Synthesis of α-Haloalkyl Esters from α-Arylthioalkyl Esters

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Benneche, T., Strande, P. and Wiggen, U., 1989. Synthesis of α-Haloalkyl Esters from α-Arylthioalkyl Esters. – Acta Chem. Scand. 43: 74–77.

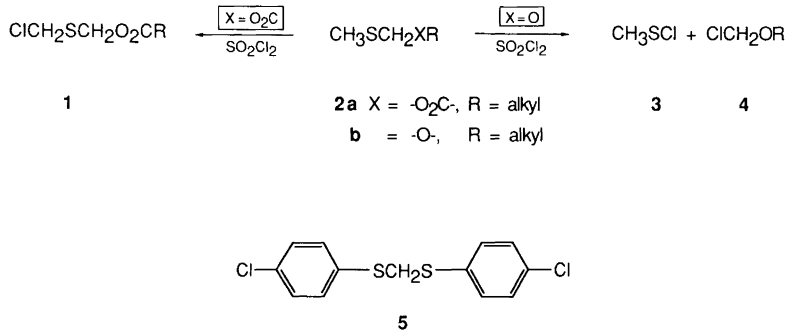
α-Monohaloalkyl esters have been prepared under mild conditions in high yields by selective cleavage of the carbon–sulfur bond in α-phenylthioalkyl esters using sulfuryl chloride or bromine. The intermediate α-phenylthioalkyl esters have been prepared by alkylation of the corresponding carboxylic acids with readily accessible α-haloalkyl phenyl sulphides.

α-Haloalkyl esters have been widely used to modify the acid function of drugs.[1] They have also been employed as acyloxymethylating[2] and amino-group protecting reagents.[3] α-Haloalkyl esters can be synthesized by several methods,[4] but the most general one is the condensation of an aldehyde or a ketone with an acid chloride in the presence of a Lewis acid.[4b]

In connection with our work on the synthesis of α-haloalkyl ethers by cleavage of methylthiomethyl ethers,[5] we were interested to see if α-haloalkyl esters could be prepared analogously. It is known, however, that the reaction of methylthiomethyl esters **2a** (Scheme 1) with sulfuryl chloride at ambient temperature results in chlorination of the methyl group to give chloromethylthiomethyl esters **1** instead of cleavage of the carbon–sulfur bond.[6] This is in sharp contrast to methylthiomethyl ethers **2b**, which are selectively cleaved by sulfuryl chloride at ambient temperature to give methanesulfenyl chloride (**3**) and chloromethyl ethers **4**.[5]

Thus if our approach to the synthesis of α-haloalkyl esters were to succeed, the methyl group had to be substituted with another group that would not be halogenated. Initially the 4-chlorophenyl group was selected, but it was found that the unsubstituted phenyl group could be used just as well. The cleavage reaction is obviously more favourable than ring halogenation. Halogenation on the acylal carbon of **8** (Scheme 2) was not expected to be a problem, since the Pummerer reaction does not take place on the acetal carbon in α-alkoxy and α-alkylthio sulfoxides under normal conditions.[7]

In the synthesis of the α-phenylthioalkyl esters **8**, α-chloroalkyl sulfides were used in preference to the corresponding bromo or iodo compounds, because the formation of dithioacetals such as **5** from the alkylation agent[8] is considerably less pronounced with α-chloroalkyl sulfides. Dithioacetal formation also appears to be cation dependent. Thus reaction of chloromethyl 4-chlorophenyl sulfide with sodium acetate in DMF gave a substantial amount of the dithioacetal **5** (ca. 11%), while the reaction with caesium acetate showed no traces of the dithioacetal in the crude product. The advantage of caesium salts over sodium salts in alkylation reactions has been reported.[9] In most cases the caesium salt was not isolated, but was made *in situ* from the acid using caesium carbonate. This procedure,



Scheme 1.

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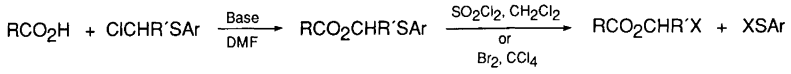

6 **7** **8** **9** **10**

	R	R'	Ar	X		R	R'	Ar	X
a	CH_3	H	4-ClC_6H_4	Cl	**g**	$CH_3COCH_2CH_2$	H	C_6H_5	Cl
b	CH_3	H	C_6H_5	Br	**h**	Ph	H	C_6H_5	Cl
c	CH_3	CH_3	C_6H_5	Cl	**i**	Ph	H	C_6H_5	Br
d	$(CH_3)_3C$	CH_3	C_6H_5	Cl	**j**	2-$CHOC_6H_4$	H	C_6H_5	Cl
e	$PhCH_2$	H	C_6H_5	Cl	**k**	2-Thienyl	H	C_6H_5	Cl
f	$CH_3O_2CCH_2CH_2$	H	C_6H_5	Cl					

Scheme 2.

however, gave a small amount (ca. 5%) of the dithioacetal. In the synthesis of **8j**, the highest yield was obtained when the base used was triethylamine.

On treatment of the α-arylthioalkyl esters **8a–k** with sulfuryl chloride in dichloromethane or bromine in tetrachloromethane, the carbon–sulfur bond was selectively cleaved to give the α-haloalkyl esters **9a–k** and the sulfenyl halide **10** (Scheme 2, Table 1). Sulfuryl chloride in dichloromethane seems to give a more rapid reaction than bromine in tetrachloromethane. Thus all starting material was consumed when **8h** was treated with 1.2 equivalents of sulfuryl chloride for 1 h at ambient temperature. The same reaction using bromine gave only about 30% conversion after 2 h at ambient temperature. The highly reactive sulfenyl halides **10** were trapped by reaction with an olefin *in situ* to give a high-boiling liquid[10] from which the α-haloalkyl esters could be separated by distillation.

We believe that the present procedure complements existing ones, since α-haloalkyl esters that otherwise would be difficult to synthesize (i.e. **9g**, **9j**) can be obtained in good yields by this method (Table 1).

Experimental

The ^1H NMR spectra were recorded at 60 or 90 MHz. The mass spectra, under electron impact conditions, were recorded at 70 eV ionizing energy. Isobutane or ammonia were used for chemical ionizing mass spectra (CI); the spectra are presented as *m/z* (% rel. int.)

(4-Chlorophenylthio)methyl acetate **8a**: *Method A*. Sodium acetate (3.27 g, 40.0 mmol) was added to a solution of bromomethyl 4-chlorophenyl sulfide[11] (4.75 g, 20.0 mmol) in DMF (60 ml). The mixture was stirred for 1 h at 60 °C, before water was added and the product extracted into diethyl ether. The ether solution was washed with 1 M sodium hydroxide (×1) and brine (×4), before it was dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography on silica gel using hexane–ethyl acetate (15:1) as the eluant. Yield 2.10 g (48 %), b.p. 90–94 °C/ 0.1–0.2 mmHg. Anal. Calcd. for $C_9H_9ClO_2S$: C 49.88; H 4.19. Found: C 50.34; H 4.34. ^1H NMR [$(CD_3)_2SO$]: δ 2.06 (s, 3 H), 5.50 (s, 2 H), 7.46 (Ar).

Table 1. Reagents and reaction conditions for the synthesis of **9a–k**.

	Amount of SO_2Cl_2 or Br_2/ mmol (equiv.)	Reaction conditions	Olefin	Yield /%[a]
9a[2b]	60.0 (1.0)	R.t. 30 min	Cyclohexene	50[b]
9b[2b]	3.6 (1.2)	R.t. 18 h	Cyclohexene	69
9c[2b]	15.3 (1.0)	R.t. 4 h	Cyclohexene	50
9d	21.0 (1.1)	R.t. 2 h	Cyclohexene	79
9e	4.8 (1.2)	0 °C 1 h, r.t. 30 min	Cyclohexene	84
9f	1.6 (1.2)	R.t. 1 h	Styrene	79
9g	7.1 (1.1)	0 °C 1 h, r.t. 30 min	4-Chlorostyrene	89
9h	3.6 (1.2)	R.t. 1 h	Styrene	84
9i	1.7 (1.2)	R.t. 16 h, 60 °C 3 h	Styrene	48[c]
9j	4.4 (1.1)	0 °C 2 h, r.t. 1 h	4-Chlorostyrene	88
9k	18.6 (1.2)	0 °C 1 h, r.t. 30 min	Styrene	83

[a]Yield of purified product. [b]Overall yield from **6**. [c]ca. 10% $PhSCH_2Br$ was formed.

Method B: Chloromethyl 4-chlorophenyl sulfide[11] (11.60 g, 60.0 mmol) was added at 0 °C to a solution of caesium acetate (15.97 g, 60.0 mmol) in DMF (180 ml). The mixture was stirred at 50 °C for 3 h before the solvent was evaporated off, water added, and the product extracted into chloroform. The chloroform solution was washed with 1 M sodium hydroxide (×1) and brine (×4), before the dried ($MgSO_4$) solution was evaporated. The crude product was used in the next step without further purification.

1-(Phenylthio)ethyl acetate **8c**. Sodium acetate (5.52 g, 66.5 mmol) was added to a solution of 1-chloroethyl phenyl sulfide[12] (13.00 g, 73.2 mmol) in DMF (210 ml). The mixture was stirred for 1 h at 50 °C and ambient temperature for 18 h and worked up as for **8a** above. Yield 47 %, b.p. 62–64 °C/0.08 mmHg. ^{1}H NMR [$(CD_3)_2SO$]: δ 1.44 (d, *J* 6 Hz, 3 H), 6.17 (q, *J* 6 Hz, 1 H), 7.2–7.6 (Ar). MS: 196 (5, *M*), 152 (25), 137 (25), 136 (17), 135 (24), 110 (74), 109 (10), 77 (7), 65 (13).

1-(Phenylthio)ethyl pivalate **8d**. 1-Chloroethyl phenyl sulfide[12] (11.0 g, 61.9 mmol) in DMF (110 ml) at 0 °C was added to a solution of pivalic acid (5.75, 56.3 mmol) and potassium *tert*-butoxide (6.32 g, 56.3 mmol) in DMF (110 ml). The mixture was stirred at ambient temperature for 24 h and worked up as for **8a** above. Yield 8.47 g (63 %), b. p. 80 °C/0.06 mmHg. Anal. $C_{13}H_{18}O_2S$: C, H. ^{1}H NMR [$(CD_3)_2SO$]: δ 1.10 (s, 9 H), 1.46 (d, *J* 7 Hz, 3 H), 6.20 (q, *J* 7 Hz, 1 H), 7.2–7.5 (Ar).

(Phenylthio)methyl phenylacetate **8e**. Caesium carbonate (4.30 g, 13.2 mmol) was added to a solution of phenylacetic acid (1.80 g, 13.2 mmol) in DMF (20 ml). The mixture was stirred at ambient temperature for 30 min, at 70 °C for 15 min, and cooled to 0 °C, before chloromethyl phenyl sulfide[11] (1.92 g, 12.0 mmol) was added. Stirring was continued at 0 °C for 30 min, then at ambient temperature for 3 h, and finally at 70 °C for 15 min, before water was added and the product extracted into diethyl ether. The ether solution was washed with 1 M sodium hydroxide (×1) and brine (×4), dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography on silica gel using hexane–ethyl acetate (40:3) as the eluant. Yield 2.17 g (70 %). Anal. $C_{15}H_{14}O_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 3.68 (s, 2 H), 5.44 (s, 2 H), 7.30 (Ph). MS: 258 (9, *M*), 228 (3), 123 (10), 119 (9), 118 (16), 109 (4), 92 (8), 91 (100).

(Phenylthio)methyl methyl succinate **8f**. Compound **8f** was prepared as for **8e** above. The crude product was used in the next step without further purification. Yield (81 %). ^{1}H NMR ($CDCl_3$): δ 2.66 (s, 4 H), 3.69 (s, 3 H), 5.43 (s, 2 H), 7.1–7.6 (Ph). MS: 254 (5, *M*), 124 (2), 123 (20), 116 (5), 115 (100), 110 (5), 109 (6), 87 (8).

(Phenylthio)methyl 4-oxopentanoate **8g**. Compound **8g** was prepared as for **8e** above. Chromatography: hexane–ethyl acetate 4:1. Yield 81 %. Anal. $C_{12}H_{14}O_3S$: C, H, O, S. ^{1}H NMR ($CDCl_3$); δ 2.18 (s, 3 H), 2.6–3.0 (m, 4 H), 5.42 (s, 2 H), 7.1–7.6 (Ph). MS: 238 (4, *M*), 208 (1), 123 (9), 110 (7), 109 (4), 100 (6), 99 (100).

(Phenylthio)methyl benzoate **8h**. Compound **8h** was prepared as for **8e** above. Chromatography: Hexane–ethyl acetate 20:1. Yield 67 %. Anal. $C_{14}H_{12}O_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 5.65 (s, 2 H), 7.1–7.6 (m, 8 H), 7.9–8.1 (m, 2 H). MS: 244 (5, *M*), 215 (1), 214 (6), 149 (1), 123 (3), 110 (3), 109 (3), 106 (7), 105 (100).

(Phenylthio)methyl 2-formylbenzoate **8j**. Triethylamine (1.80 ml, 13.2 mmol) was added to a mixture of 2-formylbenzoic acid (1.98 g, 13.2 mmol) and chloromethyl phenyl sulfide[11] (1.92 g, 12.0 mmol) in DMF. The mixture was heated at 60 °C for 18 h, before water was added and the product extracted into diethyl ether. The ether solution was washed with 1 M sodium hydroxide (×1), brine (×3), dried ($MgSO_4$) and evaporated. The residue was recrystallized from diethyl ether–light petroleum. Yield 1.65 g (53 %), m.p. 52–53 °C. Anal. $C_{15}H_{12}O_3S$: C, H. ^{1}H NMR ($CDCl_3$): δ 5.65 (s, 2 H), 7.1–8.0 (m, 9 H), 10.45 (s, 1 H). MS: 272 (2, *M*), 242 (2), 149 (8), 134 (10), 133 (100), 124 (6), 123 (6), 110 (5), 109 (3).

(Phenylthio)methyl 2-thiophenecarboxylate **8k**. Compound **8k** was prepared as for **8e** above. The crude product was used in the next step without further purification. Yield 80 %. ^{1}H NMR ($CDCl_3$): δ 5.59 (s, 2 H), 7.0–7.9 (m, 8 H).

General procedure for the synthesis of α-haloalkyl esters **9a–k**. (Amounts and reaction conditions, see Table 1). Sulfuryl chloride in dry dichloromethane (2 M) or bromine in tetrachloromethane (1 M) was added dropwise at 0 °C or ambient temperature to a solution of the α-arylthiomethyl ester in dry dichloromethane or tetrachloromethane (0.5 M). The mixture was stirred at 0 °C and/or ambient temperature before the olefin in dry dichloromethane (2 M) was added dropwise at 0 °C. Stirring was continued for 1 h before the solvent was removed and the residue distilled under vacuum.

1-Chloroethyl pivalate **9d**. B.p. 40 °C/ 10 mmHg. ^{1}H NMR [$(CD_3)_2SO$]: δ 1.16 (s, 9 H), 1.74 (d, *J* 6 Hz, 1 H), 6.55 (q, *J* 6 Hz, 1 H).

Chloromethyl phenylacetate **9e**.[13] B.p. 80–82 °C/0.05 mmHg. ^{1}H NMR ($CDCl_3$): δ 3.67 (s, 2 H), 5.66 (s, 2 H), 7.23 (Ph). MS: 184 (22, *M*), 154 (3), 149 (2), 119 (16), 91 (100).

Chloromethyl methyl succinate **9f**. B.p. 56–57 °C/0.05 mmHg ^{1}H NMR ($CDCl_3$): δ 2.68 (s, 4 H), 3.38 (s, 3 H), 5.68 (s, 2 H). MS (CI–isobutane): 181 (32, *M*+1), 115 (74), 114 (11), 101 (7), 100 (59), 55 (100).

Chloromethyl 4-oxopentanoate **9g**. B.p. 70–72 °C/0.05 mmHg. Anal. $C_6H_9ClO_3$: C, H, Cl, O. ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3 H), 2.5–3.9 (m, 4 H), 5.65 (s, 2 H). MS: 164 (1, *M*), 149 (6), 121 (1), 119 (4), 100 (2), 99 (36), 43 (100).

Chloromethyl benzoate **9h**.[13] B. p. 52–56 °C/0.05 mmHg. ^{1}H NMR (CCl_4): δ 5.80 (s, 2 H), 7.3–7.7 (m, 3 H), 7.9–8.2 (m, 2 H). MS: 170 (11, *M*), 135 (5), 106 (13), 105 (100), 77 (63).

Bromomethyl benzoate **9i**.[13] B. p. 51–53 °C/0.02 mmHg. ^{1}H NMR ($CDCl_3$): δ 6.05 (s, 2 H), 7.3–7.7 (m, 3 H), 7.9–8.2 (m, 2 H).

Chloromethyl 2-formylbenzoate **9j**. B.p. 106–110 °C/0.05 mmHg, m.p. 51–52 °C (diethyl ether–light petroleum). Anal. $C_9H_7ClO_3$: C, H. ^{1}H NMR ($CDCl_3$): δ 5.95 (s, 2 H), 7.2–8.1 (m, 4 H), 10.65 (s, 1 H). MS (CI–ammonia): 218/216 (12/34, $M+NH_4^+$), 201/199 (20/61, $M+1$), 150 (12), 149 (17), 133 (100), 121 (7), 105 (42), 104 (19).

Chloromethyl 2-thiophenecarboxylate **9k**. B.p. 69 °C/0.1 mmHg. Anal. $C_6H_5ClO_2$: C, H. ^{1}H NMR ($CDCl_3$): δ 5.90 (s, 2 H), 7.0–8.0 (m, 3 H).

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Received July 4, 1988.