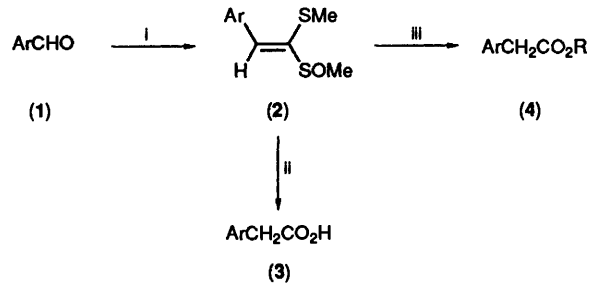
Acid Catalysed Reactions of Aryl Ketene Dithioacetal *S*-Oxides: Synthesis of Chloroketene Thioacetals and Thioesters

Alan T. Hewson,* Stewart K. Richardson and David A. Sharpe
Department of Chemistry, Sheffield City Polytechnic, Pond Street, Sheffield S1 1WB

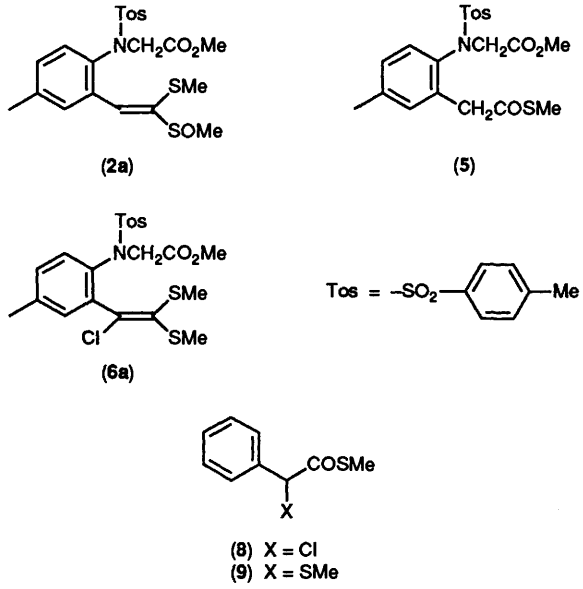
Aryl ketene dithioacetal *S*-oxides, on treatment with hydrochloric acid in dichloromethane, give chloroketene thioacetals. The same reaction in the presence of hydrogen sulphide gives *S*-methyl thioesters.

Among the many one-carbon homologation reactions of aldehydes,[1] one has been reported for the conversion of arenecarbaldehydes into arylacetic acids or their esters.[2] This involves the condensation of the aldehyde **1** with methyl methylsulphinylmethyl sulphide to give the intermediate ketene dithioacetal *S*-oxide **2** which is hydrolysed with hydrochloric acid in either dimethoxyethane (DME) or an alcohol to give the acid **3** or the ester **4**, respectively (Scheme 1).

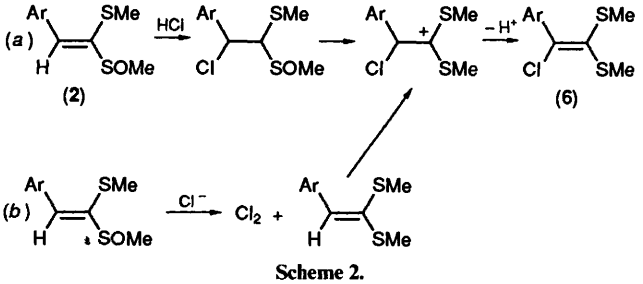


Scheme 1. *Reagents:* i, $MeSCH_2SOMe$, Triton B; ii, H_3O^+, DME; iii, H_3O^+, ROH.

In the course of synthetic studies towards virantmycin[3] we attempted to carry out the conversion of compound **2a** into the corresponding phenylacetic acid using concentrated hydrochloric acid in DME. However, a complex mixture of products resulted, and none of the desired acid could be isolated. Instead a significant amount of compound **2a** was recovered, together with 23% of the thioester **5**. Variation of the ratio of hydrochloric acid to DME or changing the solvent to tetrahydrofuran (THF), diethyl ether or dioxane failed to improve the situation, but when compound **2a** was stirred in a mixture of hydrochloric acid and dichloromethane a single product was obtained in high yield. The structure of this product was assigned as the chloroketene thioacetal **6a**. In order to test the generality of this reaction, a range of aryl ketene dithioacetal *S*-oxides was prepared from the corresponding substituted benzaldehydes (Table 1). Subsequent treatment with hydrochloric acid–dichloromethane gave the corresponding chloroketene dithioacetals **6** in high yields (Table 2). The same conversion has previously been reported using thionyl chloride–pyridine[4] and there is a report, for a single case, of a compound of the type **6** being one of the products formed on treatment of the corresponding ketene dithioacetal *S*-oxide with hydrochloric acid in ethanol.[5] In a related process, we have previously reported a novel synthesis of indoles.[6] Our consideration of the mechanistic pathway for this transformation has led us to two possibilities (Scheme 2): (*a*), addition of HCl to the electrophilic double bond of compound **2** followed by a Pummerer reaction and proton loss; (*b*), oxidation of chloride to chlorine, or an equivalent chlorinating species, by

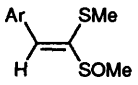


the sulphoxide group in compound **2**,[7,8] chlorination of the double bond and subsequent proton loss. If the latter were true, it might be possible to block the oxidation–reduction step and allow an alternative reaction to occur. In the event, when the ketene dithioacetal *S*-oxides **2** were dissolved in dichloromethane, which had been previously saturated with hydrogen sulphide, and the solution was treated with concentrated hydrochloric acid, the products isolated were the *S*-methyl thioesters **7**. The results from the application of this method to a range of benzaldehyde derivatives are shown in Table 3. We assume that the mechanism for this conversion involves initial addition of H^+ to compound **2**, attack by water and loss of methanesulphenic acid (Scheme 3). Confirmation for the



Scheme 2.

structures of **7c**, **7f** and **7g** was obtained by independent synthesis from the appropriate phenylacetic acid and

Table 1. Spectral and analytical data for compounds **2**. 

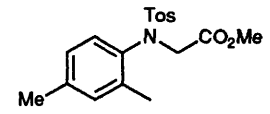
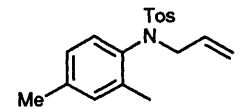
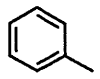
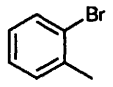
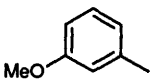
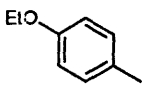
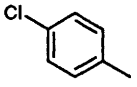
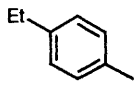
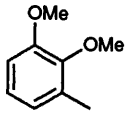
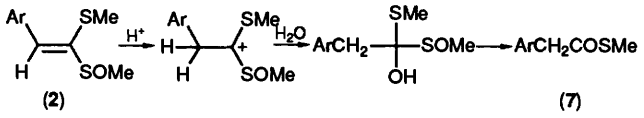
Compound (molecular formula)	Ar	Yield (%)	M.p. (°C)	% Found (% Required) C	H	N	ν/cm^{-1}	δ(CDCl$_3$)
2a ($C_{21}H_{25}NO_5S_3$)		78	Oil	54.15 (53.94)	5.5 (5.40)	3.05 (3.00)	1755, 1355, 1210, 1160	2.32 (3 H, s), 2.40 (3 H, s), 2.45 (3 H, s), 2.72 (3 H, s), 3.64 (3 H, s), 4.38 (2 H, s), 6.90–8.05 (7 H, m)
2b ($C_{21}H_{25}NO_3S_3$)		86	Oil	57.8 (57.90)	5.9 (5.79)	3.15 (3.21)	1630, 1580, 1340, 1155, 1060	2.30 (3 H, s), 2.40 (3 H, s), 2.45 (3 H, s), 2.80 (3 H, s), 4.10 (2 H, m), 4.95 (2 H, m), 5.75 (1 H, m), 6.40–8.00 (7 H, m)
2c		77	Oil				lit. ref. 2	
2d ($C_{10}H_{11}BrOS_2$)		64	33–35	41.25 (41.24)	3.8 (3.80)		1450, 1420, 1055, 1015	2.20 (3 H, s), 2.65 (3 H, s), 6.90–7.70 (5 H, m)
2e ($C_{11}H_{14}O_2S_2$)		84	Oil	54.4 (54.51)	5.9 (5.82)		1590, 1565, 1250, 1150, 1055	2.25 (3 H, s), 2.60 (3 H, s), 3.70 (3 H, s), 6.50–7.40 (5 H, m)
2f ($C_{12}H_{16}O_2S_2$)		80	50–52	56.45 (56.21)	6.5 (6.29)		1600, 1520, 1485, 1250, 1175	1.50 (3 H, t), 2.36 (3 H, s), 2.76 (3 H, s), 4.17 (2 H, q), 6.95 (2 H, d), 7.60 (1 H, s), 7.95 (2 H, d)
2g ($C_{10}H_{11}ClOS_2$)		66	Oil	56.1 (55.94)	5.05 (5.13)		1580, 1475, 1400, 1240, 1050	2.31 (3 H, s), 2.80 (3 H, s), 7.45 (2 H, d), 7.60 (1 H, s), 7.90 (2 H, d)
2h ($C_{12}H_{16}OS_2$)		56	Oil	69.15 (69.23)	7.5 (7.69)		1660, 1505, 1415, 1240, 1060	1.25 (3 H, t), 2.30 (3 H, s), 2.68 (2 H, q), 2.80 (3 H, s), 7.33 (2 H, d), 7.70 (1 H, s), 7.92 (2 H, d)
2i ($C_{12}H_{16}O_3S_2$)		80	Oil	52.8 (52.94)	6.0 (5.88)		1575, 1470, 1435, 1270, 1070	2.38 (3 H, s), 2.90 (3 H, s), 4.06 (6 H, 2 × s), 7.38 (2 H, m), 8.10 (1 H, dd), 8.25 (1 H, s)

Table 2. Spectral and analytical data for compounds **6**.

Compound (molecular formula)	Precursor	Yield (%)	M.p. (°C)	% Found (% Required) C	H	N	ν/cm^{-1}	δ_H(CDCl$_3$)
6a ($C_{21}H_{24}ClNO_4S_3$)	**2a**	100	135–136	52.05 (51.89)	5.1 (4.98)	2.95 (2.88)	1760, 1355, 1210, 1165	2.27 (3 H, s); 2.35 (3 H, s); 2.42 (3 H, s); 2.48 (3 H, s); 3.57 (3 H, s); 4.50 (2 H, d, *J* 5 Hz); 7.00–7.75 (7 H, m)
6b ($C_{21}H_{25}ClNO_2S_3$)	**2b**	100	Oil	55.5 (55.55)	5.35 (5.33)	3.1 (3.08)	1680, 1585, 1485, 1350, 1160	2.33 (2 H, s); 2.38 (3 H, s); 2.45 (3 H, s); 2.50 (3 H, s); 4.05 (2 H, m); 5.00 (2 H, m); 5.80 (1 H, m); 6.80–7.80 (7 H, m)
6c ($C_{10}H_{11}ClS_2$)	**2c**	100	Oil	52.1 (52.06)	4.9 (4.77)		1430, 1420, 1410, 1300, 1200, 1065	2.30 (3 H, s); 2.76 (3 H, s); 7.30–8.00 (5 H, m)
6d ($C_{10}H_{10}BrClS_2$)	**2d**	79	43–45	38.9 (38.79)	3.35 (3.26)		1450, 1410, 1040, 1020	2.20 (3 H, s); 2.45 (3 H, s); 6.95–7.55 (4 H, m)
6e ($C_{11}H_{13}ClOS_2$)	**2e**	82	Oil	50.65 (50.66)	5.05 (5.02)		1585, 1570, 1275, 1255	2.05 (3 H, s); 2.32 (3 H, s); 3.63 (3 H, s); 6.40–7.10 (4 H, m)

Table 3. Spectral data for compounds 7.

Compound	Precursor	Yield (%)	Mass spec.	ν/cm^{-1}	δ_H($CDCl_3$)
7c	**2c**	61	166 (M^+), 119, 91	1690, 1600, 1430, 1310	2.27 (3 H, s); 3.88 (2 H, s); 7.40 (5 H, s)
7e	**2e**	58	196 (M^+), 149, 121	1686, 1350	2.19 (3 H, s); 3.63 (2 H, s); 3.68 (3 H, s); 6.96 (4 H, m)
7f	**2f**	57	210 (M^+), 135, 107, 77, 40	1680, 1605, 1510, 1300	1.44 (3 H, t); 2.33 (3 H), s); 3.80 (2 H, s); 4.13 (2 H, q); 7.19 (4 H, m)
7g	**2g**	43	200/202 (M^+), 153/155, 125/127	1685, 1595, 1495, 1410	2.40 (3 H, s); 3.93 (2 H, s); 7.50 (4 H, m)
7h	**2h**	47	194 (M^+), 119	1690, 1315	1.22 (3 H, t); 2.23 (3 H, s); 2.63 (2 H, q); 3.75 (2 H, s); 7.11 (4 H, s)
7i	**2i**	86	226 (M^+), 151, 136, 91, 65	1690, 1590, 1480, 1275	2.14 (3 H, s); 3.63 (3 H, s); 3.90 (3 H, s); 3.93 (2 H, s); 7.04 (3 H, m)



Scheme 3.

methanethiol in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC).

Chloroketene thioacetals of the type **6** have previously been converted into α-methylthio esters by treatment with hydrochloric acid and an alcohol.[9] For our own purposes, an oxygen ester would not have been useful, but a thioester would have been ideal. We therefore briefly investigated the possibility of converting compound **6** directly into a thioester, basing our approach on the work of Seebach,[10] who used trifluoroacetic acid (TFA)–water for a related reaction. Chromatography of the reaction product from compound **6c** gave two fractions, one of which contained two components, namely *S*-methyl thioester **7c** (28%) and chlorinated derivative **8** (28%), while the other fraction gave the thiol ester **9** (19%). Presumably compound **9** arises from compound **8** by nucleophilic displacement of chloride by liberated methanethiol. The structure of compound **8** was confirmed by independent synthesis. Identical results were obtained with chloroketene dithioacetals **6d** and **6e**. This mixture of products did not appear to be useful for our purposes so was not utilised further.

Experimental

IR spectra were obtained on Pye–Unicam SP3-100 or Perkin-Elmer 737 spectrophotometers. Samples were prepared as KBr discs or liquid films. ^{1}H NMR spectra were obtained on JEOL C60 or Bruker WP80 instruments in $CDCl_3$ solution. Mass spectra were obtained on a VG Micromass 30F spectrometer. Microanalyses were performed by the City University, London. Light petroleum refers to that fraction boiling in the range 40–60 °C. Ether refers to diethyl ether.

*2-Toluene-*p*-sulphonamido-5-methylbenzoic Acid.*—Water (300 ml) was warmed slowly to 60 °C with stirring while sodium carbonate (50.3 g, 0.473 mol) was added in portions. With the temperature of the liquid maintained at 60–65 °C, 2-amino-5-methylbenzoic acid (29.78 g, 0.197 mol) was added in five portions. Then toluene-*p*-sulphonyl chloride (41.17 g, 0.217 mol) was introuced over 20 min with the temperature of the reaction mixture kept below 70 °C. This temperature was maintained for a further 20 min and then raised to 80 °C whilst charcoal (1.5 g) was added cautiously. The reaction mixture was filtered on a hot Buchner apparatus and the filtrate added to a swirled solution of 5M HCl (100 ml). The mixture was stirred for 10 min after which the solid was filtered off, washed with HCl (2M) and water, and dried at 60 °C *in vacuo* to give the product as a brown solid (60.5 g, 100%), m.p. 195–199 °C; ν_{max}(KBr) 3400–2300, 3210, 1675, 1580, 1340 and 1170; δ_H 2.30 (3 H, s), 6.47 (1 H, br s), 7.10–7.90 (7 H, m), and 10.18 (1 H, s).

N-(2-Hydroxymethyl-4-methylphenyl)toluene-4-sulphonamide.—To $LiAlH_4$ (3.8 g, 0.1 mol) in THF (30 ml) was added dropwise the above acid (15.24 g, 0.05 mol) in THF (125 ml). The reaction mixture was refluxed for 1 h and then HCl (2M) (100 ml) was carefully added and the THF layer removed. The aqueous layer was extracted with ethyl acetate and the combined organic phases were washed successively with saturated aqueous sodium hydrogen carbonate (twice), brine and then dried ($MgSO_4$). The solvent was evaporated to give the product as a brown solid used in the next step without purification (13.74 g, 94.5%). A sample was recrystallised from ethanol, m.p. 144–146 °C (Found: C, 61.95; H, 6.05; N, 4.95. $C_{15}H_{17}NO_3S$ requires C, 61.82; H, 5.88; N, 4.83%); ν_{max}(KBr) 3450, 3100, 3050, 2960, 2920, 1600, 1495, 1320 and 1150; δ_H 2.26 (3 H, s), 2.38 (3 H, s), 4.35 (2 H, s) and 6.85–7.78 (9 H, m).

N-(2-Formyl-4-methylphenyl)toluene-4-sulphonamide.—Pyridinium chlorochromate (13.82 g, 64.2 mmol) and dry dichloromethane (150 ml) were stirred and the above alcohol (12.46 g, 43 mmol), dissolved in a minimal amount of the same solvent, was added and stirring was continued for 3 h. The liquid was decanted from the solid which was washed several times with ether. The combined solvent was passed through a short pad of Merck 7734 grade silica and evaporated to give a pale brown solid (11.56 g, 93.4%), m.p. 114–115 °C (Found: C, 59.75; H, 5.51. $C_{15}H_{15}NO_3S$ requires C, 59.86; H, 5.30%); ν_{max}(KBr) 3150, 3080, 2930, 2860, 2760, 1685, 1590, 1500, 1345 and 1155; δ_H 2.34 (3 H, s), 2.37 (3 H, s), 7.05–7.9 (7 H, m), 9.75 (1 H, s) and 10.57 (1 H, s).

(E)-N-[2-(2-Methylsulphinyl-2-methylthiovinyl-4-methylphenyl]toluene-4-sulphonamide.—Under nitrogen, a mixture of the above aldehyde (3 g, 10.4 mmol), methyl methylsulphinylmethyl sulphide (2.14 g, 17.3 mmol), THF (12 ml) and Triton B (12 ml) was refluxed for 2.5 d, allowed to cool and poured into ethyl acetate. This was washed with saturated aqueous ammonium chloride and the aqueous layer extracted

with more ethyl acetate. The combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated. Column chromatography [ethyl acetate–light petrol (1:3) followed by (3:1)] gave recovered aldehyde (0.78 g) and the product as a pale yellow solid (2.34 g, 77% based on recovered starting material), m.p. 160–162 °C (Found: C, 54.25; H, 5.4; N, 3.45. $C_{18}H_{21}NS_3O_3$ requires C, 54.65; H, 5.35; N, 3.54%); ν_{max}(KBr) 3120, 2920, 2840, 1595, 1330, 1155 and 1035; δ_H 2.03 (3 H, s), 2.32 (6 H, s), 2.72 (3 H, s), 6.80–7.53 (8 H, m) and 7.60 (1 H, br s).

(E)-N-[2-(2-*Methylthio*-2-*methylsulphinylvinyl*)-4-*methylphenyl*]-N-(*prop*-2-*enyl*)*toluene*-4-*sulphonamide* **2b**.—Sodium hydride (60% dispersion; 0.183 g, 4.57 mmol) was washed with light petroleum and the solvent was removed. To the sodium hydride was added dry DMF (10 ml) followed by the above product (1.5 g, 3.79 mmol) in two portions. After 5 min, allyl bromide (0.55 g, 4.55 mmol) was introduced and the mixture heated to 40 °C for 10 min before being poured into ethyl acetate which was then washed with saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The product was obtained by column chromatography [ethyl acetate–light petroleum (1:1)] as an oil (1.42 g, 86.3%).

Methyl (E)-N-[2-(2-*methylthio*-2-*methylsulphinylvinyl*)-4-*methylphenyl*]-N-(*toluene*-4-*sulphonyl*)-2-*aminoacetate* **2a**.—Prepared in the same way as **2b** but using methyl bromoacetate instead of allyl bromide (79%).

Methyl N-(2-*Methylthiocarbonylmethyl*-4-*methylphenyl*)-N-(*toluene*-4-*sulphonyl*)-2-*aminoacetate* **5**.—The ester **2a** (150 mg) was dissolved in 1,2-dimethoxyethane (3 ml) with stirring and to this was added 10M HCl (0.5 ml). After 4 d at room temperature, the mixture was poured into water and extracted several times with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and after evaporation the residue was subjected to column chromatography [ethyl acetate–light petroleum (1:5)] to give **5** as a clear oil (31.2 mg, 23.1%) (Found: C, 57.4; H, 5.95; N, 3.1. $C_{20}H_{23}NS_2O_3$ required C, 56.99; H, 5.50; N, 3.32%); ν_{max} 2920, 1750, 1680, 1595, 1495, 1340, 1210 and 1160; δ_H 2.30 (6 H, s), 2.44 (3 H, s), 3.63 (3 H, s), 4.04 (2 H, d, *J* 17 Hz), 4.33 (2 H, s) and 6.63–7.57 (7 H, m). Further elution with ethyl acetate–light petroleum (3:1) gave recovered **2a** (61 mg, 40.7%).

Ketene Dithioacetal S-*Oxides* **2c–2i**: *General Procedure*.—To a mixture of **1** (15 mmol) and methyl methylsulphinylmethyl sulphide (15 mmol) in dry THF (25 ml) was added Triton B (1 ml of 40% solution in methanol). The mixture was refluxed for 3–4 h. Subsequent treatment was as described for **2b**.

Chloroketene Dithioacetals **6a–e**: *General Procedure*.—To a solution of **2** (3 mmol) in dichloromethane (30 ml) was added 10M hydrochloric acid (3.5 ml). The mixture was stirred vigorously for 1–2 h and then neutralised with saturated aqueous sodium hydrogen carbonate. The layers were separated, and the aqueous layer was extracted with more dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated to give crude **6**, which was purified by column chromatography.

S-*Methyl Thioesters* **7c–7i**: *General Procedure*.—Hydrogen sulphide was bubbled through dichloromethane (20 ml) for 30 min. The ketene dithioacetal *S*-oxide **2** (1 mmol) was added, followed by 10M hydrochloric acid (1 ml). The mixture was stirred for 1 h at room temperature and then treated as for **8** above.

S-*Methyl Thioesters from Phenylacetic Acids: General Procedure*.—To a suspension of lithium aluminium hydride (1 mmol) in dry ether was added dimethyl disulphide (1 mmol). After being stirred for 1 h, the mixture was filtered through Hyflo to afford a solution of methanethiol in ether which was added to a solution of the phenylacetic acid (2 mmol) and DCC (2.2 mmol) in ether at 0 °C. After 1 h, the mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography.

TFA Treatment of Chloroketene Thioacetal **6c**.—A mixture of **6c** (181 mg, 0.78 mmol) and TFA (890 mg, 7.8 mmol) was stirred for 20 min before the addition of water (140 mg, 7.8 mmol). After a further 6 h, the reaction mixture was poured into ethyl acetate–saturated aqueous sodium hydrogen carbonate. The layers were separated and the aqueous layer was extracted with more ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated. Column chromatography [ether–light petroleum (1:50)] gave **9** (31 mg, 19%), m.p. 60–62 °C (lit.,[11] 63–65.3 °C); ν_{max}(KBr) 3020, 2940, 1680; δ_H 2.23 (3 H, s), 2.30 (3 H, s), 4.61 (3 H, s) and 7.30 (5 H, s). Further elution gave a mixture of **7c** (28%) and **8** (28%) (yields estimated from NMR integration).

Acknowledgements

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