* ***4m*** (*20*) (*about 1:1 diastereomeric mixture*)

δ_H 1.14 (t, $J = 7.30$ Hz, $3H_A$), 1.19 (t, $J = 7.3$ Hz, $3H_B$), 1.31 (d, $J = 7.2$ Hz, $3H_B$), 1.48 (d, $J = 7.1$ Hz, $3H_A$), 3.48 (q, $J = 7.2$ Hz, $1H_A$), 3.80 (q, $J = 7.2$ Hz, $1H_B$), 4.12 (m, $2H_A + 2H_B$), 7.45–7.54 (m, $3H_A$+$3H_B$), 7.60–7.65 (m, $2H_A + 2H_B$); δ_C 8.9 (B), 9.7 (A), 14.0 (B), 14.2 (A), 61.8 (B), 61.9 (A), 63.6 (B), 65.6 (A), 124.8 (A), 125.2 (B), 128.9 (B), 129.2 (A), 131.8 (B), 131.9 (A), 139.9 (B), 141.5 (A), 167.8 (B), 168.5 (A). IR (Film) 691, 748, 1047, 1087, 1156, 1213, 1319, 1369, 1444, 1721, 2876, 2920, 2984, 3060 cm^{-1}.

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