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Oxidation of Sulfides with N-Bromosuccinimide in the Presence of Hydrated Silica Gel

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Abstract: An efficient and highly selective procedure for oxidation of sulfides to sulfoxides with N-bromosuccinimide (NBS) in the presence of hydrated silica gel has been developed. Hydrated silica gel supplies the water necessary for decomposition of the intermediate bromosulfonium salt to the product, allowing the reaction to employ a nonaqueous media. Also, this procedure has increased the scope of the reaction by oxidizing a wider variety of sulfides, which was not possible until now.

Keywords: N-Bromosuccinimide, NBS, oxidation, silica gel, sulfides, sulfoxides

Oxidation of sulfides is a widely utilized method for sulfoxide synthesis. This transformation can be performed with a wide variety of reagents. Among these are N-halogenated regents, such as, N-bromosuccinimide (NBS),[1–3] N-chlorosuccinimide,[2,4] N-bromocaprolacturn,[5] N-chloro-6,6-nylon,[5] chloramine and bromamine-T,[6–10] N-bromopyridine,[11] and 1-chlorobenzotriazole.[12] These reagents are capable of oxidizing sulfides to the corresponding sulfoxides in alcohol or in aqueous–organic mixed solvent media. A suggested general mechanism for oxidation of sulfides with N-halogenated reagents has been summarized in Scheme 1.

The reaction between a sulfide **1** and an N-halogenated reagent, the source of the electrophilic halogen species, initially produces an unstable

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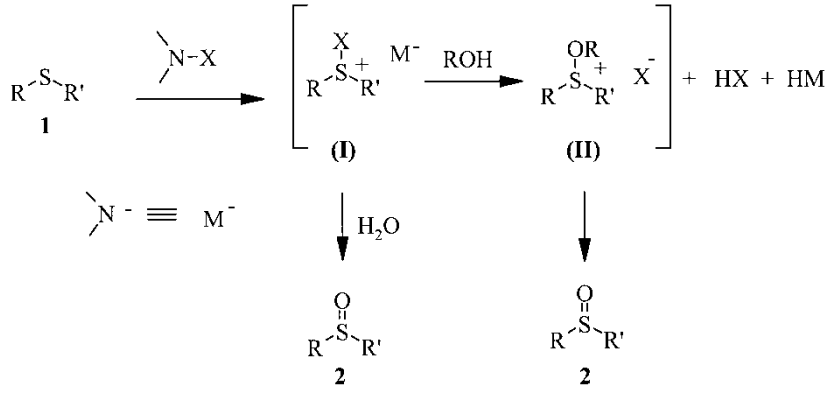


Scheme 1.

intermediate halosulfonium salt (**I**). Alcohol, if used as the reaction media, transforms intermediate (**I**) to intermediate alkoxysulfonium salt (**II**). Finally, intermediate (**II**) undergoes decomposition to produce sulfoxide **2**. If the reaction is carried out in a wet aprotic solvent, the unstable halosulfonium salt (**II**) decomposes to produce sulfoxide **2** directly.

Previously reported sulfide oxidation reactions utilizing N-halogenated reagents suffer from various drawbacks. N-Bromosuccinimide in aqueous–organic biphase reaction media oxidizes aryl sulfides to the corresponding sulfoxides but fails to oxidize alkyl-aryl and dialkyl sulfides to the expected sulfoxides because of C-S bond cleavage.[1] Sulfide oxidation with 1-chlorobenzotriazole requires low temperature ($-78^{\circ}C$) and works, for only diaryl sulfides.[12] This reagent does not produce good results in the oxidation of dibenzyl and certain dialkyl sulfide, also because of C-S bond cleavage.

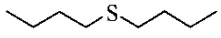
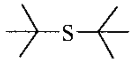
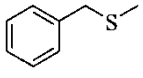
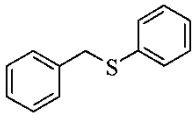
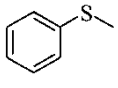
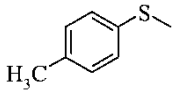
In our previously reported procedure for oxidation of sulfides to sulfoxides with molecular bromine, we utilized hydrated silica gel, which among other advantages, provided the water necessary to decompose the bromosulfonium salt to the final sulfoxide product.[13] Utilization of hydrated silica gel as the source for water in this reaction allowed us to employ a nonaqueous dicholoromethane media in this reaction. In the past, aqueous–organic biphasic media employed in such reactions was the source of water necessary to complete the reaction. Oxidation of sulfides with N-bromosuccinimide, similar to oxidation of sulfides with bromine, also proceeds through unstable bromosulfonium salt intermediates, which decompose in the presence of protic solvent to sulfoxides. Therefore, we became interested in employing hydrated silica gel in the later reaction to explore the possibility of replacing the aqueous–organic reaction media, traditionally employed in this reaction, with a nonaqueous dichloromethane media.

Herein we report the results of our investigation. Oxidation of sulfides with N-bromosuccinimide in the presence of hydrated silica gel using

dichloromethane solvent produced excellent results and also proved to be superior to the previously reported procedures. Hydrated silica gel offers a number of benefits to this reaction procedure. Hydrated silica gel eliminates the need for aqueous–organic biphasic reaction media that provide the necessary water.[1–8] Hydrated silica gel produces greater selectivity in the oxidation of sulfides by suppressing potential side reactions. Oxidation of diaryl, alkyl-aryl, and dialkyl sulfides under these reaction conditions produces the corresponding sulfoxides in excellent yields (Table 1).

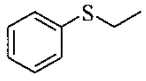
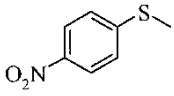
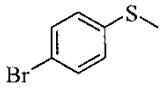
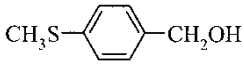
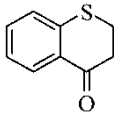
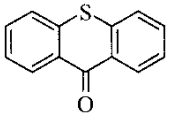
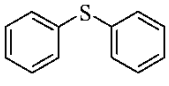
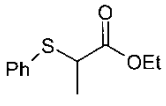
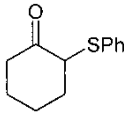
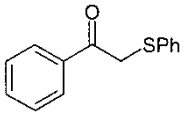
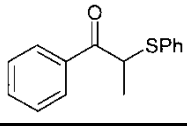
Oxidation of aryl-alkyl or dialkyl sulfides, except for the highly sterically hindered sulfide **1c**, proceeds smoothly without any observable C-S bond cleavage. Others have reported low yield for the oxidation of **1c** to **2c** using

Table 1. Oxidation of sulfides **1** to sulfoxides **2**

Entry	Sulfide (**1**)	Rxn. time (min)	Yield (%)
a		20	99
b		22	92
c		180	85
d		25	99
e		30	95
f		30	92
g		35	98
h		10	99
i		10	97

(*Continued*)

Table 1. Continued

Entry	Sulfide (**1**)	Rxn. time (min)	Yield (%)
j		15	99
k		60	93
l		45	95
m		35	90
n		150	86
o		210	92
p		240	74
q		60	96
r		50	98
s		60	97
t		50	93

benzyltrimethylammonium tribromide as the oxidizing reagent.[14] We have not observed any oxidation of the alcohol functional group present in sulfide **1m**; bromination at the α-position of the carbonyl group present in sulfides **in, q–t**; or bromination at the aromatic ring present in sulfides **1f–q**, **s–t**. In this reaction, hydrated silica gel acts as a heat sink, allowing us to carry out this exothermic reaction safely at room temperature without further controlling the reaction temperature. We did not observe any rise in the reaction temperature during the course of this reaction. Until now, NBS oxidation of dialkyl sulfides were successful only in anhydrous alcohol media at low reaction temperatures.[2] As expected, oxidation of thioanisoles **1k–1** carrying a deactivating group on the benzene ring took a longer time to finish the reaction as compared to the thioanisole **1i**, which carries an activating group. Sterically hindered sulfides **lc, lg,** and **1n–p** reacted sluggishly, as expected.

Our newly developed procedure is a simple, convenient, fast, and efficient procedure for oxidation of dialkyl, aryl-alkyl, and diaryl sulfides to the corresponding sulfoxides in high yields. By allowing the oxidation of dialkyl and aryl-alkyl sulfides without any complication from side reactions, this procedure increased the scope of this reaction.

EXPERIMENTAL

General Procedure

Distilled water (2.00 mL) was added drop by drop to 5.0 g of silica gel (40–64-μm mesh) placed in a 100-mL round-bottomed 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) was added to the flask, followed by the addition of a solution of 2.0 mmol of the sulfide under investigation. While stirring, a solution of 2.2 mmol of N-bromosuccinimide in 10 mL of CH_2Cl_2 (a cloudy yellow solution) was added drop by drop to the reaction flask. A transient yellow color was observed when N-bromosuccinimide hit the reaction mixture. Once all the N-bromosuccinimide 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. The combined organic phase was then transferred into a separatory funnel and extracted with three 20-mL portions of distilled H_2O and finally with 20 mL of 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 isolated products were determined to be pure by NMR. The products were characterized by NMR (proton and carbon) and IR. We obtained identical results when solid NBS, instead of a solution, was added to the reaction mixture in small portions. All sulfoxide products

were characterized by comparison of the NMR data with those of the previously reported in the literature.[15–18]

Data

Dibutylsulfoxide (2a).^{1}H NMR ($CDCl_3$) 0.97 (t, $J = 7.1$ Hz, 6H), 1.40–1.60 (m, 4H), 1.74–1.78 (m, 4H). 2.68 (t, $J = 7.5$ Hz, 4H). ^{13}C NMR ($CDCl_3$) 13.70, 22.10, 24.60, 52.10. IR (film) 732, 908, 1024, 1381, 1407, 1460, 2876, 2933, 2962 cm^{-1}.

Sec-butyl methyl sulfoxide (2b). ^{1}H NMR ($CDCl_3$) 0.92 (t, $J = 4$ Hz, 3H), 0.97 (t, $J = 7.2$ Hz, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 1.20 (d, $J = 6.8$ Hz, 3H), 1.28–1.49 (m, 2H), 1.80–1.86 (m, 2H), 2.42–2.46 (m, 1H), 2.47 (s, $2CH_3$, 6H), 2.64–2.66 (m, 1H). ^{13}C NMR ($CDCl_3$) 10.68, 10.75, 11.15, 11.32, 22.60, 23.10, 33.85, 34.30, 57.71, 58.20. IR (film) 951, 1030, 1386, 1425, 1460, 2881, 2936, 2975 cm^{-1}.

Di-*tert*-butyl sulfoxide (2c). ^{1}H NMR ($CDCl_3$) 1.32 (s). ^{13}C NMR ($CDCl_3$) 25.40, 57.20. IR (film) 1021, 1178, 1230, 1375, 1466, 1470, 2874, 2932, 2971 cm^{-1}.

Tetrahydrothiophene oxide 2d. ^{1}H NMR ($CDCl_3$) 2.00–2.25 (m, 2H), 2.35–2.50 (m, 2H), 2.80–2.86 (m, 4H). ^{13}C NMR ($CDCl_3$) 24.56, 53.40 IR (film) 1021, 1215, 1325, 1456, 2885, 2960 cm^{-1}.

4-Oxo-1,4-thioxane (2e). ^{1}H NMR ($CDCl_3$) 2.60–2.66 (m, 2H), 2.84–2.87 (m, 2H), 3.80–3.85 (m, 2H), 4.30–4.38 (m, 2H). ^{13}C NMR ($CDCl_3$) 46.30, 59.20. IR (film) 1020, 1031, 1066, 1120, 1225, 1395, 1410, 1475, 2872, 2935, 2978 cm^{-1}.

Benzyl methyl sulforide (2f). ^{1}H NMR ($CDCl_3$) 2.45 (s, 3H), 3.86 (d, $J = 8$ Hz, 1H), 4.10 (d, J = 8 Hz, 1H), 7.25–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$) 37.45, 60.32, 128.46, 128.94, 129.62, 130.10 IR (film) 1021, 1260, 1365, 1452, 1505, 2920, 3010, 3060 cm^{-1}.

Benzyl phenyl sulfoxide (2g). ^{1}H NMR ($CDCl_3$) 4.02 (d, $J = 12.4$ Hz, 1H), 4.10 (d, $J = 12.4$ Hz, 1H), 6.92–7.00 (m, 2H), 7.20–7.35 (m, 3H), 7.38–7.48 (m, 5H). ^{13}C NMR ($CDCl_3$) 63.20, 124.45, 128.20, 128.38, 128.83, 128.92, 130.35, 131.23, 142.16. IR (film) 695, 752, 1038, 1085, 1446, 1490, 2915, 2972, 3060 cm^{-1}.

Methyl phenyl sulfoxide (2h). ^{1}H NMR ($CDCl_3$) 2.72 (s, 3H), 7.51–7.56 (m, 3H), 7.64–7.67 (m, 2H). ^{13}C NMR ($CDCl_3$) 43.90, 123.44, 129.33, 131.0, 145.60. IR (film) 732, 955, 1092, 1296, 1415, 1446, 1471, 2923, 2980, 3065 cm^{-1}.

Methyl *p*-methylphenyl sulfoxide (2i). ^{1}H NMR ($CDCl_3$) 2.40 (s, 3H), 2.68 (s, 3H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$)

21.50, 44.00, 123.62, 130.12, 141.50, 142.62 IR (film) 808, 1042, 1080, 1495, 2872, 2926, 2982, 3052 cm^{-1}.

Ethyl phenyl sulfoxide (2j). ^1H NMR ($CDCl_3$) 1.20 (t, $J = 7.4$ Hz, 3H), 2.72–2.92 (q, $J = 7.4$ Hz, 2H), 7.50–7.62 (m, 5H). ^{13}C NMR ($CDCl_3$) 5.90, 50.20, 124.10, 129.00, 130.90, 143.16. IR (film) 732, 1048, 13.80, 1481, 2877, 2937, 2983, 3065 cm^{-1}.

Methyl *p*-nitrophenyl sulfoxide (2k). ^1H NMR ($CDCl_3$) 2.81 (s, 3H), 7.86 (d, $J = 8.8$ Hz, 2H), 8.38 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 43.90, 124.40, 124.60, 149.40, 153.26. IR (film) 750, 980, 1038, 1042, 1346, 2865, 2926, 3030 cm^{-1}.

4-Bromophenyl methyl sulfoxide (2l). ^1H NMR ($CDCl_3$) 2.70 (s, 3H). 7.52 (d, $J = 9$ Hz, 2H), 7.65 (d, $J = 9$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 43.84, 125.12, 125.34, 132.48, 144.90. IR (film) 1010, 1044, 1388, 1476, 2868, 2930, 3032 cm^{-1}.

4-Hydroxymethylphenyl methyl sulfoxide (2m). ^1H NMR ($CDCl_3$) 2.65 (s, 3H), 3.16 (bs, OH), 4.66 (s, 2H), 7.49 (d, $J = 8.6$ Hz, 2H), 7.54 (d, $J = 8.6$ Hz, 2H). ^{13}C NMR ($CDCl_3$) 43.26, 63.60, 123.54, 127.32, 140.96, 145.20. IR (film) 826, 967, 1098, 1210, 1312, 1430, 2880 2926, 3020, 3058, 3364 cm^{-1}.

Thiooxochroman-4-one-S-oxide (2n). ^1H NMR ($CDCl_3$) 2.85–2.89 (m, 1H), 3.38–3.43 (m, 3H), 7.66 (dd, $J = 7.5$, 7.4 Hz, 1H), 7.70 (dd, $J = 7.5$, 7.4 Hz, 1H), 7.92 (d, $J = 7.5$ Hz, 1H), 8.12 (d, $J = 7.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$) 29.69, 45.97, 127.78, 128.20, 128.56, 131.45, 133.98, 145.00, 191.45. IR (film) 785, 1056, 1182, 1296, 1336, 1443, 2945, 2975, 3016, 3068 cm^{-1}.

Thioxanthanone S-oxide (2o). ^1H NMR ($CDCl_3$) 7.35–7.50 (m, 2H), 7.55–7.64 (m, 2H), 8.55–8.70 (m, 2H). ^{13}C NMR ($CDCl_3$) 125.86, 126.26, 129.15, 129.80, 132.20, 137.25, 180.60. IR (film) 1069, 1158, 1328, 1445, 1581, 1646, 3058 cm^{-1}.

Diphenyl sulfoxide (2p). ^1H NMR ($CDCl_3$) 7.40–7.45 (m, 6H), 7.58–7.65 (m, 4H). ^{13}C NMR ($CDCl_3$) 124.70, 129.33, 130.90, 145.46. IR (film) 738, 1042, 1145, 1443, 1474, 3062 cm^{-1}.

Ethyl-α-sulfinylphenylpropionate (2q). (about 2:1 diastereomeric mixture). ^1H NMR ($CDCl_3$) 1.18 (t, $J = 7.4$ Hz, $3H_A$). 1.20 (t, $J = 7.4$ Hz, $3H_B$). 1.36 (d, $J = 7.1$ Hz, $3H_B$), 1.51 (d, J = 7.1 Hz, $3H_A$), 3.52 (q, j = 7.1 Hz, $1H_A$), 3.84 (q, j = 7.1 Hz, $1H_B$) 4.15 (m, $2H_A + 2H_B$), 7.44–7.48 (m, $3H_A + 3H_B$), 7.49–7.60 (m, $2H_A + 2H_B$). ^{13}C NMR ($CDCl_3$) 9.22 (B), 9.51 (A), 13.95 (B), 14.16 (A), 61.74 (B), 61.80 (A), 63.76 (B), 65.85 (A), 124.65 (A), 125.22 (B), 128.95 (B), 129.20 (A), 131.60 (B), 132.08 (A), 140.60 (B), 142.10 (A), 167.84 (B), 168.74 (A). IR (film) 710, 1072, 1097, 1167, 1245, 1328, 1375, 1468, 1746, 2875, 2926, 2961, 2984, 3060 cm^{-1}. Literature data.[14] Compound **2qA**: ^1H NMR (300 MHz) 1.17

(t, $J = 7.2$, 3H), 1.49 (d, $J = 7.3$, 3H). 3.50 (bq, $J = 7.3$, 1H), 4.10 (m, 2H), 7.4–7.75 (m, 5H); ^{13}C NMR (75 MHz) 9.69, 14.04, 61.86, 65.80, 124.73, 129.149, 131.65, 142. 02, 168.55. Compound **2qB**: ^{1}H NMR (300 MHz) 1.21 (t, $J = 7.2$, 3H), 1.32 (d, $J = 7.0$, 3H), 3.81 (q, $J = 7.0$, 1H), 4.10 and 4.13 (each 1H, d, $J = 7.2$, 3.5), 7.4–7.75 (5H); ^{13}C NMR (75 MHz) 8.93, 14.00, 61.72, 63.68, 125.11, 128.94, 131.74, 140.33, 167.70.

2-(Sulfinylphenyl)-cyclohexanone (2r) (about 3:l diastereomeric mixture). ^{1}H NMR ($CDCl_3$) 1.62–2.58 (m, 16H), 3.42 (dd, $J = 6$ Hz, 10.6H 1H), 3.60 (dd, $J = 7.6$ Hz, 1H), 7.46–7.51 (m, 6H), 7.60–7.65 (m, 4H). ^{13}C NMR ($CDCl_3$) 22.72, 2310, 24.05, 24.36, 26.30, 27.90, 42.28, 42.90, 73.04, 73.90, 124.88, 125.27, 128.00, 128.95, 131.13, 131.87, 140.92, 142.20, 205.27, 205.80. IR (film) 768, 1068, 1104, 1170, 1462, 1718, 2874, 2960, 3072 cm^{-1}.

2-(Sulfinylphenyl) acetophenone (2s). ^{1}H NMR ($CDCl_3$) 4.34 (d, $J = 14.1$ Hz, 1H), 4.63 (d, $J = 14.1$, 1H), 7.40–7.56 (m, 7H), 7.60–7.69 (m, 1H), 7.80–7.88 (m, 2H). ^{13}C NMR ($CDCl_3$) 65.75, 124.12, 128.65, 129.22 (2C), 131.45, 134.10, 135.78, 143.22, 191.28. IR (film) 756, 1046, 1108, 1094, 1267, 1452, 1464, 1684, 2922, 2964, 3010, 3060 cm^{-1}. Literature data (200 MHz)[21]; ^{1}H NMR 4.29 (d, $J = 14$, 1H), 4.56 (d, $J = 14$, 1H), 7.5 (m, 6H), 7.7 (m, 2H), 7.89 (d, 2H).

1-Phenyl-2-(phenylsulfinyl)-1-propanone (2t) (diastereomeric mixture). ^{1}H NMR ($CDCl_3$) 1.34 (d, $J = 6.8$ Hz, 3H), 1.65 (d, $J = 7.20$ Hz, 3H), 4.60 (q, $J = 7.2$ Hz, 1H), 4.87 (q, $J = 6.80$ Hz, 1H), 7.20–7.95 (m, 20H). ^{13}C NMR ($CDCl_3$) 9.88, 12.50, 66.64, 68.34, 125.40, 125.92, 129.16, 129.27, 129.32, 129.32, 129.46, 129.64, 132.12, 132.42, 134.40, 134.62, 136.40, 136.92, 140.73, 142.45, 194.92, 196.66. IR ((film) 730, 746, 1080, 1125, 1242, 1324, 1464, 1680, 2882, 2963, 3068 cm^{-1}. Literature data: ^{1}H NMR (100 MHZ)[22] 1.32 (d, $J = 7$ Hz, 1.2H), 1.65 (d, $J = 7$ Hz, 1.8H), 4.62 (q, $J = 7$ Hz, 0.6H), 4.87 (q, $J = 7$ Hz, 0.4H), 7.10–8.00 (m, 10H).

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