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Simple and Efficient Oxidation of Sulfides to Sulfones Using Catalytic Ruthenium Tetroxide

Carmen Mª Rodríguez, Jesús M. Ode, José Mª Palazón, Victor S. Martín*

Centro de Productos Naturales Orgánicos "Antonio González"
Instituto Universitario de Bio-Orgánica
Carretera La Esperanza, 2
38206 La Laguna, Tenerife, SPAIN

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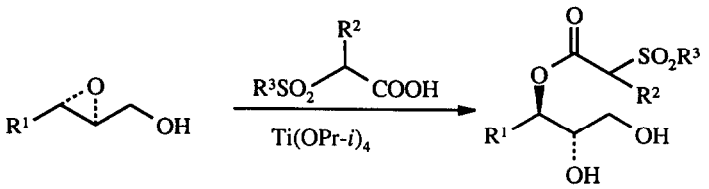
Abstract: A procedure for the oxidation of sulfides to sulfones using ruthenium tetroxide as catalyst and periodic acid as stoichiometric oxidant in a biphasic system (CCl_4, CH_3CN, H_2O) is reported.

In the course of our synthetic studies directed towards the enantioselective total synthesis of bioactive natural products[1] containing polyfunctionalized γ–lactones[2] we have been very interested in the use of either β-aryl- or β-alkylsulphonyl carboxylic acid as useful reagent for the regioselective opening of chiral 2,3-epoxyalcohols.[3] Such reagents could be conveniently prepared from the suitable β-sulfidecarboxylic acid by appropriate oxidation.



Recently we have reported an improved procedure to oxidise primary alcohols, double bonds and aromatic compounds to carboxylic acid, using ruthenium tetroxide as catalyst and periodic acid as stoichiometric oxidant.[4] Although a great number of reagents are known to convert sulfides to sulfones,[5] in our hands, of those have found none have found an optimum relation between reaction rate, yields and simplicity of the experimental procedure. To the best of our knowledge, the only precedent in the literature of such a conversion using ruthenium tetroxide is the pioneer work of Djerassi and Engle[6] in which cases of a similar oxidation were reported.[6] We considered that the above-mentioned improved procedure could be a reliable way to perform the oxidation of our sulfides to the corresponding sulfones in a simple and efficient manner.

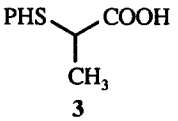
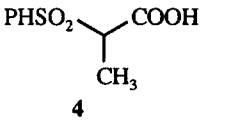
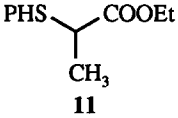
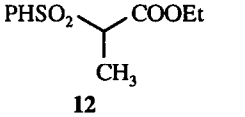
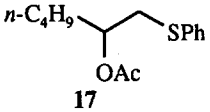
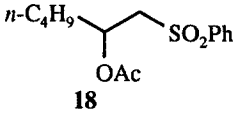
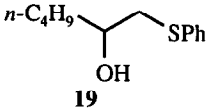
We now wish to report that the treatment of a sulfide with ruthenium tetroxide in a catalytic manner (2 %) using periodic acid[4] as stoichiometric oxidant, in the biphasic system reported by Sharpless et al.,[8] although with different dilution conditions, provides an excellent way to achieve the above-mentioned oxidation with excellent yields, with short periods of reaction time and an extremely simple experimental procedure (**Table I**).

The procedure is extremely simple to perform and does not require inert atmosphere. In a typical experiment, to a stirred solvent mixture of CH_3CN, CCl_4 and water (0.33:0.33:0.5 mL/mmol relative to oxidizable product) should be sequentially added the sulfide, ruthenium tetroxide (2%) ($RuCl_3.3H_2O$ is also effective) and periodic acid, at room temperature, until a complete reaction is observed (TLC or GC). The optimal range of the temperature reaction is between 20 and 40°C. Thus, only when the procedure is performed on a large scale (>30 mmol) is it necessary to control the temperature under 40°C in order to avoid spilling by

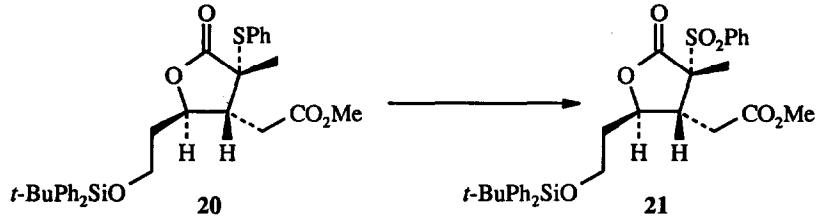
overheating. In this case, the combination of stirring and a cooling bath or the latter alone was sufficient to maintain the temperature into the optimal range.

The great solubility of both periodic and iodic acid in the solvent mixture allows the reaction to be performed in very concentrated solutions (>0.8 M solution). This highly concentrated reaction mixture led to one of the most interesting features of this method: the simplicity of the work-up procedure. Thus, when the reaction is finished, simple dilution with ether produces precipitation of the ruthenium salts and iodic acid, which can be easily removed by filtration. This feature makes the procedure especially attractive for the *oxidation of sulfides to water soluble sulfones*, in which other classical oxidation procedures[5] may fail.

Table I. Oxidation of sulfides with H_5IO_6-RuO_4

Entry	Starting sulfide	Reactn. time (h).	Product	Yield %
1.	Ph-S-CH_2-COOH **1**	0.5	Ph-SO_2-CH_2-COOH **2**	92
2.	 **3**	1.5	 **4**	88
3.	Et-S-CH_2-COOH **5**	1	Et-SO_2-CH_2-COOH **6**	90
4.	Ph-S-Ph **7**	3	Ph-SO_2-Ph **8**	76
5.	Ph-S-CH_2-COOEt **9**	1	Ph-SO_2-CH_2-COOEt **10**	89
6.	 **11**	1.5	 **12**	86
7.	Et-S-CH_2-COOEt **13**	1	Et-SO_2-CH_2-COOEt **14**	90
8.	$(CH_3)_3C$-S-CH_2-COOEt **15**	2	$(CH_3)_3C$-SO_2-CH_2-COOEt **16**	84
9.	 **17**	2	 **18**	86
10.	 **19**	2	Irresolvable mixture	—

The procedure can be used in more elaborated molecules when some standard protecting group are present. For instance the oxidation of the lactone **20** can be effectively oxidized to the sulfone **21** in 82% isolated yield.



In general terms, these oxidations can be performed over any substrate which does not have a sensitive group to ruthenium tetroxide oxidations,[8] otherwise complex mixtures may be obtained (entry 10, **Table I**).

In summary, we feel that this procedure is a very simple, fast and convenient method to perform the oxidation of sulfides to sulfones, providing a broader usefulness of ruthenium oxidation in organic chemistry.

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Experimental Section

Materials and Methods. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC-200 and/or Bruker AMX-400 spectrometer in $CDCl_3$ as solvent, chemical shifts are reported relative to Me_4Si. Low and high resolution mass spectra were obtained from a VG Micromass ZAB-2F spectrometer. Optical rotations were determined for solutions in chloroform or ethanol with a Perkin-Elmer Mod. 241 polarimeter. Infrared spectra were recorded on a Perkin-Elmer Mod. 402 spectrophotometer. GC analyses were performed on a Hewlett-Packard HP 5790-A with a capillary column OV-1, 25 m.. Column chromatography was performed on silica gel 0.005-0.2 mm., and TLC and PLC on silica gel, all Merck products. Visualization of spots was effected with UV light and/or phosphomolybdic acid in ethanol stain. All solvents were purified by standard techniques. Anhydrous magnesium sulphate was used for drying solutions.

General procedure for sulfide oxidations. Oxidation of 2-phenylthioacetic acid (1) to 2-benzenesulphonylacetic acid (2).

A 100 mL round-bottomed flask was charged with 2-phenylthioacetic acid **1** (5 g, 0.03 mol), carbon tetrachloride (9.8 mL,0.33 mL/mmol), acetonitrile (9.8 mL,0.33 mL/mmol), water (14.85 mL, 0.5mL/mmol) and periodic acid (14.25 g, 0.062 mol, 2.1 equiv). The flask contents were stirred at room temperature until both phases became clear. To the flask was added ruthenium trichloride hydrate (123.46 mg, 0.59 mmol, 0.02 equiv), and the reaction mixture was vigorously stirrred for 0.5 h. Then ether (175mL) was added and the vigorous stirring was continued for 10 min. The reaction mixture was then dried ($MgSO_4$) and filtered through qualitative Whatman filter paper 2. The solid residue was then washed with ether (3x30mL). The combined organic phases were concentrated. The crude product was purified by flash-chromatography affording 2-benzenesulphonylacetic acid **2** (5.48 g, 92 % yield) as a white solid: m.p. 113 °C [Lit.[9] 111-112 °C]; ^{1}H NMR δ: 4.15 (s, 2H), 7.62 (m, 3H), 7.97 (m, 2H); ^{13}CNMR, δ: 60.45 (t), 128.5 (d), 129.36 (d), 134.47 (d), 135.58 (s), 192.28 (s); IR ($CHCl_3$) (cm^{-1}): 2950, 2850, 1700, 1340, 1290, 1180, 960, 870, 780; MS *m/z*(relative intensity): 200 (M^+) (6), 156 (19), 141 (45); HRMS calcd. for $C_8H_8O_4S$: 200.0143, obsd. 220.0162.

Oxidation of 2-phenylthiopropionic acid (3) to 2-benzenesulphonylpropionic acid (4).

The general procedure was used to oxidize **3** (1 g, 5.49 mmol) in 1.5 h, yielding, after chromatography **4** (1.03 g, 88% yield): ^{1}H NMR, δ: 1.53 (d, J=7Hz, 3H), 3.50 (q, J=7Hz, 1H), 7.60 (m, 3H), 7.88 m, 2H), 10.5 (s, 1H); ^{13}C NMR ($CDCl_3$, δ: 11.86 (q), 65.26 (d), 129.20 (d), 129.33 (d), 134.46 (d), 136.68 (s), 169.85 (s); IR ($CHCl_3$) (cm^{-1}): 3169, 2986, 2943, 1725, 1380, 1325, 1222, 1153, 1084; MS *m/z* (relative intensity): 214 (M^+) (5), 170 (6), 141 (15), 77 (97); HRMS calcd. for $C_9H_{10}O_4S$ (M^+) 214.0299, obsd. 214.0304.

Oxidation of 2-ethylthioacetic acid (5) to 2-ethylsulphonylacetic acid (6).

The general procedure was used to oxidize **5** (1 g, 8.33 mmol) in 1h, yielding, after chromatography **6** (1.14 g, 90% yield): ^{1}H NMR, δ: 1.43 (t, J=7.4Hz, 3H), 3.31 (q, J=7.4Hz, 2H), 4.04 (s, 2H), 9.09 (s, 1H); ^{13}C NMR, δ: 6.35 (q), 48.28 (t), 56.33 (t), 165.24 (s); IR ($CHCl_3$) (cm^{-1}): 3203, 2985, 2945, 1739, 1457, 1326, 1142, 1105, 903; MS *m/z* (relative intensity): 152 (M^+) (4), 135 (4), 108 (4), 60 (100); HRMS calcd. for $C_4H_8O_4S$ (M^+) 152.0143, obsd. 152.0156.

Oxidation of diphenylsulfide (7) to diphenylsulphone (8).

The general procedure was used to oxidize **7** (1 g, 5.38 mmol) in 3h, yielding, after chromatography and recrystallization, **8** (890.7 mg, 76% yield): m.p. 126 °C; ^{1}H NMR, δ: 7.50 (m, 6H), 7.95 (m, 4H); ^{13}C NMR, δ: 127.60 (d), 129.26 (d), 133.16 (d), 141.71 (s); IR ($CHCl_3$)(cm^{-1}): 2985, 1319, 1309, 1157, 1107, 1071; MS *m/z*(relative intensity): 218 (M^+) (15), 141 (4), 77 (70); HRMS calcd. for $C_{12}H_{10}O_2S$ (M^+) 218.0401, obsd. 218.0411.

Oxidation to ethyl 2-phenylthioacetate (9) to ethyl 2-benzenesulphonylacetate (10).

The general procedure was used to oxidize **9** (1 g, 5.1 mmol) in 1 h, yielding, after chromatography, **10** (1.03 g, 89% yield): ^{1}H NMR, δ: 1.21 (t, J=7.16 Hz, 3H), 4.11 (s, 2H), 4.14 (q, J=7.16Hz, 2H), 7.62 (m, 3H), 7.95 (m, 2H); ^{13}C NMR, δ: 13.74 (q), 60.96 (t), 62.15 (t), 128.41 (d), 129.14 (d), 134.15 (d), 138.0 (s), 162.27 (s); IR ($CHCl_3$) (cm^{-1}): 2985, 2940, 1736, 1448, 1331, 1282, 1084, 1025; MS *m/z* (relative intensity): 229 (M^++1) (10), 183 (8), 141 (30); HRMS calcd. for $C_{10}H_{12}O_4S$ (M^+) 228.0456, obsd. 228.0492.

Oxidation to ethyl 2-phenylthiopropionate (11) to ethyl 2-benzenesulphonylpropionate (12).

The general procedure was used to oxidize **11** (1 g, 4.76 mmol) in 1.5 h, yielding, after chromatography, **12** (991 mg, 86% yield): ^{1} HNMR, δ: 1.70 (t, J=7.16Hz, 3H), 1.57 (d, J=7.08Hz, 3H), 3.48 (q, J=7.08Hz, 1H), 4.10 (q, J=7.16Hz, 2H), 7.57 (m, 3H), 7.90 (m, 2H); ^{13}C NMR, δ: 11.52 (q), 13.68 (q), 62.0 (t), 65.34 (d), 128.97 (d), 129.16 (d), 132.86 (s), 134.10 (d), 166.03 (s); IR ($CHCl_3$) (cm^{-1}): 2986, 2940, 1736, 1448, 1325, 1150, 1085, 1020; MS *m/z* (relative intensity): 243 (M^++1) (23), 197 (18), 77 (100); HRMS calcd. for $C_{11}H_{14}O_4S$ (M^+) 242.0613, obsd. 242.0657.

Oxidation to ethyl 2-ethylthioacetate (13) to ethyl 2-ethylsulphonylacetate (14).

The general procedure was used to oxidize **13** (1 g, 90% yield): ^{1}H NMR, δ: 1.32 (t, J=7.12Hz, 3H), 1.44 (t, J=7.45 Hz, 3H), 3.29 (q, J=7.45 Hz, 2H), 3.94 (s, 2H), 4.28 (q, J=7.12Hz, 2H); ^{13}C NMR, δ: 6.41 (q), 13.84 (q), 48.09 (t), 56.71 (t), 62.47 (t), 162.97 (s); IR ($CHCl_3$) (cm^{-1}): 2986, 2928, 1740, 1368, 1321, 1150, 1104, 1023; MS *m/z* relative intensity): 180 (M^+) (11), 153 (55), 135 (72), 88 (51); HRMS calcd. for $C_6H_{12}O_4S$ (M^+) 180.0456; calcd. 180.0452.

Oxidation of ethyl 2-*tert*-butylthioacetate (15) to ethyl 2-*tert*-butylsulphonylacetate (16).

The general procedure was used to oxidize **15** (1 g, 5.68 mmol) in 2 h, yielding, after chromatography, **16** (983.2 mg, 84% yield): ^{1}H NMR, δ: 1.26 (t, J=7.2Hz, 3H), 1.40 (s, 9H), 3.92 (s, 2H), 4.22 (q, J=7.2Hz, 2H); ^{13}C NMR, δ: 13.78 (q), 23.19 (q), 52.72 (t), 61.38 (s), 62.18 (t), 162.54 (s); IR ($CHCl_3$) (cm^{-1}): 2980, 2938, 1742, 1462, 1368, 1313, 1289, 1125; MS *m/z* (relative intensity): 209 (M^++1) (11), 193 (4), 135 (16), 57 (100); HRMS calcd. for $C_8H_{16}O_4S$ (M^+): 208.0628, obsd. 208.0612.

Oxidation of 2-acetyloxy-1-phenylthiohexane (17) to 2-acetyloxy-1-benzenesulphonylhexane (18).

The general procedure was used to oxidize **17** (1 g, 3.96 mmol) in 2 h, yielding, after chromatography **18** (969.2 mg, 86% yield): ^{1}H NMR, δ: 0.82 (t, J=6.66 Hz, 3H), 1.20 (m, 4H), 1.60 (m, 2H), 1.74 (s, 3H), 3.24 (dd, J=14.8, 3.36 Hz, 1H), 3.44 (dd, J=14.8,8.02 Hz, 1H), 5.21 (m, 1H), 7.58 (m, 3H), 7.87 (m, 2H); ^{13}C NMR, δ: 13.67 (q), 20.57 (q), 22.11 (t), 26.70 (t), 33.74 (t), 59.25 (t), 68.11 (d), 128.07 (d), 129.23 (d), 133.71 (d), 139.70 (s), 169.72 (s); IR ($CHCl_3$) (cm^{-1}): 2957, 2934, 1737, 1374, 1242, 1148, 1085, 1025; MS *m/z* (relative intensity): 285(M^++1) (6), 225 (9), 185 (15), 143 (61); HRMS calcd. for $C_{14}H_{21}O_4S$ (M^++1) 285.1160, obsd. 285.1166.

Oxidation of (2R,3R,4R)-2-methyl-2-phenylthio-3-methoxycarbonylmethyl-4-(2'-*tert*-butyldiphenylsilyloxy)ethyl-γ-butyrolactone (20) to (2R,3R,4R)-2-methyl-2-benzenesulphonyl-3-methoxycarbonylmethyl-4-(2'-*tert*-butyldiphenylsilyloxy)ethyl-γ-butyrolactone (21).

The general procedure was used to oxidize **20** (100 mg, 0.176 mmol, 91% yield): $[\alpha]_D^{25}$ +43.03° (c 2.54, $CHCl_3$); ^{1}H NMR, δ: 1.09 (s, 9H), 1.60 (s, 3H), 1.76 (m, 2H), 2.78 (dd, J=17.4, 5.5 Hz, 1H), 2.99 (ddd, J=8.4, 5.5, 5.5 Hz, 1H), 3.54 (dd, J=17.4, 8.4 Hz, 1H), 3.79 (s, 3H), 3.87 (t, J=6.1 Hz, 2H), 4.99 (ddd, J=9.8,9.8, 2.4 Hz, 1H), 7.44 (m, 6H), 7.58 (m, 3H), 7.69 (m, 4H), 7.82 (m, 2H); ^{13}C NMR, δ: 19.18 (q), 20.71 (s), 26.67 (q), 33.28 (t), 36.76 (t), 48.92 (d), 52.14 (q), 60.08 (t), 69.77 (s), 79.85 (d), 127.74 (d), 128.80 (d), 129.74 (d), 130.68 (d), 131.39 (d), 134.32 (s), 134.64 (s), 135.58 (d), 170.86 (s), 171.66 (s); IR ($CHCl_3$) (cm^{-1}): 2956, 2932, 1772, 1738, 1448, 1310, 1214, 1112, 1082; MS *m/z* (relative intensity): 563 (6), 537 (93), 395 (93), 365 (25), 323 (48), 199 (70); HRMS calcd. for $C_{31}H_{35}SSi$ 563.1923, obsd. 563.1914.

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