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Cleavage of Carbon–Sulfur Bonds in the Synthesis of α-Haloalkyl Carbonates

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α-Chloroalkyl and α-bromoalkyl carbonates have been prepared by cleavage of α-arylthioalkyl carbonates with sulfuryl chloride or bromine, respectively. The α-arylthioalkyl carbonates are prepared by reaction of the hemithioacetal **1** with chloroformates or by a destannylative tin-Pummerer rearrangement of α-stannyl sulfoxides.

We have previously shown that the carbon–sulfur bond in *O,S*-acetals and in α-arylthioalkyl esters is readily cleaved by sulfuryl chloride or bromine.[1] A natural extension of these investigations was to see whether the carbon–sulfur bonds in α-arylthioalkyl carbonates (**3**, Scheme 1) could be similarly cleaved to give α-haloalkyl carbonates.

α-Haloalkyl carbonates have many synthetic applications,[2,3] but one of the most important is probably the preparation of prodrugs by reaction with a carboxylic group in biologically active compounds.[3]

α-Chloroalkyl carbonates are prepared by reaction of α-chloroalkyl chloroformates with alcohols under basic conditions.[2,4,5] α-Fluoroalkyl, α-bromoalkyl, α-iodoalkyl as well as α-chloroalkyl carbonates can be made by reaction of an aldehyde with a haloformate.[3] This method has, however, its limitations because of the instability of a number of haloformates to the reaction conditions. α-Bromoalkyl carbonates have been made by halogen exchange.[6] Radical halogenation of dialkyl carbonates[7,8] and addition of hydrobromic acid to alkenyl carbonates[9] are other ways to prepare α-haloalkyl carbonates.

Here we report that α-chloroalkyl and α-bromoalkyl carbonates can be prepared by cleavage of the carbon–sulfur bond in α-arylthioalkyl carbonates by sulfuryl chloride or bromine.

We have prepared the α-thioalkyl carbonates **3** either by reaction of the hemithioacetal **1** with the chloroformates **2** or by a destannylative tin-Pummerer rearrangement of the α-stannyl sulfoxides **4** (Scheme 1). The former method is used for α-thioalkyl carbonates which are unsubstituted at the acetal carbon. Attempts to extend this method to substituted α-thioalkyl carbonates led only to decomposition of the hemithioacetal **5** and formation of the thiocarbonate **6** (Scheme 1).

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The reaction between the hemithioacetal **1** and the chloroformates **2** is best performed with pyridine as base in dichloromethane at 0 °C. Other nitrogen bases or carbonic anhydrides lead to contamination of the product with large amounts of thiocarbonates.

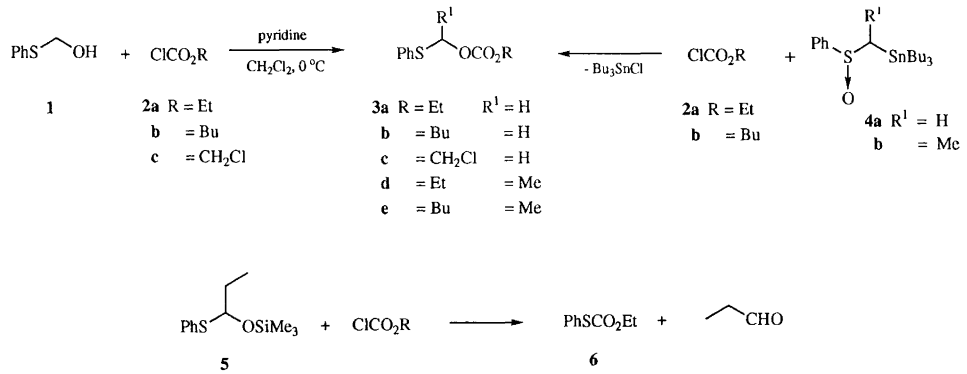
The tin-Pummerer rearrangement of α-stannyl sulfoxides[10] **4** could be used in the synthesis of α-thioalkyl carbonates substituted at the acetal carbon (**3d** and **3e**) (Scheme 1).

α-Chloroalkyl carbonates **7** were readily prepared by reaction of α-thioalkyl carbonates **3** with sulfuryl chloride in dichloromethane at 0 °C or ambient temperature (Scheme 2). Thus the bis(chloromethyl) carbonate (**7c**), which previously has been synthesized in 85% purity,[11] can now be prepared in high purity (>95% by GLC) in 73% yield.

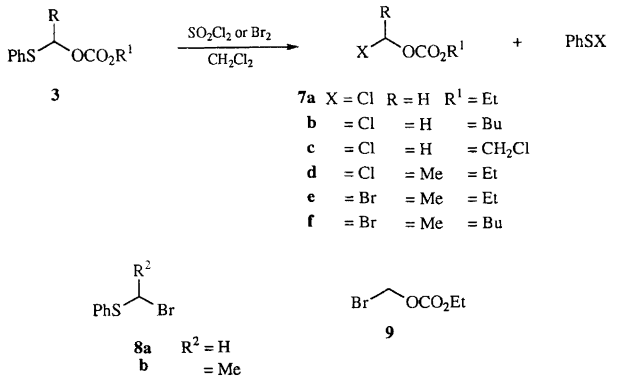
Treatment of the unsubstituted α-thioalkyl carbonate **3a** with bromine did not give a clean cleavage of the carbon–sulfur bond. The major product was the α-bromo sulfide **8a**, and the α-bromoalkyl carbonate **9** was only the minor product. On the other hand, the methyl substituted α-thioalkyl carbonates **3d** and **3e** were cleaved mainly between the carbon and the sulfur with bromine to give the α-bromo carbonates **7e** and **7f** which could be isolated in 55% and 62% yield, respectively. Only minor amounts of the α-bromo sulfide **8b** was observed. The methyl group apparently increases the nucleophilicity of the sulfur atom compared with the acyl group, resulting in the preferential cleavage of the carbon–sulfur bond instead of the carbon–oxygen bond. The α-bromo sulfide **8b** was prepared separately by reacting the acetal **3d** with TMSBr.

Experimental

The NMR spectra were recorded in $CDCl_3$ at 200 MHz (^1H) and at 50 MHz (^{13}C).The mass spectra, under



Scheme 1.



Scheme 2.

electron impact conditions, were recorded at 70 eV ionizing energy. Methane was used for chemical ionization (CI); the spectra are presented as *m/z* (% rel. int.).

Ethyl (phenylthio)methyl carbonate (**3a**).

Method A. Ethyl chloroformate (5.30 ml, 55.6 mmol) in dichloromethane (25 ml) was added dropwise over 45 min to a mixture of (phenylthio)methanol[12] (7.05 g, 50.3 mmol) and pyridine (4.90 ml, 61.0 mmol) in dichloromethane (50 ml) at 0 °C. The mixture was stirred under N_2 for 30 min, diluted with dichloromethane and washed with 1 M HCl. The HCl phase was extracted with dichloromethane, the combined organic phase washed with 1 M Na_2CO_3 and the Na_2CO_3 phase extracted with dichloromethane. The combined dichloromethane phase was dried ($MgSO_4$) and evaporated. The crude product was purified by fractional distillation. Yield 7.72 g (72%), b.p. 93–100 °C/0.01 mmHg. Anal. $C_{10}H_{12}O_3S$: C, H. ^{1}H NMR: δ 1.32 (t, *J* 7 Hz, CH_3), 4.24 (q, *J* 7 Hz, CH_3CH_2), 5.46 (s, SCH_2O), 7.2–7.55 (m, Ph). ^{13}C NMR: δ 14.9 (CH_3), 64.5 (CH_3CH_2), 72.0 (SCH_2O), 126.9, 128.5, 130.0, 133.7 (Ph), 153.5 (CO). MS: 212 (74, *M*), 138 (11), 123 (81), 110 (100), 109 (36), 77 (21).

Method B. Ethyl chloroformate (92 µl, 0.97 mmol) was added to a solution of (phenylsulfinyl)methyl(tributyl)-stannane[13] (325 mg, 0.76 mmol) in dichloromethane (3 ml) and the solution stirred under N_2 at 40–50 °C for 21 h. More ethyl chloroformate (40 µl, 0.42 mmol) and dichloromethane (1 ml) were added and the mixture was stirred for another 15 h before being cooled and the solvent evaporated off. The residue was dissolved in diethyl ether and cooled to 0 °C. Excess aqueous potassium fluoride was added and the mixture stirred for 30 min. Water was added and the mixture extracted with diethyl ether (×3). The organic phase was washed with water (×3), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using ethyl acetate–hexane (1:9) for elution. Yield 60 mg (37%). Physical data are given above.

Butyl (phenylthio)methyl carbonate (**3b**).

Method A. Compound **3b** was prepared from (phenylthio)methanol[12] (48.6 mmol) and butyl chloroformate as described for **3a** (method A) except that butyl chloroformate was added over 70 min and the resulting mixture stirred for 60 min. A portion (6.71 g) of the crude product (11.40 g) was purified by fractional distillation. Yield 3.66 g (53%), b.p. 95–105 °C/<0.01 mmHg. Anal. $C_{12}H_{16}O_3S$: C, H. ^{1}H NMR: δ 0.94 (t, *J* 7 Hz, CH_3), 1.25–1.75 (m, $CH_3CH_2CH_2$), 4.18 (t, *J* 7 Hz, OCH_2CH_2), 5.46 (s, SCH_2O), 7.2–7.55 (m, Ph). ^{13}C NMR: δ 14.4 (CH_3), 19.5 (CH_3CH_2), 31.1 (OCH_2CH_2), 68.4 (OCH_2CH_2), 72.0 (OCH_2S), 126.9, 128.5, 129.9, 133.7 (Ph), 153.6 (CO). MS: 240 (24, *M*), 123 (41), 110 (98), 109 (22), 77 (18).

Method B. Butyl chloroformate (280 µl, 2.17 mmol) was added to a solution of phenylsulfinylmethyl(tributyl)-stannane[13] (773 mg, 1.80 mmol) in dichloromethane (5.5 ml). The mixture was stirred under N_2 at 45–55 °C for 44 h, cooled and the solvent evaporated off. The residue was dissolved in diethyl ether and cooled to 0 °C. Excess aqueous potassium fluoride was added and the mixture stirred for 30 min and filtered. The filter was washed with diethyl ether and the aqueous phase separated. The organic phase was washed with water (×2) and dried ($MgSO_4$). The crude product was purified by flash chromatography on silica gel using ethyl acetate–hexane (5:95). The product obtained after flash chroma-

tography was kept under oil-pump vacuum for 7 h. Yield 173 mg (40%). Physical data are given above.

Chloromethyl (phenylthio)methyl carbonate (**3c**). Chloromethyl chloroformate (525 µl, 5.90 mmol) in dichloromethane (5 ml) was added dropwise over 30 min to a mixture of (phenylthio)methanol[12] (710 mg, 5.07 mmol) and pyridine (490 µl, 6.09 mmol) in dichloromethane (5 ml) at 0 °C. The mixture was stirred under N_2 for 70 min and worked up as described for **3a** (method A). The crude product was purified by flash chromatography on silica gel using ethyl acetate–hexane (5:95) for elution. Yield 967 mg (82%), liquid. ^{1}H NMR: δ 5.52 (s, SCH_2O), 5.75 (s, $ClCH_2O$), 7.25–7.55 (m, Ph). ^{13}C NMR: δ 72.3, 73.5 (2 × CH_2), 127.9, 129.2, 131.0, 133.6 (Ph), 152.8 (CO). MS: 232/234 (36/13, *M*), 158/160 (8/3), 125 (7), 123 (100), 109 (31), 79 (13), 77 (14). Mol.wt.: obs. 231.9953, calc. for $C_9H_9ClO_3S$: 231.9961.

Ethyl 1-(phenylthio)ethyl carbonate (**3d**). Ethyl chloroformate (114 µl, 1.20 mmol) was added to a solution of 1-phenylsulfinylethyl(tributyl)stannane[13] (449 mg, 1.01 mmol) in dichloromethane (3 ml) and the mixture stirred under N_2 at 40–45 °C for 22 h. The reaction mixture was cooled, the solvent evaporated off and the residue dissolved in diethyl ether. Excess aqueous potassium fluoride was added and the mixture was stirred for 5 min and filtered. The filter was washed with diethyl ether and the organic layer separated and dried ($MgSO_4$). The crude product was purified by flash chromatography on silica gel using ethyl acetate–pentane (5:95) for elution. Yield 43 mg (19%), liquid. ^{1}H NMR: δ 1.29 (t, *J* 7 Hz, CH_3CH_2), 1.55 (d, *J* 6.5 Hz, $CHCH_3$), 4.18 (q, *J* 7 Hz, OCH_2), 6.04 (q, *J* 6.5 Hz, $CHCH_3$), 7.3–7.6 (m, Ph).

Butyl 1-(phenylthio)ethyl carbonate (**3e**). Butyl chloroformate (250 µl, 1.93 mmol) was added to a solution of 1-phenylsulfinylethyl(tributyl)stannane[13] (689 mg, 1.56 mmol) in dichloromethane (5 ml). The mixture was stirred at 50–55 °C under N_2 for 48 h and worked up as for butyl (phenylthiomethyl) carbonate (**3b**) (Method B). The product obtained after flash chromatography was kept under oil pump vacuum for 3 h. Yield 99 mg (25%), liquid. ^{1}H NMR: δ 0.93 (t, *J* 7 Hz, CH_3CH_2), 1.2–1.75 (m, $CH_3CH_2CH_2$) 1.55 (d, *J* 6.5 Hz, $CHCH_3$), 4.12 (t, *J* 6.5 Hz, OCH_2), 6.04 (q, *J* 6.5 Hz, CH), 7.3–7.6 (m, Ph). ^{13}C NMR: δ 14.4 (CH_3CH_2), 19.6, 21.7 (CH_3CH_2, CH_3CH), 31.2 (OCH_2CH_2), 68.2 (OCH_2), 80.5 (CH), 127.9, 128.3, 130.2, 133.8 (Ph), 153.2 (CO). MS: 254 (12, *M*), 166 (5), 138 (10), 137 (32), 136 (43), 135 (67), 110 (100), 109 (72), 77 (23). Mol.wt.: obs. 254.0962, calc. for $C_{13}H_{18}O_3S$: 254.0977.

Reaction of 1-(trimethylsilyloxy)propyl phenyl sulfide (**5**) *with ethyl chloroformate.* A 0.5 M solution of TBAF in THF (6.3 ml, 3.2 mmol) was added dropwise to a mixture of 1-(trimethylsilyloxy)propyl phenyl sulfide[14] (754 mg, 3.14 mmol) and ethyl chloroformate (300 µl, 3.15 mmol) in THF (3 ml) at 0 °C. The mixture was stirred under N_2 for 11 h during which it reached ambient temperature. The mixture was cooled, treated with saturated ammonium chloride and extracted with diethyl ether. The ether phase was washed with water and saturated sodium chloride and dried ($MgSO_4$). Subjecting the crude product to flash chromatography on silica gel using light petroleum (b.p. 40–60 °C)–ethyl acetate (95:5) for elution furnished *O*-ethyl *S*-phenyl thiocarbonate (**6**).[15] Yield 356 mg (62%), liquid. ^{1}H NMR: δ 1.32 (t, *J* 7 Hz, CH_3), 4.29 (q, *J* 7 Hz, CH_2), 7.3–7.6 (m, Ph). ^{13}C NMR: δ 15.0 (CH_3), 64.1 (CH_2), 127.3, 128.5, 128.8, 134.1 (Ph), 168.4 (CO). MS: 182 (9, *M*), 138 (16), 137 (6), 123 (31), 110 (100), 109 (49), 77 (9).

Chloromethyl ethyl carbonate[4] (**7a**). Sulfuryl chloride (1.51 g, 11.2 mmol) in dichloromethane (5 ml) was added dropwise to a solution of ethyl (phenylthio)methyl carbonate (2.12 g, 10.0 mmol) in dichloromethane (20 ml) at 0 °C. The solution was stirred under N_2 at ambient temperature for 80 min, cyclohexene (0.972 g, 11.9 mmol) was added dropwise at 0 °C and the mixture stirred at ambient temperature for 60 min before the solvent was evaporated off at reduced pressure and the residue distilled. Yield 0.976 g (70 %), b.p. 63 °C/25 mmHg. ^{1}H NMR: δ 1.35 (t, *J* 7 Hz, CH_3), 4.30 (q, *J* 7 Hz, CH_3CH_2), 5.74 (s, $ClCH_2$). ^{13}C NMR: δ 14.7 (CH_3), 65.2 (CH_3CH_2), 72.1 ($ClCH_2$), 152.3 (CO). MS (CI): 139/141 (100/36, *M*+*H*), 111/113 (4/1), 59 (34).

Butyl chloromethyl carbonate (**7b**). Sulfuryl chloride (100 µl, 1.23 mmol) was added dropwise to butyl (phenylthio)methyl carbonate (271 mg, 1.13 mmol) in dichloromethane (2.8 ml) at 0 °C. The solution was stirred under N_2 at 0 °C for 65 min, and then at ambient temperature for 45 min before cyclohexene (140 µl, 1.38 mmol) was added dropwise at 0 °C. The solution was stirred for 30 min at 0 °C, the solvent evaporated off at reduced pressure and the residue distilled in a Kugelrohr apparatus, oven temperature 90–100 °C/8 mmHg. Yield 132 mg (70%). Anal. $C_6H_{11}ClO_3$: C, H. ^{1}H NMR: δ 0.94 (t, *J* 7 Hz, CH_3), 1.25–1.75 (m, $CH_3CH_2CH_2$), 4.23 (t, *J* 6.5 Hz, OCH_2CH_2), 5.73 (s, $ClCH_2O$). ^{13}C NMR: δ 14.4 (CH_3), 19.5 (CH_3CH_2), 31.0 (OCH_2CH_2), 69.2 (OCH_2CH_2), 72.2 ($ClCH_2$), 152.5 (CO). MS (CI): 167/169 (14/5, *M*+*H*), 139 (4), 111/113 (100/32), 73 (9).

Bis(chloromethyl) carbonate[11] (**7c**). Sulfuryl chloride (0.450 ml, 5.55 mmol) was added dropwise to chloromethyl (phenylthio)methyl carbonate (1.166 g, 5.01 mmol) in dichloromethane (12.5 ml) at 0 °C. The solution was stirred under N_2 at 0 °C for 5 min, and then at ambient temperature for 4 h before cyclohexene (0.610 ml, 6.03 mmol) was added dropwise at 0 °C. The solution was stirred at ambient temperature for 1 h before the solvent was evaporated off at reduced pressure and the residue distilled. Yield 0.578 g (73%), b.p. 62–

64 °C/7 mmHg. ^{1}H NMR: δ 5.78 (s, CH_2). ^{13}C NMR: δ 72.5 (CH_2), 151.1 (CO). MS (CI): 159/161/163 (68/36/5, $M+H$), 109 (8), 83 (7), 81 (60), 79 (100), 49 (24).

1-Chloroethyl ethyl carbonate[2] (**7d**). Sulfuryl chloride (140 µl, 1.73 mmol) was added dropwise to ethyl 1-(phenylthio)ethyl carbonate (350 mg, 1.55 mmol) in dichloromethane (3.9 ml) at 0 °C. The solution was stirred under N_2 at 0 °C for 30 min before cyclohexene (185 µl, 1.83 mmol) was added dropwise. The solution was stirred for 1 h at ambient temperature before the solvent was evaporated off at reduced pressure and the residue distilled in a Kugelrohr apparatus, oven temperature 85 °C/20 mmHg. Yield 151 mg (64%). ^{1}H NMR: δ 1.33 (t, J 7 Hz, CH_3CH_2), 1.83 (d, J 6 Hz, $CHCH_3$), 4.27 (q, J 7 Hz, CH_3CH_2), 6.43 (q, J 6 Hz, $CHCH_3$). ^{13}C NMR: δ 14.8 (CH_3CH_2), 25.8 (CH_3CH), 65.1 (CH_3CH_2), 84.3 (CH), 151.9 (CO).

1-Bromoethyl ethyl carbonate[6] (**7e**). Bromine in tetrachloromethane (1.2 ml 1.0 M, 1.2 mmol) was added dropwise to ethyl 1-(phenylthio)ethyl carbonate (227 mg, 1.0 mmol) in tetrachloromethane (2 ml) at ambient temperature. The solution was stirred under N_2 at ambient temperature for 1 h, cyclohexene (132 µl, 1.30 mmol) added dropwise at 0 °C and the solution stirred for 1 h at ambient temperature before the solvent was evaporated off. The residue was subjected to flash chromatography on silica gel using diethyl ether–pentane (5:95) for elution (R_f 0.24, note: the fractions were evaporated at 20 °C/100 mmHg). Yield 109 mg (55%). ^{1}H NMR: δ 1.33 (t, J 7 Hz, CH_2CH_3), 2.02 (d, J 6 Hz, $CHCH_3$), 4.27 (q, J 7 Hz, CH_2), 6.60 (q, J 6 Hz, CH).

1-Bromoethyl butyl carbonate (**7f**). The title compound was prepared as for **7e** above and purified by flash chromatography on silica gel using ethyl acetate–hexane (5:95) for elution (R_f 0.23). Yield 141 mg (62%).^{1}H NMR: δ 0.93 (t, J 7.5 Hz, CH_3CH_2), 1.3–1.75 (m, $CH_3CH_2CH_2$), 2.02 (d, J 6 Hz, $CHCH_3$), 4.21 (t, J 6.5 Hz, OCH_2), 6.60 (q, J 6 Hz, CH). ^{13}C NMR: δ 13.6 (CH_3CH_2), 18.8 (CH_3CH_2), 26.8 (CH_3CH), 30.5 (OCH_2CH_2), 68.9 (OCH_2), 75.5 (CH), 152.6 (CO).

1-Bromoethyl phenyl sulfide (**8b**). Bromo(trimethyl)silane 25.0 µl (0.193 mmol) was added dropwise to ethyl 1-(phenylthio)ethyl carbonate (40 mg, 0.18 mmol) in dichloromethane (1 ml) at 0 °C. The mixture was stirred at 0 °C under N_2 for 15 min, evaporated and the NMR spectrum recorded immediately. Yield of crude product 27 mg (70%). ^{1}H NMR: δ 2.09 (d, J 7 Hz, CH_3), 5.49 (q, J 7 Hz, CH), 7.3–7.6 (m, Ph).

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