Phenyltrimethylammonium Tribromide for Selective Oxidation of Sulfides to Sulfoxides. A Convenient Synthesis of Sulfinyl-^{18}O-Labelled Sulfoxide Carboxylic Acids

József Rábai,*[a] István Kapovits,[a] Béla Tanács,[b] József Tamás[c]

[a] Institute of Organic Chemistry, Eötvös University, H-1518 Budapest 112, P.O. Box 32, Hungary
[b] Institute of Isotopes of the Hungarian Academy of Sciences, H-1525 Budapest, P.O. Box 77, Hungary
[c] Central Research Institute for Chemistry, Hungarian Academy of Sciences, H-1525 Budapest, P.O. Box 17, Hungary

Various sulfides can be oxidized selectively to the corresponding sulfoxides in high yields using phenyltrimethylammonium tribromide in aqueous pyridine solution. This method allows ^{18}O-labelled sulfoxides to be prepared with no loss of isotope enrichment of the (^{18}O)water used.

Although many procedures are known for the oxidation of sulfides to sulfoxides,[1] few of them are also convenient for the preparation of sulfinyl-^{18}O-labelled sulfoxides.[2-8] These methods use halogenating agents such as solid complexes of bromine with tertiary amines,[2,3] bromine,[4,5] iodobenzene dichloride,[6] sulfuryl chloride[7] or *tert*-butyl hypochlorite[8] in a mixture of (^{18}O)water and an appropriate solvent.

We report here a general method for high-yield preparation of both ^{18}O-labelled and unlabelled sulfoxides. In this new procedure a stable,[9] crystalline and commercially available reagent, phenyltrimethylammonium tribromide (PTAB)[10,11] is used as a substitute for bromine. We have found that the reaction of sulfides **1a–z** with PTAB at room or lower temperatures in aqueous pyridine solution results in the selective, sulfone-free (TLC) formation of sulfoxides **2a–z** (Scheme, Table 1).

Representative sulfides were treated with PTAB in a mixture of anhydrous pyridine and (^{18}O)water (67 ± 2 atomic % ^{18}O) to afford sulfinyl-^{18}O-labelled sulfoxides. The analysis (IR, MS) of these labelled products showed that the formation and isolation of (^{18}O)sulfoxides take place with no loss of isotope enrichment of the (^{18}O)water used, and without any isotopic oxygen (^{18}O) incorporation into the carboxylic and aminosulfonyl groups in the case of the (^{18}O)sulfoxide carboxylic acids (Table 2).

Melting points were determined on a Boëtius micro melting point apparatus and are corrected. IR spectra were recorded on a Specord IR 75 (Zeiss, Jena) spectrophotometer, ^{1}H-NMR spectra were recorded on a Varian A60 D spectrometer. Mass spectra were obtained using an AEI MS-902 and/or a VG-MM-12F1A spectrometer, with either EI (70 eV) or chemical ionization (isobutane, 200 eV) and direct insertion technique. (^{18}O)Water samples were analyzed using MS-902 instrument (15 eV) and introduced via balloon. Analytical TLC plates were purchased from Merck. Pyridine was purified and dried by distillation over P_2O_5.

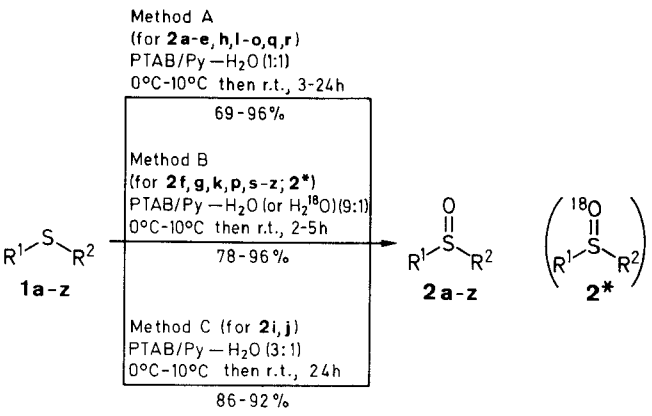
Sulfides **1a, 1c, 1d, 1f–h, 1k–m**, and PTAB are commercially available. Sulfides **1b**,[29] **1e**,[30] **1i**,[31] **1j**,[32] **1n–o**,[33] **1p**,[34] **1q–s**,[35] **1v**,[28] **1x**,[35] **1y**,[36] and **1z**[37] were prepared according to literature procedures.

2-(2-Aminosulfonylphenylthio)benzoic acid (1t):
2-Iodobenzenesulfonamide[38] (339 g, 1.2 mol) is dissolved in 2.5 N KOH (3.2 L, 8.0 mol) under an Ar atmosphere. Then Cu bronze (13 g) and thiosalicylic acid (186 g, 1.2 mol) are added and the mixture is refluxed for 7.5 h. It is filtered into 6 N HCl (1.2 L, 7.2 mol). The precipitate obtained is filtered, washed with H_2O and recrystallized to afford a white solid; yield: 332 g (90%); mp 179–181 °C (EtOH/H_2O), 181–183 °C (acetone/H_2O).

$C_{13}H_{11}NO_4S_2$ (309.4) calc. C 50.47 H 3.58 N 4.53 O 20.69 S 20.73
found 50.21 3.82 4.24 20.22 20.43

IR (KBr): ν = 3450–2400 (OH), 3352, 3250 (NH), 1692 (C=O), 1330, 1158 cm^{-1} (SO_2).

2-(2-Methylaminosulfonylphenylthio)benzoic acid (1u):
2-Iodo-*N*-methylbenzenesulfonamide[35] (120 g, 0.406 mol), thiosalicylic acid (62 g, 0.402 mol) and Cu_2O (28.6 g, 0.20 mol) are dissolved in pyridine (600 mL) under an Ar atmosphere with heating and then boiled for 2 h. The mixture is cooled to r.t., then poured into a mixture of crushed ice (1.2 kg) and conc. HCl (1.2 L). The precipitate formed (**1u** + CuI) is filtered and washed with H_2O, then treated with 0.6 N NaOH (1.6 L) for 0.5 h to dissolve **1u**.



1, 2 (2*)	R^1	R^2
a	$-(CH_2)_4-$	
b	$-(CH_2)_3CH(Me)-$	
c	$-(CH_2)_5-$	
d	Pr	Pr
e	Me	2-$O_2NC_6H_4CH_2$
f(*)	$PhCH_2$	$PhCH_2$
g(*)	$PhCH_2$	Ph
h	Me	Ph
i	Me	4-$O_2NC_6H_4$
j	Me	2-$O_2NC_6H_4$
k(*)	Me	4-$HO_2CC_6H_4$
l	Me	2-benzothiazolyl
m	Ph	Ph
n	Ph	4-$HO_2CC_6H_4$
o	Ph	3-$HO_2CC_6H_4$
p(*)	Ph	2-$HO_2CC_6H_4$
q	4-$HO_2CC_6H_4$	4-$HO_2CC_6H_4$
r	3-$HO_2CC_6H_4$	3-$HO_2CC_6H_4$
s(*)	2-$HO_2CC_6H_4$	2-$HO_2CC_6H_4$
t(*)	2-$HO_2CC_6H_4$	2-$H_2N(O_2)SC_6H_4$
u(*)	2-$HO_2CC_6H_4$	2-(Me)$HN(O_2)SC_6H_4$
v	2-$HO_2CC_6H_4$	1-naphthyl
w	2-$HO_2CC_6H_4$	8-carboxy-1-naphthyl
x	8-carboxy-1-naphthyl	8-carboxy-1-naphthyl
y	8-carboxy-1-naphthyl	1-naphthyl
z	8-carboxy-1-naphthyl	Ph

Scheme

Most of the Cu(I) species are removed as Cu_2O by filtration, while the last traces precipitated by a few drops of Na_2S solution. The Cu free alkaline solution thus obtained is added to 6 N HCl (250 mL). The precipitate formed is filtered, washed with H_2O and recrystallized to afford a white solid; yield: 105 g (81 %); mp 223–224 °C ($MeOH/H_2O$).

$C_{14}H_{13}NO_4S_2$ (323.4) calc. C 51.99 H 4.05 N 4.33 O 19.79 S 19.83
found 51.70 4.04 4.40 19.91 19.74

IR (KBr): ν = 3400–2200 (OH), 3308 (NH), 1675 (C=O), 1320, 1158 cm^{-1} (SO_2).

^{1}H-NMR (pyridine-d_5/TMS): δ = 2.75 (s, 3 H, CH_3), 7.1–7.7 (m, 6 H_{arom}), 8.1–8.5 (m, 2 H_{arom}).

2-(8-Carboxy-1-naphthylthio)benzoic acid (1w):
Thiosalicylic acid (40 g, 0.26 mol) is dissolved in 1.6 N KOH (500 mL, 0.80 mol) under an Ar atmosphere, then Cu bronze (3 g) and 8-iodo-1-naphthoic acid[39] (80 g, 0.27 mol) are added and the mixture is refluxed for 3 h. It is made alkaline with KOH (5 g), diluted with H_2O (500 mL) and filtered into 6 N HCl (200 mL). The precipitate is filtered, washed with H_2O, and recrystallized to afford a pale yellow solid; yield: 59.2 g (70 %); mp 268–271 °C ($AcOH/H_2O$).

$C_{18}H_{12}O_4S$ (324.3) calc. C 66.65 H 3.73 O 19.73 S 9.89
found 66.42 3.82 19.36 9.63

IR (KBr): ν = 3400–2200 (OH), 1685 (C=O), 1587, 1559, 1498 (C=C_{arom}), 1286, 1259, 1209 (C–O), 824, 763, 740 cm^{-1}.

Table 1. Phenyltrimethylammonium Tribromide Oxidation of Sulfides **1**.

Product[a]	Method[b]	Time (h)	Yield[c] (%)	mp (°C)[d] (solvent)	Molecular Formula[e] or Lit. mp (°C)[d]	IR (KBr) (cm^{-1})[f] ν_{max}(S=O)
2a	A	3	69	105–107/16	105–107/16[12]	1032 (CCl_4)
2b	A	3	78	110–112/21[g]	72–74/1.3[14]	1030 (CCl_4)
2c	A	3	83	122/16[h]	127–128/20[16]	1040 (CCl_4)
2d	A	3	84	72/1.3	72/1.3[17]	1040 (CH_2Cl_2), 1062 (CCl_4)
2e	A	3	82	79–80[i] ($CHCl_3/Et_2O$)	$C_8H_9NO_3S$ (199.2)	1058 (CH_2Cl_2)
2f	B	2	88	135–136 ($EtOH/H_2O$)	135–136[15]	1030, 1045 (CH_2Cl_2), 1055 (CCl_4)
2g	B	2	96	122–123 ($EtOH/H_2O$)	125.5[18]	1034, 1045 (CH_2Cl_2), 1050 (CCl_4)
2h	A	3	85	140–142/17	140–142/17[19]	1053 (CCl_4)
2i	C	24	86	151.5–152.5 ($CHCl_3$)	152–153[20]	1048, 1056 (CH_2Cl_2), 1064 (CCl_4)
2j	C	24	92	101–102 ($CHCl_3$)	101–102[21]	1062, 1072 (CH_2Cl_2), 1080 (CCl_4)
2k	B	2	78	232.5–233 (H_2O)	232.5–233[22]	1000
2l	A	20	78	70.5–71.5[j] (hexane)	66–68[23]	1064, 1064 (CH_2Cl_2), 1076 (CCl_4)
2m	A	24	89	71.5–72.5 (benzene/pentane)	70–71[4]	1033, 1050 (CCl_4)
2n	A	18	93	196–197 ($EtOH/H_2O$)	197.5–198.5[24]	1048
2o	A	14	96	186–187 ($EtOH/H_2O$)	$C_{13}H_{10}O_3S$ (246.3)	982, 1044 (CH_2Cl_2)
2p	B	2	89	166–167 ($EtOH/H_2O$)	164–165[25]	975, 1030 (CH_2Cl_2)
2q	A	24	96	346–348[e] (DMF/H_2O)	335–337[26]	1052
2r	A	24	87	293–294 ($EtOH/H_2O$)	$C_{14}H_{10}O_5S$ (290.3)	1028
2s	B	2	92	320–321 ($EtOH/H_2O$)	310–315[27]	970
2t	B	2	92	160–165 (H_2O)	$C_{13}H_{11}NO_5S_2 \cdot 0.5H_2O$ (334.4)	1005
2u	B	2	91	124–126[k] (H_2O)	$C_{14}H_{13}NO_5S_2 \cdot H_2O$ (357.4)	1016
2v	B	5	94	247–250 (AcOH)	247–250[28]	968, 947
2w	B	2	95	226–228[l] (H_2O)	$C_{18}H_{12}O_5S$ (340.4)	985
2x	B	2	82	223–225 (H_2O)	$C_{22}H_{14}O_5S \cdot H_2O$ (408.4)	980
2y	B	5	96	214–218[m] (H_2O)	$C_{21}H_{14}O_3S \cdot H_2O$ (364.4)	1022
2z	B	5	96	225–227 ($EtOH/H_2O$)	$C_{17}H_{12}O_3S$ (296.3)	1010 or 992, 1040 (CH_2Cl_2)

[a] Homogeneous by TLC. Attempts to prepare 1,1'-dinaphthyl, 4-nitrodiphenyl, and phenyl *t*-butyl sulfoxides were unsuccessful.
[b] Sulfide/PTAB molar ratio = 1.0 : 1.04; using Py/H_2O (1 : 1) (Method A), (9 : 1) (Method B), and (3 : 1) (Method C) as solvent.
[c] For recrystallized or distilled products based on **1**.
[d] For **2a–d** and **2h** bp (°C)/mbar is given.
[e] Satisfactory microanalyses obtained: C ±0.39, H ±0.36, S ±0.39. Sulfoxides **2t–y** were analyzed as obtained after washing with H_2O and drying.
[f] Refers to KBr, unless otherwise stated (CCl_4 or CH_2Cl_2).
[g] *cis*/*trans* Diastereomeric ratio = 60 : 40, as determined by ^{1}H-NMR (cf. Ref. 13).
[h] Mp 66–67 °C; (Lit. [15] mp 67–68.2 °C).
[i] ^{1}H-NMR ($CDCl_3$/TMS): δ = 2.65 (s, 3 H, CH_3), 4.15 (d, 1 H, J_{AB} = 12.5 Hz, CH_2), 4.68 (d, 1 H, J_{AB} = 12.5 Hz, CH_2), 7.4–7.8 (m, 3 H_{arom}), 8.1–8.3 (m, 1 H_{arom}).
[j] ^{1}H-NMR ($CDCl_3$/TMS): δ = 3.10 (s, 3 H, CH_3), 7.4–7.7 (m, 2 H_{arom}), 7.9–8.2 (m, 2 H_{arom}).
[k] ^{1}H-NMR (pyridine-d_5/TMS): δ = 2.60 (s, 3 H, CH_3), 7.3–9.3 (m, 8 H_{arom}).
[l] Forms stable solvates on recrystallization;[e] e.g.: M × dioxane (428.4); mp 227–232 °C (dioxane/H_2O = 9 : 1); IR (KBr): ν = 985 (S=O) cm^{-1}.
[m] Mp 225–227 °C ($AcOH/H_2O$); IR (KBr): ν = 1000 (S=O) cm^{-1}.

Table 2. (^{18}O)Sulfoxides **2*** Prepared

Product	IR (KBr) cm^{-1} $\nu(S=^{16}O)$	$\nu(S=^{18}O)$	^{18}O-enrichment[a] (%)
2f*	1030	992	70 ± 2 (EI)
2g*	1034	1002	71 ± 2 (EI)
2k*	1008	968	68[b,c]
2p*	970	936	70 ± 2 (EI)
2s*	970	933	72 ± 1[c] (EI)
2t*	1005	970	68 ± 2[c] (EI)
2u*	1015	982	68 ± 2[c] (CI)

[a] Determined by MS using EI (electron impact) or CI (chemical ionisation) method.
[b] Estimated by IR method (cf. Ref. 27).
[c] Analyzed as the corresponding methyl (dimethyl, **2s***) ester prepared with CH_2N_2/Et_2O in MeOH at 0°C. There was no sign of the presence of $^{18}OCH_3$.

Sulfoxides 2a–z; General Procedure:

Method A (for **2a–e,h,l–o,q,r**): To a magnetically stirred and ice-cooled solution of sulfide **1** (100 mmol) in aq pyridine (1:1; 40 mL for **1a–e,h,l–o**; 160 mL for **1q,r**) $PhMe_3N^+Br_3^-$ (PTAB, 39.0 g, 104 mmol) is added in portions to keep the reaction temperature between 0°C and 10°C. When the addition is complete, the mixture is stirred at r.t. for the time given in Table 1. Then the unreacted PTAB is decomposed by 40% $NaHSO_3$ (1 mL). Ice/water (100 g for **2a–e,h,l–o**; 400 g for **2q,r**) is added and the mixture is acidified with 2 N H_2SO_4 (30 mL for **2a–e,h,l–o**; 400 mL for **2q,r**). The solid precipitates formed (**2m–o,q,r**) are filtered, washed with H_2O, dried, and recrystallized.

For the isolation of the sulfoxides **2a–e,h,l** the diluted (H_2O) and acidified mixtures are extracted with $CHCl_3$ (10 × 50 mL). The combined organic layers are washed with 2 N Na_2CO_3 (2 × 10 mL), and dried ($MgSO_4$). The solvent is removed and the crude products obtained are purified by distillation or recrystallization.

Method B (for **2f,g,k,p,s–z**): A solution of sulfide **1** (10 mmol) in a mixture of pyridine (18 mL) and H_2O (2 mL) is treated with PTAB (3.90 g, 10.4 mmol) as described above. The reaction mixture is then poured into ice-cold 2 N H_2SO_4 (250 mL). The precipitate formed is filtered, washed with cold H_2O and dried.

Method C (for **2i,j**): A solution of sulfide **1** (10 mmol) in a mixture of pyridine (6 mL) and H_2O (2 mL) is treated with PTAB (3.90 g, 10.4 mmol) as described above. The acidified mixture is extracted with $CHCl_3$ (5 × 10 mL). The rest of the procedure for the isolation of sulfoxides **2i**, and **2j** is the same as given in Method A.

(^{18}O)Sulfoxides (**2f***, **g***, **k***, **p***, **s***, **t***, **u***; Table 2) are prepared at a 0.2–1.0 mmol scale with Method B, using a pyridine/$H_2{}^{18}O$ (67 ± 2) atomic % ^{18}O) solvent mixture (9:1). The yields are the same as in case of unlabelled sulfoxides.

The authors thank H. Medzihradszky-Schweiger for microanalyses, A. Csámpai and F. Ruff for ^1H-NMR and IR spectral analyses. Two of the authors (J.R., I.K.) acknowledge the Hungarian Academy of Sciences for financial support (Hungarian Scientific Research Foundation, No. 1234).

Received: 2 November 1989; revised: 26 February 1990

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