A New Methodology for Obtaining α-Oxo Ester Equivalents: Sulfanylation of α-Sulfonyl Carboxylic Esters in a Solid/Liquid Phase Transfer Catalytic System

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A new, convenient procedure for the synthesis of a wide range of α-methylsulfanyl-α-phenylsulfonyl carboxylic esters has been developed and their facile conversion to the corresponding α-oxo esters demonstrated.

In the course of our studies of the reactions of α-sulfonyl carbanions[1] we became interested in α-sulfonyl carboxylic esters, which, by sulfanylation, could lead to esters containing the $>C(SR)SO_2R$ group,[2-4] the synthetic equivalent of a C=O group. α-Oxo esters are of interest not only because of their biological importance, but also as synthetic precursors of α-amino esters.[5]

Although sulfanylation reactions in homogeneous media have been extensively investigated,[6] the few studies in the literature that have used phase transfer catalysis are limited to nitriles.[7-8] It was reported that disulfides are not convenient sulfanylating agents due to the liberation of the RS^- anion which inhibits the catalytic process by formation of a lipophilic ion pair RS^-Q^+ with the cation of the catalyst.

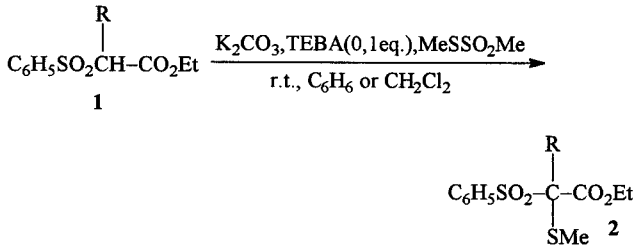
In a previous study[9] on sulfanylation of benzylic sulfones by phase transfer catalysis using NaOH as base and Herquat as catalyst, we were able to avoid this drawback by employing *S*-methyl methanethiosulfonate as the sulfanylating agent, which leads to a less nucleophilic $^-SO_2CH_3$ leaving group.

More recently, the solid-liquid system consisting of solid K_2CO_3 in the presence of triethylbenzylaminium chloride (TEBA), introduced by Makosza et al.[10] for the carbon alkylation of active methylene compounds, was employed in our laboratory for sulfanylation of some α-sulfinyl ketones.[11] We found that this methodology could be very convenient for sulfanylation of α-sulfonyl carboxylic esters containing fairly strongly acidic CH groups, in addition to the fact that the use of K_2CO_3 as base instead of NaOH avoids the hydrolysis of the ester.

In fact, when several alkyl **1a–e** and arylacetic **1f–j** α-phenylsulfonyl carboxylic esters were submitted to reaction with *S*-methyl methanethiosulfonate at room temperature in benzene, in the presence of solid K_2CO_3 and TEBA,[10] the corresponding monosulfanylated derivatives **2a–e** and **2f–j** were obtained in good yields. It is noteworthy that only a slight decrease of yield and an increase of the reaction time were observed when some selected α-sulfonyl esters **1a**, **b** and **f** were sulfanylated under the same reaction conditions, employing dichloromethane as solvent (Table).

Proof that these sulfanylation reactions really occur by phase transfer catalysis was obtained by performing the reaction of *S*-methyl methanethiosulfonate with ethyl α-phenylsulfonylpropionate **(1b)** and phenylacetate **1f** in the presence of K_2CO_3 in benzene and in the absence of TEBA, which afforded the corresponding sulfanylated products **2b** and **2f** in only 6 and 20% yield, respectively.

Table. Sulfanylation of Some Ethyl α-Phenylsulfonyl Carboxylates **1a–j**



Starting Sulfonyl Esters **1**	R	Time (h) in C_6H_6	Time (h) in CH_2Cl_2	Products **2** (Yields %)[a] in C_6H_6	Products **2** (Yields %)[a] in CH_2Cl_2
a	H	1	2	75	75
b	Me	1	2	96	92
c	Et	4		70	
d	*i*-Pr	6		39	
e	Hex	4		86	
f	C_6H_5	4	6	86	79
g	C_6H_4OMe (*p*)	4		56	
h	C_6H_4Cl (*p*)	4		72	
i	$C_6H_4NO_2$ (*p*)	4		75	
j	C_6H_4Me (*p*)	4		43	

[a] Isolated.

The superiority of this method over the conventional homogeneous one becomes evident upon comparison with the reaction of the sulfonyl esters **1b** and **1f** with *S*-methyl methanethiosulfonate in the presence of NaH in DMSO, which afforded the corresponding sulfanylated products **2b** and **2f** in much lower yields (55 and 64%, respectively).

Of the available methods for the transformation of α-sulfanylated α-sulfonyl esters,[2-4] the thermal decomposition elaborated in our laboratory for the obtention of aldehydes and ketones[4,12] seemed to be most appropriate since, unlike acid hydrolysis, it should not affect the ester group.

The thermal decomposition of ethyl α-sulfonyl-α-sulfanyl phenyl acetate **(1f)** took place at 150°C to give ethyl phenylglyoxylate in 93% yield. It is noteworthy that a higher temperature (160°C) was necessary for thermal decomposition of the corresponding propionate **1b**, obtained by de-ethoxycarbonylative sulfanylation of the α-sulfonyl (methyl) malonic ester[10] to give ethyl pyruvate in 68% yield.

Thus, in summary, the method reported here, sulfanylation in phase transfer catalysis, at room temperature

using solid K_2CO_3, catalytic amounts of TEBA and *S*-methyl methanethiosulfonate as sulfanylating agent, followed by thermal decomposition, represents a simple and general route to aliphatic and aromatic α-oxo esters.

Microanalyses were performed on a Perkin Elmer 2400 CHN elemental analyser. Mps were determined in a Thomas Hoover Kofler hot-stage apparatus, using a Dynamics Optics AHT microscope and are uncorrected. All ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer. Chemical shifts are expressed in ppm relative to $SiMe_4$ as internal standard. NMR samples were prepared using $CDCl_3$ (99.8 atom %D, containing 0.03 % v/v TMS, Aldrich). Gravity chromatography was performed on Merck Kieselgel 60 (70–230 mesh).

Ethyl α-phenylsulfonylcarboxylates **1a–b** and **1e–j** were prepared by a modified procedure of condensation of $NaSO_2Ph$ with the appropriate α-bromo esters. Compounds **1c** and **1d** were prepared by alkylation of phenylsulfonylacetate **1a**.

Ethyl Phenylsulfonylacetate (1a); Typical Procedure:
A solution of ethyl bromoacetate (42 g, 0.25 mol) and $NaSO_2Ph$ (49 g, 0.30 mol) in EtOH (200 mL) was refluxed for 12 h and left standing at r.t. for an additional 12 h. The solvent was removed under reduced pressure and, after addition of H_2O (200 mL), the oily layer was separated and dissolved in CH_2Cl_2 (50 mL). After extraction of the aqueous layer with CH_2Cl_2 (3 × 50 mL), the combined extracts were dried (Na_2SO_4) and concentrated. The crude solid residue was purified by recrystallization from EtOH/H_2O, affording 47 g (82%) of pure sulfonyl ester, mp 41–43 °C (lit.[14] 41–42 °C).

Ethyl 2-(Phenylsulfonyl)propanoate **(1b)**:
Yield 86%, bp 162 °C/1 Torr (lit.[14] 132 °C/0.2 Torr).

Ethyl 2-(Phenylsulfonyl)octanoate **(1e)**:
Yield 78%, bp 174 °C/0.6 Torr, ^{1}H NMR: δ = 0.86 (t, *J* = 7 Hz, 3H), 1.15 (t, 3H), 1.25–1.29 (m, 8H), 1.98–2.00 (m, 2H), 3.86–3.94 (dd, 1H), 4.10 (q, *J* = 7 Hz, 2H), 7.56–7.89 (m, 5H).
Anal. calc. for $C_{16}H_{24}O_4S$: C, 61.51; H, 7.74. Found: C, 61.71; H, 7.78.

Ethyl Phenyl(phenylsulfonyl)acetate **(1f)**:
Yield 72%, white crystals (EtOH/H_2O), mp 100.3–101.1 °C (lit.[14] 100–101 °C).

Ethyl (4-Methoxyphenyl)phenylsulfonylacetate **(1g)**:
Yield 61%, white crystals, mp 80.2–81.2 °C (EtOH/H_2O).
^{1}H NMR: δ = 1.22 (t, 3H), 3.80 (s, 3H), 4.16–4.26 (m, 2H), 5.05 (s, 1H), 6.79–7.65 (m, 4H).
Anal. calc. for $C_{17}H_{18}O_5S$: C, 61.06; H, 5.43. Found: C, 60.88; H, 5.48.

Ethyl (4-Chlorophenyl)phenylsulfonylacetate **(1h)**:
Yield 66%, white crystals (EtOH/H_2O) mp 87.6–88.9 °C.
^{1}H NMR: δ = 1.22 (t, 3H), 4.09–4.32 (m, 2H), 5.07 (s, 1H), 7.25–7.68 (m, 4H).
Analc. calc. for $C_{16}H_{15}O_4ClS$: C, 56.72; H, 4.46. Found: C, 56.82; H, 4.61

Ethyl (4-Nitrophenyl)phenylsulfonylacetate **(1i)**:
Yield 71%, white crystals (CH_2Cl_2 /hexane), mp 128.5–129.8 °C.
^{1}H NMR: δ = 1.23 (t, 3H), 4.14–4.30 (m, 2H), 5.20 (s, 1H), 7.46–8.20 (m, 4H).
Anal. calc. for $C_{16}H_{15}O_6NS$: C, 55.01; H, 4.33. Found: C, 55.11; H, 4.45.

Ethyl (4-Methylphenyl)phenylsulfonylacetate **(1j)**:
Yield 69%, white crystals (EtOH/H_2O), mp 104.5–106.5 °C.
^{1}H NMR: δ = 1.21 (t, 3H), 2.33 (s, 3H), 4.12–4.22 (m, 2H), 5.07 (s, 1H), 7.08–7.65 (m, 4H).
Anal. calc. for $C_{17}H_{18}O_4S$: C, 64.13; H, 5.70. Found: C, 63.74; H, 5.61.

Ethyl 2-Phenylsulfonylbutanoate (1c); Typical Procedure:
To a suspension of NaH (1.05 g, 21.9 mmol, 50% in mineral oil, washed twice with anhyd hexane) in anhyd DMSO (20 mL), a solution of **1a** (5.00 g, 21.9 mmol) in anhyd DMSO (30 mL) was added dropwise via syringe, with stirring at r.t. After H_2 evolution had ceased, a solution of 6.80 g (62.0 mmol) of EtBr in anhyd DMSO (20 mL) was added. After stirring for 4 h at 60 °C, the mixture was allowed to cool and poured into cold H_2O (100 mL) and extracted with CH_2Cl_2 (4 × 35 mL). The combined extracts were washed with H_2O and dried ($MgSO_4$). After solvent removal, the crude product was recrystallized from EtOAc/hexane, affording 4.20 g (75%) of white crystals; mp 61–63 °C (lit.[15] 62–63 °C).
^{1}H NMR: δ = 0.98 (t, *J* = 7 Hz, 3H), 1.17 (t, 3H), 1.85–2.19 (m, 2H), 3.83–3.90 (dd, 1H), 4.06–4.18 (q, *J* = 7 Hz, 2H), 7.27–7.90 (m, 5H).

Ethyl 3-Methyl-2-phenylsulfonylbutanoate **(1d)**:
Yield 42%, white crystals (EtOH/H_2O), mp 58–60 °C (lit.[16] 59.5–60.5 °C).
^{1}H NMR: δ = 0.97–1.25 (dd, 6H), 1.06 (t, 3H), 2.48–2.52 (m, 1H), 3.76 (d, 1H), 3.90–4.00 (m, 2H), 7.49–7.91 (m, 5H).

Sulfanylation by Phase Transfer Catalysis; General Procedure:
A mixture of the appropriate α-sulfonyl ester (1.70 mmol), finely powdered K_2CO_3 (3.6 mmol), TEBA (10 mol%) and anhyd benzene or CH_2Cl_2 (10 mL) was stirred at r.t. for 1 h. After this time, *S*-methyl methanethiosulfonate (2.10 mmol) dissolved in anhyd benzene or CH_2Cl_2 (3 mL) was added. The mixture was further stirred for the periods mentioned in the Table. The solid was removed by suction filtration and washed with CH_2Cl_2 (20 mL). The organic extract was washed with H_2O (2 × 20 mL) and dried ($MgSO_4$). After solvent removal, the crude product was purified by recrystallization or by column chromatography.

Ethyl (Methylsulfanyl)phenylsulfonylacetate **(2a)**:
Yield 75%, white crystals (EtOH/H_2O), mp 80.7–82.2 °C.
^{1}H NMR: δ = 1.19–1.26 (t, *J* = 7 Hz, 3H), 2.37 (s, 3H), 4.13–4.23 (q, *J* = 7 Hz, 2H), 4.53 (s, 1H), 7.56–7.98 (m, 5H).
Anal. calc. for $C_{11}H_{14}O_4S_2$: C, 48.16; H, 5.14. Found: C, 48.09; H, 5.10.

Ethyl 2-Methylsulfanyl-(2-phenylsulfonyl)propanoate **(2b)**:
Yield 96%, purified by column chromatography using hexane/acetone (4:1) as eluent.
^{1}H NMR: δ = 1.19–1.27 (t, 3H), 1.84 (s, 3H), 2.30 (s, 3H), 4.13–4.26 (m, 2H), 7.51–7.99 (m, 5H).
Anal. calc. for $C_{12}H_{16}O_4S_2$: C, 49.98; H, 5.59. Found: C, 50.28; H, 5.51.

Ethyl 2-Methylsulfanyl-(2-phenylsulfonyl)butanoate **(2c)**:
Yield 70%, purified by column chromatography using benzene/EtOAc (4:0.5) as eluent.
^{1}H NMR: δ = 1.02–1.09 (t, *J* = 7 Hz, 3H), 1.16–1.23 (t, 3H), 2.01–2.19 and 2.46–2.70 (m, 2H), 2.27 (s, 3H), 4.10–4.21 (q, *J* = 7 Hz, 2H), 7.50–7.94 (m, 5H).
Anal. calc. for $C_{13}H_{18}O_4S_2$: C, 51.63; H, 6.00. Found C, 51.42; 5.72.

Ethyl 3-Methyl-2-methylsulfanyl-2-phenylsulfonylbutanoate **(2d)**:
Yield 39%. Purified by column chromatography using toluene/EtOAc (4:1) as eluent.
^{1}H NMR: δ = 1.08–1.23 (dd, 6H), 1.21–1.30 (m, 3H), 2.33–2.52 (m, 1H), 2.38 (s, 3H), 4.18–4.30 (m, 2H), 7.47–7.97 (m, 5H).
Anal. calc. for $C_{14}H_{20}O_4S_2$: C, 53.14; H, 6.37. Found: C, 53.04; H, 6.16.

Ethyl 2-Methylsulfanyl-(2-phenylsulfonyl)octanoate **(2e)**:
Yield 86%, colorless liquid after washing the crude oily residue with hexane at −20 °C.
^{1}H NMR: δ = 0.88 (t, 3H), 1.20 (t, *J* = 7 Hz, 3H), 1.26–1.58 (m, 8H), 1.96–2.10 and 2.43–2.57 (m, 2H), 2.27 (s, 3H), 4.15 (q, *J* = 7 Hz, 2H), 7.50–7.93 (m, 5H).
Anal. calc. for $C_{17}H_{26}O_4S_2$: C, 56.95; H, 7.31. Found: C, 57.20; H, 7.02.

Ethyl Methylsulfanylphenyl(phenylsulfonyl)acetate **(2f)**:

Yield 86%, white crystals (EtOH/H_2O), mp 113.7–114.7°C.

^{1}H NMR: $\delta = 1.31$ (t, $J = 7$ Hz, 3H), 2.46 (s, 3H), 4.38 (q, $J = 7$ Hz, 2H), 7.21–7.54 (m, 5H).

Anal. calc. for $C_{17}H_{18}O_4S_2$: C, 58.26; H, 5.18. Found: C, 58.34; H, 5.02.

Ethyl (4-Methoxyphenyl)methylsulfanyl(phenylsulfonyl)acetate **(2g)**:

Yield 56%, white crystals (EtOH/H_2O), mp 89.4–91.2°C.

^{1}H NMR: $\delta = 1.33$ (t, 3H), 2.45 (s, 3H), 3.81 (s, 3H), 4.30–4.45 (m, 2H), 6.72–6.80 and 7.10–7.56 (m, 4H).

Anal. calc. for $C_{18}H_{20}O_5S_2$: C, 56.82; H, 5.30. Found: C, 56.70; H, 5.30.

Ethyl (4-Chlorophenyl)methylsulfanyl(phenylsulfonyl)acetate **(2h)**:

Yield 72%, white crystals (EtOH/H_2O), mp 100.0–101.2°C.

^{1}H NMR: $\delta = 1.33$ (t, $J = 7$ Hz, 3H), 2.42 (s, 3H), 4.38 (q, $J = 7$ Hz, 2H), 7.20–7.56 (m, 4H).

Anal. calc. for $C_{17}H_{17}ClO_4S_2$: C, 53.05; H, 4.45. Found: C, 52.87; H, 4.58.

Ethyl Methylsulfanyl(4-nitrophenyl)(phenylsulfonyl)acetate **(2i)**:

Yield 75%, white crystals (EtOH/H_2O), mp 159.2–160.5°C.

^{1}H NMR (CD_2Cl_2/TMS): $\delta = 1.31$ (t, $J = 7$ Hz, 3H), 2.36 (s, 3H), 4.36 (q, $J = 7$ Hz, 2H), 7.33–7.63 and 8.06–8.13 (m, 4H).

Anal. calc. for $C_{17}H_{17}NO_6S_2$: C, 51.63; H, 4.33. Found: C, 51.53; H, 4.14.

Ethyl (4-Methylphenyl)methylsulfanyl(phenylsulfonyl)acetate **(2j)**:

Yield 53%, white crystals (EtOH/H_2O), mp 104.5–106.5°C.

^{1}H NMR: $\delta = 1.33$ (t, $J = 7$ Hz, 3H), 2.43 (s, 3H), 3.80 (s, 3H), 4.37 (q, $J = 7$ Hz, 2H), 6.74 (d, $J = 9$ Hz, 2H), 7.13 (d, $J = 9$ Hz, 2H), 7.26–7.51 (m, 5H).

Anal. calc. for $C_{18}H_{20}O_4S_2$: C, 59.13; H, 5.53. Found: C, 59.13; H, 5.57.

Sulfanylation Using NaH/DMSO; Typical Procedure:

To a suspension of NaH (0.22 g, 4.6 mmol, 50% in mineral oil, washed twice with anhyd hexane), in anhyd DMSO (4 mL), **1b** (1.0 g, 4.1 mmol) in anhyd DMSO (4 mL) was added via syringe, under N_2. As soon as the gas evolution had ceased, 0.62 g (4.9 mmol) of *S*-methyl methanethiosulfonate in anhyd DMSO (2 mL) was added via syringe. The mixture was further stirred for 6 h at r.t., poured into sat. NH_4Cl, acidified with HCl to pH 3 and extracted with CH_2Cl_2 (4 × 20 mL). The organic extract was washed with H_2O (20 mL) and dried (Na_2SO_4). After removal of solvent, the orange oil (1.0 g) was purified by column chromatography using benzene/$CHCl_3$ (3:1) as eluent, affording 0.70 g (55%) of **2b**.

The above procedure was applied to the sulfenylation of sulfonyl ester **1f** and the reaction monitored by ^{1}H NMR spectroscopy. After 2 h the crude mixture consisted of 36% of **1f** and 64% of **2f**. The same result was observed after 4 h.

Thermal Decomposition of Ethyl (Methylsulfanyl)phenyl(phenylsulfonyl)acetate (2f):

A short-path distillation apparatus was charged with 0.50 g (1.4 mmol) of sulfonyl ester **2f**. Distillation under reduced pressure (7 Torr), mantaining the external bath at 150°C, yielded 0.34 g of a yellow oil. The oil was dissolved in CH_2Cl_2 (5 mL) and dried ($MgSO_4$). After removal of the solvent, the crude product was purified by column chromatography using hexane/acetone (9.5:0.5) as eluent. The resulting colorless liquid (0.24 g, 95%) was characterized by ^{1}H NMR as ethyl phenylglyoxylate.[17]

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