A New Synthesis of α-Alkylthio-ketones (α-Sulphenylated Ketones)[1]

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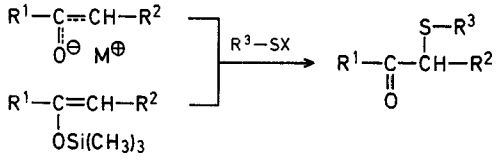
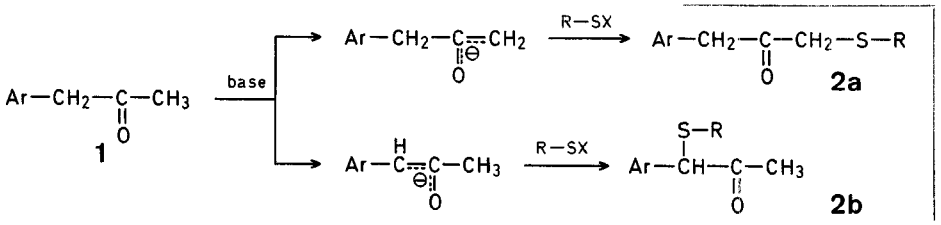
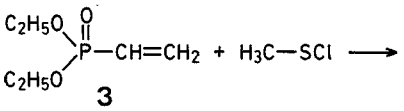
α-Alkylthio-ketones (α-sulphenylated ketones) are useful intermediates in organic synthesis[2]. These compounds are usually prepared by sulphenylation of enol derivatives such as metal enolates[3] or enol silyl ethers[4].

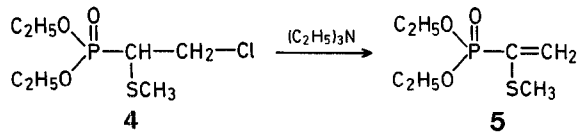


However, in the case of unsymmetrical ketones in which both possible enolate anions can be generated, these methods can not always be used to obtain the desired regioisomeric α-alkylthio-ketones. For example, to obtain the isomer **2a** it would be necessary to sulphenylate the thermodynamically less stable enolate anion derived from the ketone **1**:



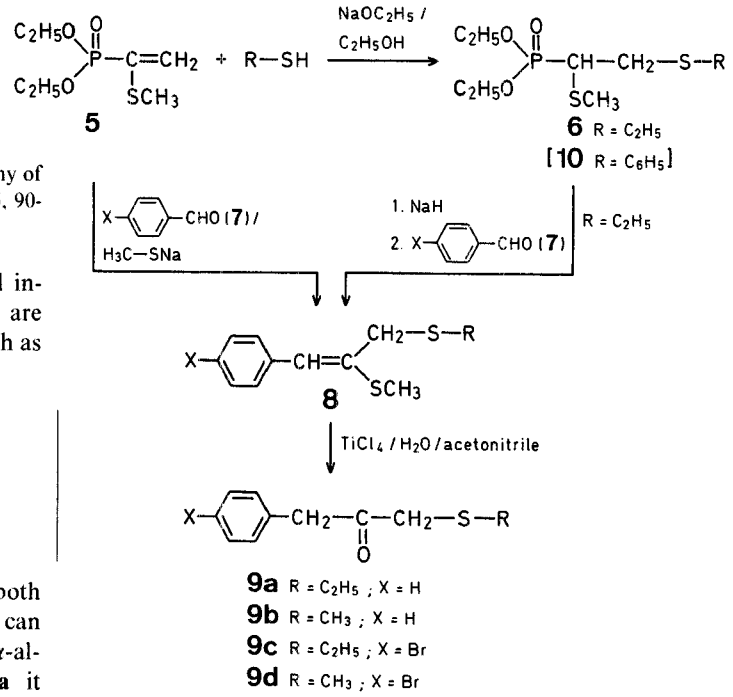
We have now developed a new method for the synthesis of the regioisomeric α-alkylthio-ketones of the type **2a** using the recently synthesized[5] diethyl 1-methylthioethenephosphonate **(5)** as starting material. As we have now found compound **5** can be conveniently prepared on a large scale by the addition of methanesulphenyl chloride to diethyl ethenephosphonate **(3)**[6] and dehydrochlorination of the resultant diethyl 2-chloro-1-methylthioethanephosphonate **(4)**.





Using compound **5** as starting material, the title compounds **9** are prepared either by reaction of **5** with ethanethiol in ethanol in the presence of sodium ethoxide to give diethyl 2-ethylthio-1-methylthioethanephosphonate **(6)** [the phenylthio analog **10** may be prepared in a similar manner], carbonyl olefination of the benzaldehyde **7** with **6**, and hydrolytic cleavage of the resultant enethiol ether **8**, or by reaction of **5** with the benzaldehyde **7** and sodium methanethiolate to give **8** in a one-step reaction, followed by cleavage of **8**.

The following points are worthy of note: The reaction of **5** with thiols is carried out in the presence of only 0.1 mol equiv of sodium ethoxide; the use of equimolecular amounts of sodium ethoxide leads to mixtures of products. In the one-step conversion **5**→**8**, side reactions may be prevented by adding the sodium methanethiolate portionwise to a boiling solution of **5** and **7** in tetrahydrofuran. The mild hydrolysis of **8** using two equivalents of titanium(IV) chloride renders possible the selective cleavage of the enethiol ether to give **9** in good yield. However, the ethylthiomethyl ketones **9a** and **9c** are always contaminated by small amounts (up to 6%) of the corresponding methylthiomethyl ketones **9b** and **9d**, respectively, of unknown origin; due to this fact, correct microanalyses could not be obtained.



Mass spectra were recorded on a LKB 2091 mass spectrometer. ^{1}H-N.M.R. spectra were recorded at 60 MHz using a Perkin-Elmer R-12 instrument. ^{13}C- and ^{31}P-N.M.R. spectra were recorded on a FT Jeol FX-60 instrument. G.L.C. analyses were performed on Varian Aerograph 2700, detector FID, carrier gas N_2, glass column 2 m, 10% OV 101, temperature programmed from 70 to 290 °C, 10 °C/min.

Diethyl 2-Chloro-1-methylthioethanephosphonate (4):
To a solution of diethylethenephosphonate[8] (**3**; 22 g, 0.134 mol) in tetrachloromethane (60 ml), methanesulphenyl chloride[9] (11.1 g, 0.134 mol) is added dropwise at room temperature with slight external cooling and the mixture is allowed to stand overnight. The solvent is evaporated and the residue is distilled in vacuo to give pure **4**; yield: 27.5 g (83%); b.p. 95–100 °C/0.6–0.8 torr: n_D^{21}: 1.4812 (Ref.[6], b.p. 110–112 °C/2 torr; n_D^{20}: 1.4810).

Diethyl 1-Methylthioethenephosphonate (5):
To a stirred solution of diethyl 2-chloro-1-methylthioethanephosphonate (**4**; 35 g, 0.142 mol) in ether (200 ml), triethylamine (14.34 g, 0.142 mol) is added dropwise. Stirring is continued for 4 h and the mixture then allowed to stand overnight. The precipitated triethylamine hydrochloride is filtered off and the ether evaporated. The residue is distilled in vacuo to give pure **5**; yield: 25.6 g (86%); b.p. 72–76 °C/0.01–0.05 torr; n_D^{18}: 1.4862.

^{1}H-N.M.R. (CCl_4/TMS_{int}): δ = 1.32 (t, 6H); 2.30 (s, 3H); 4.05 (dq, 4H); 5.60 (d, 1H, J_{PH} = 43.3 Hz, *trans*-C=CH); 6.12 ppm (d, 1H, J_{PH} = 22.7 Hz, *cis*-C=CH).

^{31}P-N.M.R. (CCl_4/H_3PO_{4ext}): δ = 12.8 ppm.

Addition of Thiols to Compound 5:

Diethyl 2-Ethylthio-1-methylthioethanephosphonate **(6):** Sodium (~0.1 g) is dissolved in ethanol (60 ml) under a nitrogen atmosphere and ethanethiol (2.709 g, 0.0436 mol) is added. After a few minutes, diethyl 1-methylthioethenephosphonate (**5**; 9.15 g, 0.0436 mol) is added with stirring and the mixture is allowed to stand at room temperature overnight. Water (90 ml) and ether (60 ml) are added and the layers are separated. The aqueous layer is extracted with ether (3 × 15 ml), the combined organic layers are washed with saturated sodium chloride solution (10 ml), dried with magnesium sulphate, and evaporated to give crude **6**; yield: 11.7 g (98%). Product **6** is purified by distillation in vacuo; yield: 9 g (76%); b.p. ~100 °C/0.001 torr.

$C_9H_{21}O_3PS_2$	calc.	C 39.71	H 7.72	P 11.40	S 23.53
(272.35)	found	39.90	7.50	11.64	23.05

M.S.: *m/e* = 272 (6%), 225 (100), 165 (66).

^{1}H-N.M.R. (CCl_4/$HMDSO_{int}$): δ = 1.2 (t, 3H); 1.3 (t, 6H); 2.2 (s, 3H); 2.25–3.0 (m, 5H); 3.75–4.35 ppm (m, 4H).

Diethyl 1-Methylthio-2-phenylthioethanephosphonate **(10):** Prepared in a similar manner from thiophenol (2.2 g, 0.02 mol) and diethyl 1-methylthioethenephosphonate (**5**; 4.2 g, 0.02 mol) in ethanol (50 ml) containing sodium ethoxide (from ~0.08 g of sodium); yield of crude **10**: 6.84 g (86%); yield of distilled **10**: 5.8 g (73%); b.p. ~115 °C/0.2 torr.

$C_{13}H_{21}O_3PS_2$	calc.	C 48.73	H 6.61	P 9.67
(320.4)	found	48.88	6.40	9.42

M.S.: *m/e* = 320 (11%), 273 (100), 211 (25).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.31 (t, 6H); 2.22 (s, 3H); 2.25–3.8 (m, 3H); 3.9–4.45 (m, 4H); 7.2–7.6 ppm (m, 5H).

^{31}P-N.M.R. ($CDCl_3$/H_3PO_{4ext}): δ = 22.36 ppm.

3-Ethylthio-2-methylthio-1-phenylpropene (8a):

Sodium hydride (0.12 g, 5 mmol) is added to a stirred solution of diethyl 2-ethylthio-1-methylthioethanephosphonate (**6**; 1.36 g, 5 mmol) and benzaldehyde (**7**, X = H; 0.53 g, 5 mmol) in tetrahydrofuran (20 ml) under nitrogen. Stirring and refluxing are continued for 1 h; G.L.C. analysis then shows that the reaction is complete. Water (15 ml) and ether (75 ml) are added and the layers are separated. The aqueous layer is extracted with ether (3 × 5 ml); the combined organic layers are washed with saturated sodium chloride solution (10 ml), dried with magnesium sulphate, and evaporated to give crude **8a**; yield: 0.913 g (81%). The product is column-chromatographed on silica gel using benzene as eluent to give **8a** as an *E*/*Z* mixture; yield: 0.751 g (67%).

M.S.: *m/e* = 224 (44%), 164 (49), 163 (15), 115 (100).

^{1}H-N.M.R. (CCl_4/$HMDSO_{int}$): δ = 1.2 (t, 3H); 2.2, 2.25 (2s, *E*/*Z*, 3H); 2.45 (q, 2H); 3.3, 3.36 (2s, *E*/*Z*, 2H); 6.2, 6.5 (2s, *E*/*Z*, 1H); 7.05–7.65 ppm (m, 5H).

1-(4-Bromophenyl)-3-ethylthio-1-methylthiopropene (8c):

Prepared in the same manner as **8a** from diethyl 2-ethylthio-1-methylthioethanephosphonate (**6**; 1.0526 g, 3.87 mmol) and 4-bromobenzaldehyde (**7**, X = Br; 0.7159 g, 3.87 mmol); yield of chromatographed **8c** as an *E*/*Z* mixture: 0.722 g (62%).

M.S.: *m/e* = 302, 304 (11, 12%), 193/195 (9/11), 164 (11), 162 (84), 115 (100).

^{1}H-N.M.R. (CCl_4/$HMDSO_{int}$): δ = 1.25 (double t, 3H); 2.2 (s, 3H); 2.4 (q, 2H); 3.3 (br s, 2H); 6.0, 6.3 (2s, *E*/*Z*, 1H); 7.05–7.5 ppm (m, 4H).

2,3-Bis[methylthio]-1-phenylpropene (8b):

To a stirred, boiling solution of diethyl 1-methylthioethenephosphonate (**5**; 1.05 g, 5 mmol) and benzaldehyde (**7**, X = H; 0.53 g, 5 mmol) in tetrahydrofuran (15 ml), sodium methanethiolate (0.35 g, 5 mmol) is added portionwise under nitrogen. Refluxing is continued for 30 min and the progress of the reaction is monitored by G.L.C. analysis. Water (10 ml) and ether (10 ml) are added and the layers are separated. The aqueous layer is extracted with ether (3 × 5 ml); the combined organic layers are washed with saturated sodium chloride solution (10 ml), dried with magnesium sulphate, and evaporated to give crude **8b**; yield: 0.94 g. The product is column-chromatographed on silica gel using benzene as eluent to give **8b** as an *E*/*Z* mixture; yield: 0.713 g (70%).

M.S.: *m/e* = 210 (33%), 164 (14), 115 (100).

^{1}H-N.M.R. (CCl_4/$HMDSO_{int}$): δ = 1.9 (s, 3H); 2.1 (s, 3H); 3.25, 3.33 (2s, *E*/*Z*, 2H); 6.12, 6.38 (2s, *E*/*Z*, 1H); 6.91–7.6 ppm (m, 5H).

^{13}C-N.M.R. ($CDCl_3$/TMS_{int}): δ = 12.47, 12.73, 13.12, 13.90 (2 S—$\underline{C}H_3$, *E*/*Z*); 33.52, 39.24 ($\underline{C}H_2$ group, *E*/*Z*); 121.50, 124.62, 125.0, 126.05, 126.44, 127.22, 131.25, 134.24, 134.89, 135.53 ppm (C_{olefin} + C_{arom}).

1-(4-Bromophenyl)-2,3-bis[methylthio]-propene (8d):

Prepared in the same manner as **8b** from diethyl 1-methylthioethenephosphonate (**5**; 1.05 g, 5 mmol), 4-bromobenzaldehyde (**7**, X = Br; 0.925 g, 5 mmol), and sodium methanethiolate (0.35 g, 5 mmol); yield of chromatographed **8d** as an *E*/*Z* mixture: 0.933 g (64%).

M.S.: *m/e* = 288, 290 (41, 31%), 162 (100), 147 (25), 115 (67).

^{1}H-N.M.R. (CCl_4/$HMDSO_{int}$): δ = 1.93, 2.00 (2s, *E*/*Z*, 3H); 2.22 (s, 3H); 3.31 (s, 2H); 6.1, 6.38 (2s, *E*/*Z*, 1H); 7.0–7.6 ppm (m, 4H).

3-Alkylthio-1-aryl-2-propanones (9); General Procedure:

Titanium(IV) chloride (0.456 g, 2.4 mmol) is added dropwise to a stirred, cooled (−15 °C) solution of a 2,3-bis[alkylthio]-1-arylpropene (**8**; 1.2 mmol) in acetonitrile (10–15 ml). After the addition is complete the stirred mixture is allowed to reach room temperature. After 20 min, water (86.4 mg, 4.8 mmol) is added and stirring is continued until G.L.C. analysis reveals completion of the reaction (usually after 2–3 h). Ether (10 ml) and a cold saturated ammonium chloride solution (15 ml) are added and the layers are separated. The aqueous layer is extracted with ether (4 × 5 ml); the combined organic layers are washed with saturated sodium chloride solution (5 ml), dried with magnesium sulphate, and evaporated. The crude product **9** is purified by preparative layer chromatography on silica gel using benzene as eluent; R_f ~ 0.22–0.26.

3-Ethylthio-1-phenyl-2-propanone **(9a);** yield: 78%; purity: 97% (G.L.C.); the product is contaminated with 3% of **9b.**

M.S.: *m/e* = 194 (36%), 118 (11), 91 (100), 75 (81).

^{1}H-N.M.R. (CCl_4/$HMDSO_{int}$): δ = 1.1 (t, 3H); 2.33 (q, 2H); 3.0 (s, 2H); 3.71 (s, 2H); 7.05–7.3 ppm (m, 5H).

3-Methylthio-1-phenyl-2-propanone **(9b);** yield: 73%; purity: >99.5% (G.L.C.).

$C_{10}H_{12}OS$	calc.	C 66.63	H 6.71	S 17.79
(180.3)	found	66.27	6.72	17.77

M.S.: *m/e* = 180 (35%), 91 (100), 61 (67).

^{1}H-N.M.R. (CCl_4/$HMDSO_{int}$): δ = 1.9 (s, 3H); 3.02 (s, 2H); 3.8 (s, 2H); 7.3–7.5 ppm (m, 5H).

1-(4-Bromophenyl)-3-ethylthio-2-propanone **(9c);** yield: 72%; purity: 94% (G.L.C.); the product is contaminated with 6% of **9d.**

M.S.: *m/e* = 272, 274 (6, 6%), 212, 214 (6, 6), 197, 199 (2, 2), 169, 171 (29, 27), 75 (100).

^{1}H-N.M.R. (CCl_4/$HMDSO_{int}$): δ = 1.1 (t, 3H); 2.34 (q, 2H); 3.04 (s, 2H); 3.7 (s, 2H); 7.0, 7.38 ppm (AA'BB', 4H).

1-(4-Bromophenyl)-3-methylthio-2-propanone **(9d);** yield: 80%; purity: >99% (G.L.C.).

$C_{10}H_{11}BrOS$	calc.	C 46.34	H 4.28	S 12.37
(259.2)	found	46.34	4.35	12.16

M.S.: *m/e* = 258, 260 (21, 22%), 169, 171 (40, 39), 61 (100).

^{1}H-N.M.R. (CCl_4/$HMDSO_{int}$): δ = 1.9 (s, 3H); 2.98 (s, 2H); 3.7 (s, 2H); 7.0, 7.38 ppm (AA'BB', 4H).

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[1] Part XXXII of the series: *Organosulphur Compounds*, Part XXXI; J. Drabowicz, P. Łyżwa, M. Mikołajczyk, paper submitted to *Phosphorus Sulfur*.

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