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α-Chloromercaptals from α-Chloroacetals and Thiols

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Abstract: *α-Chloromercaptals are prepared in good yields by a $CoCl_2$-trimethylchlorosilane catalysed transdithioacetalization of α-chloroacetals with thiols in acetonitrile.*

INTRODUCTION

Recently, we developed a mild and efficient method for the α-halogenation of dimethylacetals with MnO_2-trimethylchlorosilane (TMCS) [1] Owing to the possibility of the sulphur atom to employ the 3d orbitals, sulphur derivatives are generally much more versatile synthetic intermediates with respect to the corresponding oxygenated ones,[2] we were therefore stimulated to develop a method for an easy transformation of α-haloacetals into the corresponding α-halomercaptals

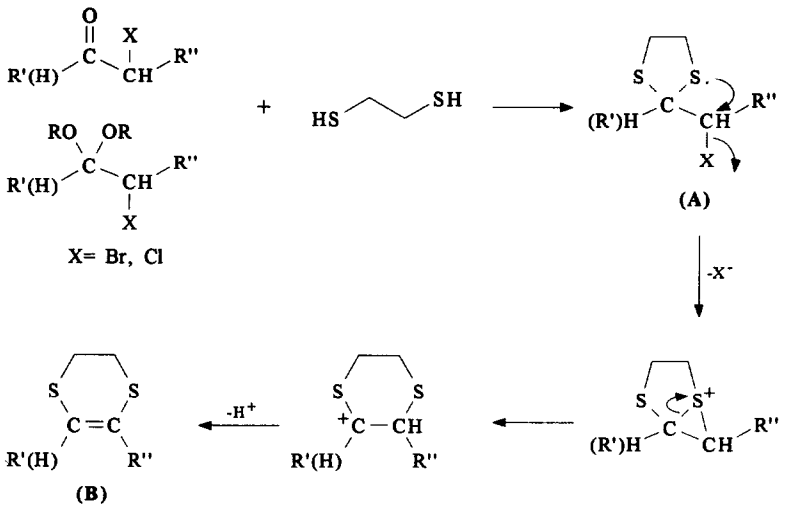
Rothstein[3] reported first the synthesis of α-halomercaptals *in situ* by transdithioacetalisation, however, all the subsequent attempts to prepare these derivatives failed,[4,5] mainly observing C-halogen bond cleavage and rearranged products Like the parent carbonyl compounds, α-haloacetals, indeed, react with 1,2-ethanedithiol under acidic conditions, affording the biological active dihydro-1,4-dithiines [5] 2-(1-Haloalkyl)-1,3-dithiolanes (A) has been suggested as the intermediates (see Scheme) in the rearrangement to dihydro-1,4-dithiines (B) [5]

We now report the easy preparation and isolation of the till now elusive[6] 2-(1-chloroalkyl)-1,3-dithiolanes by a $CoCl_2$-TMCS promoted transdithioacetalisation of α-chloroaldehyde dimethylacetals with 1,2-ethanedithiol; the reaction with other mercaptans gives the corresponding derivatives. The only reported example of isolated α-chloromercaptals is the preparation of the polychlorinated derivatives 2-dichloromethyl- and 2-trichloromethyl-1,3-dithiolane, by reaction of the ethanedithiol with dichloroacetaldehyde diethylacetal[7] or trichloroacetaldehyde,[8] respectively

RESULTS AND DISCUSSION

The acetal is a well-known protecting group for the carbonyl function under basic or neutral conditions, so that a nucleophilic attack requires an acid catalysis activation [9]An 1 1 mixture of α-chlorohexanal dimethylacetal and

1,2-ethanedithiol was thus tested using a number of Lewis acids (BF_3, Nafion-H, TMCS, $ZnCl_2$, $SnCl_2$, $NiCl_2$, $MnCl_2$, $CoCl_2$) in different solvents, in order to find out conditions mild enough to obtain satisfacory yields of α-chloromercaptal and to prevent the subsequent rearrangement



Scheme

The couple $CoCl_2$-TMCS was the most effective catalyst, the better performances being observed in acetonitrile as solvent. On using $CoCl_2$ or TMCS alone, however, only a partial conversion of the α-chloroacetal was obtained. The observed synergism may be rationalized by a Si-Cl bond loosening in consequence of a $CoCl_2$ complexation of the TMCS chlorine, so that the Si nucleus becomes electrophilic enough to activate the acetal group

A series of α-chlorodimethylacetals has been treated at room temperature with $CoCl_2$-TMCS and 1,2-ethanedithiol on obtaining the corresponding α-chloromercaptals in good yields (Table 1) [10] The reactions are very fast (10-30') and the final mixture must be immediately worked up, since α-chloromercaptals slowly rearrange, mainly giving dihydro-1,4-dithiines. This rearrangement should occur at a greater extent with α-bromomercaptals, owing to the easier bromide displacement by sulphur,[11] on starting, indeed, from α-bromohexanal dimethylacetal, the main product is the dihydro-1,4-dithiine, even in the early stage of the reaction

Other mercaptans may be used (Table 2), mercaptoethanol (item 11) and 1,3-propanedithiol (item 9) afford in high yields 2-(1-chloroalkyl)-1,3-oxathiolane and 2-(1-chloroalkyl)-1,3-dithiane, respectively Non chelating mercaptans, like thiophenol (item 10) and ethyl mercaptan (item 12), give rise to a different behaviour, with the first one, probably owing to its size, the O,S acetal is the main product, while with the second a little amount of 1,1,2-trithioethoxyhexane (8 4%), formed during reaction work-up (GC monitoring), accompanies the expected α-chloromercaptal

TABLE 1· The preparation of α-chloromercaptals by reaction of α-chloroacetals with thiols.

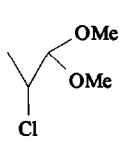
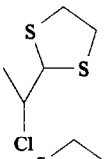
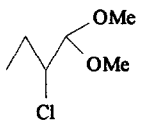
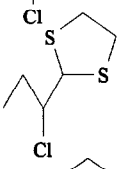
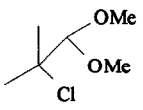
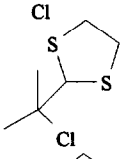
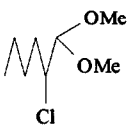
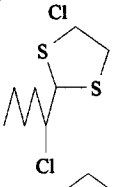
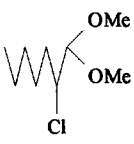
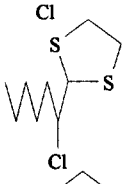
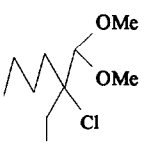
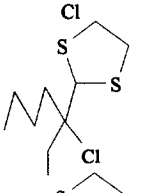
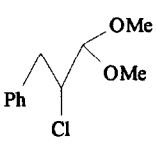
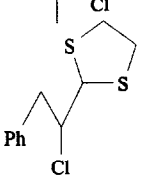
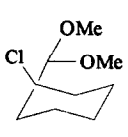
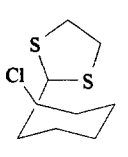
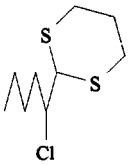
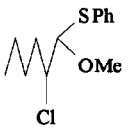
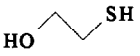
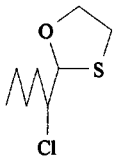
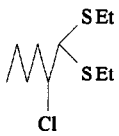
ITEM	SUBSTRATE	PRODUCT	TIME(min)	YIELD(%)
1			60	80
2			30	85
3			30	79
4			60	92
5			60	87
6			60	70
7			60	77
8			30	91

TABLE 2· The reaction of 2-chlorohexanal dimethyl acetal with thiols.

ITEM	THIOL	PRODUCT	TIME(min)	YIELD(%)
9			60	88
10[a)]	Ph – SH		30	47
11			240	66
12[b)]	Et – SH		15	68

a) Substrate Ph-SH $CoCl_2$ TMCS= 1 1 1 1
b) Substrate Et-SH $CoCl_2$ TMCS= 1 3 1 1

Also on a large scale the yields are satisfactory (see Experimental), thus making this procedure very attractive for the preparation of these potentially useful synthetic intermediates α-Chlorodithioacetals are very sensible to acidic conditions, but are stable enough to be distilled and to be stored indefinitely at -10°C

EXPERIMENTAL PART

The ^1H NMR spectra have been recorded on a Bruker FP80 or on a Varian XL200 spectrometer Mass spectra have been obtained on a HP 5989A MS Engine Reagents and solvents are standard grade commercial products, and have been used without further purification The α-chloroacetals have been prepared by chlorination of aldehyde dimethylacetals with MnO_2-TMCS [1]

General procedure for the preparation of α-chloromercaptals. To a solution of $CoCl_2$ (1 1 mmoles) in acetonitrile (4 ml), α-chlorodimethylacetal (1 1 mmoles), 1,2-ethanedithiol (1 1 mmoles) and then TMCS (1 1 mmoles) are added under stirring at room temperature The reaction is monitored by TLC, using ethyl ether/n-hexane (0 5 9 5) as

eluant.[12] After the time reported in Table 1, the mixture is extracted with n-hexane (3 x 5 ml) and the extracts collected and washed with 5% $NaHCO_3$ (5 ml). To complete the extraction, the mother liquor is diluted with 5% $NaHCO_3$ (10 ml) and extracted with a further n-hexane (10 ml). The organic phases are collected, dried over Na_2SO_4, and evaporated The crude product is purified by preparative TLC or by bulb to bulb distillation in an air bath thermostat Yields are on isolated products.

Special cases.- a) In item 12, 3 3 mmoles of ethyl mercaptan are used,[13] *b)* The amount of thiophenol in item 10 is lowered to 1,1 mmoles since, also on a stoichiometrical ratio (2.2 mmoles), the O,S acetal is formed preferentially, probably owing to sterical hindrance.

Large scale preparation. Starting from hexanal dimethylacetal (14 4 g, 80 mmoles), 1,2-ethanedithiol (7.52 g, 80 mmoles), TMCS (8 72 g, 80 mmoles) and $CoCl_2$ (10 4 g, 80 mmoles) in CH_3CN (280 ml), the corresponding α-chlorodithioethyleneacetal is obtained in 92% yield

2-(1-chloropentyl)-1,3-dithiolane

B p 87-92°C /0 02 mmHg

^1H NMR ($CDCl_3$). 0 95 (3H, t, CH_3-C), 1.08-1.92 (4H, m, C-$(CH_2)_2$-C); 1 94-2 40 (2H, m, C-CH_2-CCl); 3.22 (4H, m, -S$(CH_2)_2$S-); 3 92 (1H, m, -CHCl-); 4 75 (1H, d, S-CH-S).

m/z 210 (M^+, 7), 105 (100)

Found· C, 45 7, H, 7 2, Cl, 16 6; S, 30 5 $C_8H_{15}ClS_2$ requires C, 45.71; H, 7.20; Cl, 16.65; S, 30 45%.

2-(1-chloro-2-phenylethyl)-1,3-dithiolane

B p 155-160°C /0 05 mmHg

^1H NMR ($CDCl_3$) 3 06 (2H, m, Ph-$C\underline{H}_2$-CCl), 3 32 (4H, m, -S$(CH_2)_2$S-), 4 18 (1H, m, -CHCl-), 4 76 (1H, d, S-CH-S); 7 28 (5H, m, -C_6H_5).

m/z. 244 (M^+, 4), 105 (100).

Found C, 54 0, H, 5 4, Cl, 14 4, S, 26 2. $C_{11}H_{13}ClS_2$ requires C, 54 10, H, 5 37, Cl, 14.33, S, 26.21%

2-chloroethyl-1,3-dithiolane

B.p. 127-132°C /14-15 mmHg

^1H NMR ($CDCl_3$) 1 59 (3H, d, CH_3-CCl), 3 22 (4H, m, -S$(CH_2)_2$S-); 4 06 (1H, m, -CHCl-); 4 69 (1H, d, S-CH-S)

m/z 168 (M^+, 17), 105 (100)

Found C, 35 8, H, 5.4, Cl, 20 8, S, 38.0 $C_5H_9ClS_2$ requires C, 35 72, H, 5 40; Cl, 20 82; S, 38 07%

2-(1-chloropropyl)-1,3-dithiolane

B p· 87-95°C /0 03 mmHg

^1H NMR ($CDCl_3$)·1 03 (3H, t, CH_3-C), 1 72 and 2 04 (2H, m, C-CH_2-CCl), 3 22 (4H, m, -S$(CH_2)_2$S-), 3 86 (1H, m, -CHCl-); 4 72 (1H, d, S-CH-S).

m/z: 182 (M^+, 11); 105 (100)

Found. C, 39 5; H, 6 1, Cl, 19 2, S, 35.1 $C_6H_{11}ClS_2$ requires C, 39.56, H, 6.09; Cl, 19.21; S, 35.13%

2-(1-chloro-1-methylethyl)-1,3-dithiolane

B p 109-114°C / 0 1 mmHg

^{1}H NMR ($CDCl_3$): 1.66 (6H, s, 2x-CH_3); 3.22 (4H, m, -S(CH_2)$_2$S-), 4.88 (1H,s, S-CH-S)
m/z: 182 (M^+, 11); 105 (100)
Found: C,. 39.6; H, 6.1; Cl, 19.1; S, 35 1. $C_6H_{11}ClS_2$ requires C, 39 56; H, 6.09; Cl, 19.21, S, 35 13%.

2-(1-chlorocyclohexyl)-1,3-dithiolane
B.p.: 111-116°C / 0.03 mmHg
^{1}H NMR ($CDCl_3$): 0 96-1 98 (10H, m, -C_6H_{10}), 3.22 (4H, m, -S(CH_2)$_2$S-), 4.83 (1H, s, S-CH-S)
m/z: 222 (M^+, 5); 105 (100)
Found. C, 48.6; H, 6.9; Cl, 15 7; S, 28 8. $C_9H_{15}ClS_2$ requires C, 48.64, H, 6 81; Cl, 15.75; S, 28 80%

2-(1-chlorohexyl)-1,3-dithiolane
B.p : 97-104°C / 0.02 mmHg
^{1}H NMR ($CDCl_3$) 0 85 (3H, t, CH_3-C);1.08-2 03 (8H, m, C-(CH_2)$_4$-CCl), 3 22 (4H, m, -S(CH_2)$_2$S-); 3 90 (1H, m, -CHCl-); 4.71 (1H, d, S-CH-S).
m/z: 224 (M^+, 6); 105 (100).
Found C, 48.2, H, 7 6; Cl, 15 6, S, 28 6 $C_9H_{17}ClS_2$ requires C, 48.20; H, 7.65; Cl, 15 61, S, 28 54%.

2-(1-chloro-1-ethylpenthyl)-1,3-dithiolane
B.p . 88-95°C / 0 02 mmHg
^{1}H NMR ($CDCl_3$) 0 87 (3H, t, CH_3-C), 0.96 (3H, t, CH_3-C-CCl), 1.16-1.47 (4H, m, CH_3-(C$\underline{H}_2$)$_2$-C), 1.73-2 10 (4H, m, 2x-C-CH_2-CCl), 3 22 (4H, m, -S(CH_2)$_2$S-), 4 95 (1H, s, S-CH-S)
m/z.238 (M^+, 6), 105 (100).
Found: C, 50.5; H, 8 0, Cl, 14 7, S, 26.8. $C_{10}H_{19}ClS_2$ requires C, 50 41, H, 8 04; Cl, 14.69, S, 26.86%.

2-(1-chloropenthyl)-1,3-dithiane
B p.. 106-110°C / 0 02 mmHg
^{1}H NMR ($CDCl_3$) 0.85 (3H, t, CH_3-C), 1 14-1 86 (6H, m, C-(CH_2)$_2$-C), 1 86-2 32 (4H, m, C-CH_2-CCl and S-C-CH_2-C-S), 2 85 (4H, m, 2xS-CH_2), 4 06 (1H, m, -CHCl-), 4 29 (1H, d, S-CH-S).
m/z· 224 (M^+, 10); 119 (100)
Found. C, 48.2, H, 7 7; Cl, 15.7; S, 28 5 $C_9H_{17}ClS_2$ requires C, 48 20, H, 7 65, Cl, 15 61, S, 28 54%

2-(1-chloropenthyl)-1,3-oxathiolane
B p 102-108°C / 1 mmHg
^{1}H NMR ($CDCl_3$) 0 91 (3H, t, CH_3-C), 1 18-2 07 (6H, m, C-(CH_2)$_3$-CCl), 3 00 (2H, m, S-CH_2-C), 3 92 (2H, m, O-CH_2-C), 4 44 (1H, m, -CHCl-), 5 16 and 5 22 (1H, d, S-CH-O)
m/z 194 (M^+, 5), 89 (100)
Found. C, 49 4, H, 7 8, Cl, 18 1, S, 16 5 $C_8H_{15}ClOS$ requires C, 49 47, H, 7 79, Cl, 18 02, S, 16 48%

2-chlorohexanal diethyl mercaptal
B p 108-112°C / 1 5 mmHg
^{1}H NMR ($CDCl_3$) 0 90 (3H, t, CH_3-C), 1 17 (6H, t, 2xCH_3-C-S), 1.22-2 28 (6H, m, C-(CH_2)$_3$-CCl); 2.57 (4H, q,

2xCH_2S), 3.91 (1H, d, -CHCl-); 4.06 (1H, d, S-CH-S).
m/z 240 (M^+, 26), 204 (M^+-36, 64), 179 (M^+-61, 57); 135 (62); 81 (100).
Found. C, 49.9; H, 8 8; Cl, 14.5, S, 26 6 $C_{10}H_{21}ClS_2$ requires C, 49.98; H, 8.82; Cl, 14.57, S, 26.63%

2-thioethoxyhexanal diethyl mercaptal
B p.: 120-125°C / 1 5 mmHg.
^{1}H NMR ($CDCl_3$).0 91 (3H, t, CH_3-C), 1 28 (9H, t, 3xCH_3-C-S), 1.35-2.03 (6H, m, C-(CH_2)$_3$-C), 2 45-2 81 (6H, m, 3xC-CH_2-S); 2.93 (1H, m, C-C<u>H</u>-SEt); 4.03 (1H, d, -C<u>H</u>(SEt)$_2$)
m/z: 266 (M^+, 7), 135 (100)
Found C, 54 0; H, 9 9, S, 36 1 $C_{12}H_{26}S_3$ requires C, 54 11, H, 9.85; S, 36.04%.

1-methoxy-1-thiophenoxy-2-chlorohexane
B p 105-108°C / 0 01 mmHg
^{1}H NMR ($CDCl_3$) 0 90 (3H, t, CH_3-C), 1 18-2 17 (6H, m, C-(CH_2)$_3$-CCl), 3 52 (3H, s, C-OCH_3); 4 02 (1H, m, -CHCl), 4 64 and 4 74 (1H, d, S-CH-S), 7.15-7 61 (5H, m, -C_6H_5)
m/z 258 (M^+, 13), 222 (M^+-36, 18), 153 (7), 149 (M^+-109, 64); 113 (98), 81 (100)
Found C, 60 5; H, 7 4, Cl, 13 6, S, 12 3 $C_{13}H_{19}ClOS$ requires C, 60 45, H, 7 42, Cl, 13 55, S, 12 39%

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6 E J Corey and D Seebach obtain (unpublished results, see *Synthesis*, **1969**, p 17) 2-(1-chlorocyclohexyl)-

1,3-dithiane by reaction of corresponding hydroxyadduct with thionyl chloride

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10. Also the parent α-chloroaldehydes are successfully transformed, α-chlorohexanal, for example, gives the ethylendithioacetal derivative in 86% yield. Differently, starting from some α-chloroketones we were not able to isolate the mercaptals, owing to their rapid rearrangement; 3-chloro-2-octanone affords mainly the dihydro-1,4-dithiine derivative (63%).

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12 On GC monitoring, special care must be applied towards a clean glass-liner, with an injector temperature around 150 °C Some rearrangement of the α-chloromercaptals is, however, sometimes observed.

13. On using a large excess of ethyl mercaptan (1 ml), 1,1,2-trithioethoxyhexane is obtained in 66% yield