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SYNTHESIS OF MESOCYCLIC AND MACROCYCLIC THIACROWN ETHERS CONTAINING $-SCH_2SCH_2S-$ UNITS USING THIO(BISCHLOROMETHANE)

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Abstract: Oxidative cleavage of 1,3,5-trithiane **1** by thionyl chloride is promoted by a catalytic quantity of a Lewis acid like zinc bromide or aluminum chloride and results in the formation of pure thiobis(chloromethane)(**2**). This reagent has been successfully employed in the straightforward synthesis of a novel series of thiacrown ethers possessing methylene bridges between the heteroatoms. These molecules have chemical and physical properties that differ considerably in their solubilities from those of their ethylenic or propylenic counterparts.

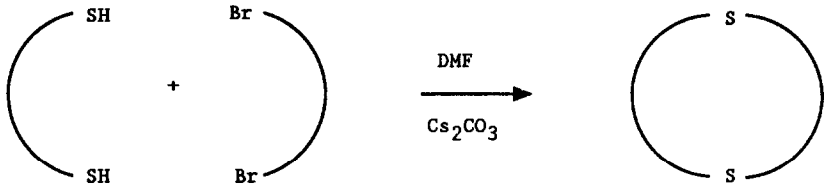
Introduction.

Macrocyclic thiacrown ethers, in analogy with their oxygen counterparts, have been the subject of increased interest during the past two decades. Because of the softness of sulfur with respect to oxygen these molecules are especially apt for complexation with heavy-metal ions as Hg^{2+}, Ag^{+}, Cd^{2+} and Pb^{2+}.[1-4] The enormous structural diversity of the metal complexes has stimulated various groups to examine the synthesis and properties of such coordination compounds.

A strategy that has been developed in our laboratory for the preparation of these systems is the nucleophilic cyclization of α,ω-cesium dithiolates with a bifunctional dihalide.[5] This is illustrated for the general synthesis of ring compounds in eq. 1.

In the majority of macrocycles synthesized thus far[1], the sulfide ligating sites are separated by ethylenic ($-CH_2-CH_2-$) or propylenic ($-CH_2-CH_2-CH_2-$) bridges[4,5] giving rise to a peculiar inside-outside

Eq. 1



arrangement of the sulfur atoms with respect to the ring system[1].

In connection with an effort to systematically study conformational effects of thia crownethers we had need of methods to prepare compounds containing the $-SCH_2S-$ fragment. It is known from previous studies that the presence of these one-carbon bridges usually imposes a certain rigidity[6,12] on the ring system resulting in a preferential all-cis conformation of the S atoms with respect to the macrocycle. However, apart from simple systems like 1,3,5-trithiane and 1,3-dithiane no systematic and effective general synthetic strategy for the preparation of thiacrowns containing $-SCH_2S-$ fragments has been developed.

A large scale route to $ClCH_2SCH_2Cl$ was clearly of interest in the anticipation that this unit could be successfully employed in the cesium salt method that we had developed previously[5].

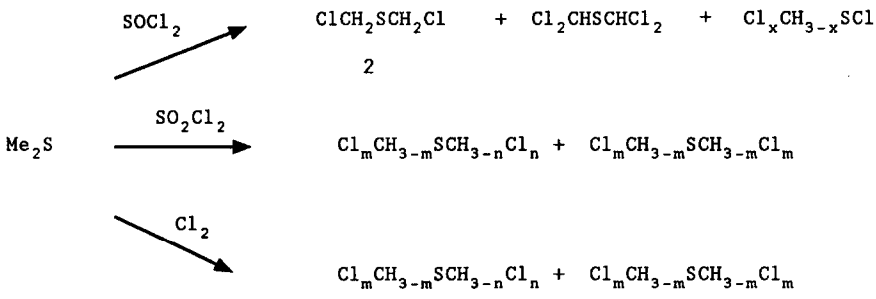
The incorporation of $-CH_2SCH_2-$ units in macrocycles presents, however, a synthetic problem. It does not seem likely that condensation approaches involving formaldehyde or derivatives thereof will be met with success. Following the approach given in eq. 1, nucleophilic substitution on XCH_2SCH_2CX is called for. Oxidation of this unit should allow in principle introduction of sulfoxide and sulfone units without the danger of overoxidation of the other sulfide linkages.

In this report we describe a convenient and improved one pot synthesis of $ClCH_2SCH_2Cl$ based on the catalytic action of zinc bromide on the ring cleavage of trithiane and its straightforward use in the preparation of a novel series of thiacrowns possessing rigid thioketal fragments.

Results and discussion.

Although various syntheses of **2** have been described,[7-10] none proved in our hands satisfactory for the large scale preparation that we envisaged. In Scheme 1, the various approaches available, all depending on the chlorination of dimethylsulfide with a variety of chlorinating agents, are illustrated[7,8]. The obvious disadvantage of these methods is the lack of selectivity during the chlorination reaction and the subsequent difficulties to fractionate the products with a variable degree of chlorination.

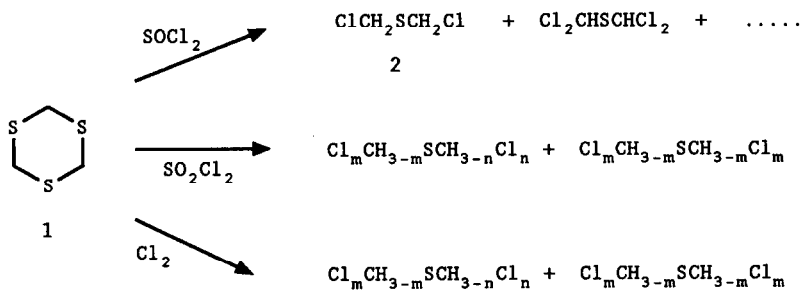
Scheme 1



Better results, however, are obtained in the reaction of trithioformaldehyde (1,3,5-trithiane)(**1**) with thionyl chloride, sulfur mono- or dichloride[7,9] to yield a higher fraction of the desired *sym*-dihalides (Scheme 2). However, the high yields previously reported for the $SOCl_2$[7,9] and the SCl_2[8] methods were in our hands not reproducible and substantial quantities of higher chlorinated products were isolated together with monochlorinated materials, which constituted up to 50 % of the main fraction.

We observed that a catalytic amount (1 %) of a Lewis acid like zinc bromide or aluminum chloride significantly improves the selectivity and the yield (usually about 90%) of the reaction when carried out in tetrachloromethane as solvent.(The application of zinc bromide did not result in halogen scrambling). We suspect that the Lewis acid acts as a carrier of chlorine from thionyl chloride; a low steady state concentration of chlorine is ensured leading to a smooth cleavage of **1**. Zinc bromide is

Scheme 2



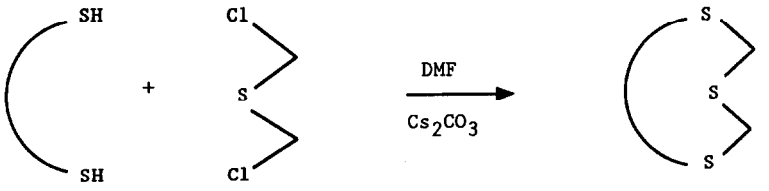
easiest to use; halide exchange is not a significant factor because of the low concentration of the catalyst.

This improved reaction might be of substantial value since it is easily performed on large scale (up to 500 gram).

Reaction of thiobis(chloromethane), **2**, with α,ω-cesium dithiolates (see eq. 2) proved useful for the preparation of a number of novel thiacrowns (compounds **3-6**) possessing methylenic spacers between the heteroatoms (Scheme 3).

We have observed in 1,3,5-trithiane and 1,3-dithiane that the sulfide linkages are forced into a basket-like cis arrangement[6].

Eq. 2



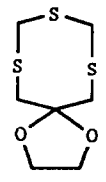
For the compounds **3-6** it has not yet proved possible to obtain an X-ray structure although we anticipate that similar effects apply. If the sulfides are located on one face of the macrocycle, the tendency to facially coordinate a metal ion increases. Such effects are found for 12-S-3 and 9-S-3[1]. One should note the tendency of sulfides separated by two-carbon bridges to arrange themselves exodentate[1].

The physical properties of the synthesized compounds could well reflect the higher degree of rigidity exerted by the presence of the

-SCH_2S- fragment. The low solubility of 1,3,5-trithiane and to a lesser extent 1,3-dithiane in solvents like chloroform, methylene chloride and ethanol suggest this whereas the homologous 1,4-dithiane readily dissolves in most common organic solvents.

In analogy with this observation, **4** and **6** are also poorly soluble in common organic solvents; moreover **4** decomposes without melting above 150°C. The larger ring systems **3** and **5** on the other hand resemble their ethylenic counterparts like 1,4-dithiane in that they are reasonably soluble in toluene and methylene chloride allowing their purification by means of column chromatography in contrast to **4** and **6** that proved

Scheme 3



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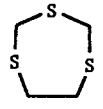

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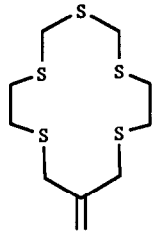

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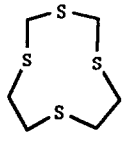

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difficult to purify due to the low solubility in most organic solvents.

In summary, we have described in this paper a novel method for the preparation of thiacrowns containing methylenic spacers between the heteroatoms. This has opened up a new area of research in the chemistry of sulfur containing ligands and their complexation behavior toward metal ions.

Experimental section.

All reactions were performed under inert atmosphere. Solvents were dried and degassed prior to use according to standard procedures. Cesium carbonate, thionyl chloride and sulfur dichloride were purchased from Aldrich and were used as received. Dithiols were prepared as described in earlier reports[4].

Thio(bischloromethane) (2)

A suspension of freshly prepared 1,3,5-trithiane **1** (138 g, 1.0 mol) in 500 mL of CCl_4 was treated with a mixture of zinc bromide (21 g, 9.3 mmol) and $SOCl_2$ (260 g, 2.18 mol). The suspension was refluxed for 24 h. yielding a brick-red solution. The mixture was distilled at atmospheric pressure using a Widmer column to separate the fraction, 153- 155.5 °C, yield 117 g. (0.85 mol, 85 %) ^{1}H-NMR ($CDCl_3$) 4.82 (s). M/e$^+$ = 132.00, 129.93, 128.95, 127.01, 97.07, 95.10, 85.06, 83.03, 78.90, 77.95, 75.98, 64.06, 50.96, 48.96, 46.07, 45.06, 44.03, 37.94, 36.03, 35.02. exact mass M^+= 131.079 (calcd. 131.079 for $C_2H_4SCl_2$); IR (neat, cm^{-1}) 3015 s, 2953 m, 2784 m, 1517 s, 1397 s, 1334 s, 1234 m, 1218 s, 1179 w, 1143 w, 1097 w, 891 w, 843 w, 743 s, 721 s, 660 s.

Analogous results were obtained when aluminum chloride was used as catalyst.

1,3,5-trithiepane (4).

A solution of 1,2-ethanedithiol (2.73 g, 29 mmol) and **2** (3.8 g, 29 mmol) in 75 mL DMF was slowly (16 h.) added to a warm (55-60°C), vigorously stirred suspension of 2 equiv. of Cs_2CO_3 (19.5 g, 58 mmol) in 500 mL DMF. The mixture was stirred for an additional period of 5 h at room temperature after which time the solvent was removed in vacuo. The solid residue was extracted repeatedly with water to remove the residual DMF, CsCl and Cs_2CO_3. The combined solids were washed with ether and dried to provide an off-white powder (dec.> 150°C), yield 2.67 g (17.6 mmol, 60 %). M/e$^+$ = 152.11, 138.07, 109.94, 106.09, 92.01, 89.03, 77.98, 76.01, 74.11, 64.05, 61.06, 59.99, 47.04, 46.05, 41.96; exact mass M^+= 151.979 (calcd. 151.979 for $C_4H_8S_3$).

1,3,5,8-tetrathiacyclodecane (6)

A solution of bis 2-mercaptoethylsulfide[4] (3.14 g, 20.4 mmol) and **2** (2.67 g, 20.4 mmol) in 75 mL DMF was slowly (20 h.) added to a warm (55-60°C), vigorously stirred suspension of 2 equiv. of Cs_2CO_3 (13.3 g, 41 mmol) in 350 mL DMF. The mixture was filtered and the solvent was removed in vacuo leaving a yellow oily residue. The filtercake was

extracted repeatedly with portions of chloroform. The combined chloroform layers were concentrated rendering an off-white oil. The combined oil fractions were chromatographed over silica using toluene/dichloromethane (1:3) as eluent; yield 3.52 g of an off-white solid (16.6 mmol, 81 %). ^{1}H-NMR ($CDCl_3$) 2.95 (m,4H), 2.83 (m,4H), 3.87 (m,2H). M/e$^+$= 212.16, 198.09, 152.09, 124.05, 106.08, 92.01, 87.08, 77.97, 76.00, 64.05, 61.04, 59.97, 59.04, 58.08, 46.04, 45.02; exact mass M^+= 211.983 (calcd. 211.982 for $C_6H_{12}S_4$).

Spiro-5,5-(1,3 dioxolane)-1,3,7-trithiacyclooctane (3)

A solution of spiro-2,2-(1,3 dioxolane)-1,3 propanedithiol[4] (0.83 g, 5.0 mmol) and **2** (0.65 g, 5.0 mmol) in 75 mL DMF was slowly (20 h) added to a warm (55-60°C), vigorously stirred suspension of 2 equiv. of Cs_2CO_3 (3.26 g, 10.0 mmol) in 350 mL DMF. The mixture was filtered and the solvent was removed in vacuo leaving an oily residue. The filter cake was extracted repeatedly with chloroform. The combined chloroform layers were concentrated to provide a yellow oil which was chromatographed over silica gel using toluene/dichloromethane (1:3) as eluent; yield 0.89 g of a white creamy solid (4.0 mmol, 80 %) M/e$^+$ = 224.14, 212.10, 210.07, 164.09, 152.03, 131.06, 118.04, 99.01, 89.91, 89.00, 86.11, 76.02, 60.01; ^{1}H-NMR ($CDCl_3$) 2.68 (m,4H), 3.87 (m,4H), 4.05 (s,4H); IR (KBr, cm^{-1}) 2957 s, 2922 s, 2889 s, 1585 s, 1539 s, 1500 s, 1473 s, 1435 m, 1387 m, 1295 s, 1255 s, 1190 m, 1029 m, 986 s, 948 s, 912 m, 811 s, 660 s, 645 s; exact mass M^+ = 223.436 (224.123 calcd. for $C_7H_{12}S_3O_2$).

3,6,8,10,13-pentathia-1-methylenecyclotetradecane (5)

A solution of 3,7-dithia-5-methyleneundecane-1,11-dithiol[4] (1.17 g, 5.0 mmol) and **2** (0.65 g, 5.0 mmol) in 75 mL DMF was slowly (20 h) added to a warm (55-60°C), vigorously stirred suspension of 2 equiv. of Cs_2CO_3 (3.26 g, 10.0 mmol) in 350 mL of DMF. The yellow mixture was filtered and the solvent was removed in vacuo leaving a yellowish oily residue. The filter cake was extracted repeatedly with chloroform. The combined chloroform layers were concentrated to provide a colorless oil. The combined

oil fractions were chromatographed over silica gel using toluene/dichloromethane (1:3) as eluent, yield 1.12 g of a light-yellow solid (3.75 mmol, 75 %). ^{1}H-NMR ($CDCl_3$) 2.73 (m,8H), 3.31 (s,4H), 3.98 (m,4H), 5.03 (s(br),2H); M/e$^+$ = 177.91, 164.90, 153.94, 152.94, 151.92, 147.94, 146.97, 145.98, 137.89, 123.91, 118.90, 117.93, 104.94, 98.91, 91.91, 86.00, 85.01, 77.91, 75.94, 60.85, 59.89; exact mass 223.436 (224.123 calcd. for $C_9H_{18}S_5$). IR (KBr, cm^{-1}) 3074 s, 3038 s, 2955 s, 2374 s, 2235 s, 1822 s, 1721 s, 1694 s, 1669 s, 1634 s, 1418 m, 1374 s, 1264 m, 1220 m, 1185 m, 1138 s, 1070 m, 953 s, 909 m, 881 s, 832 s, 702 m.

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