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BORIC ACID MEDIATED PREPARATION OF MESOCYCLIC THIOCROWN ETHERS CONTAINING XYLYLENE UNITS.MOLECULAR STRUCTURES OF 3,8-DIBENZO-1,6-DITHIACYCLODECANE AND 2,5,8-TRITHIA-(9)-p-BENZENOPHANE

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Abstract: Reaction of a dithiol with $B(OH)_3$ and base in MeOH followed by reaction with xylylene dibromides proceeds selectively to give the corresponding *ortho, meta* or *para*-cyclophanes in good yield (70-86 %). The syntheses of examples of all three types of benzenophanes are discussed. The molecular structures of 3,8-dibenzo-1,6-dithiacyclodecane (**8**) and 2,5,8-trithia-(9)-*p*-benzenophane (**5**) have been determined by X-ray crystallography. Crystal data for **8**: space group $P2_1/c$ with a=8.2745(10), b=4.9330(10), c=16.5500(12) A, β=100.37(1)°, Z=2; R=0.043 (R_w=0.045) for 949 reflections (I>2.5σ(I)). Crystal data for **5** (150K): Space group $P2_1/c$ with a=10.310(1), b=7.430(1), c=17.681(2) A, β=113.27(1)°, Z=4; R=0.065 (R_w=0.065) for 1969 reflections (I>2.5σ(I)).

Introduction

Macrocyclic compounds bearing multiple sulfide units are effective ligands for complexation of heavy metals including Hg, Ag or Cd[1-7]. This phenomenon opens the possibility of applying these thioethers in the extraction of such metals[8] resulting in interesting perspectives for environmental and medicinal chemistry.

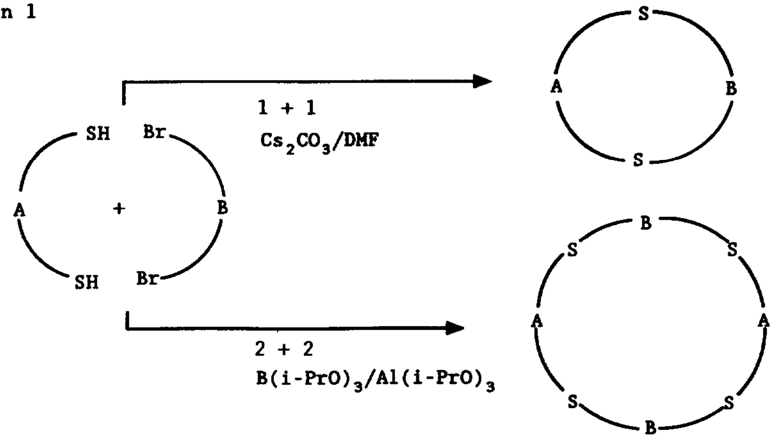
The availability of thiocrown ethers has been increased due to the development of more effective syntheses[1]. In particular, synthetic routes based on procedures involving free radicals[9], cesium[10], molybdenum[11] and $BF_3.Et_2O$[12] have allowed the isolation of a structurally large variety of thiocrown ethers.

In this paper we report a new, $B(OH)_3$ based cyclization reaction for the preparation of mesocyclic sulfides bearing rigid xylyl fragments.

Results and discussion

As illustrated in Equation 1, reaction of a dithiol with various dihalides under influence of cesium (in some instances potassium) carbonate gives rise to the formation of chiefly the 1+1 cyclic thioethers^{10}. On the other hand in the presence of $(i\text{-PrO})_3B/(i\text{-PrO})_3Al$ in some cases at least 2+2 coupled products are formed^{13a}. An advantage of these methods, in addition to the good yields, is their applicability in the presence of functional groups such as ketones and alkenes^{10,13}.

Equation 1



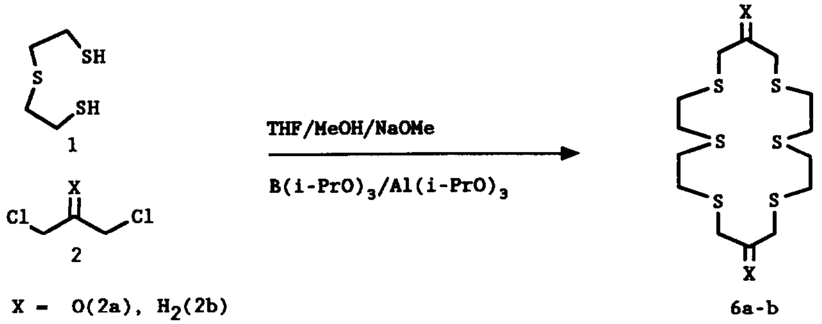
However, the scope of the 2+2 approach is rather narrow and seems limited to two- and three carbon building blocks. Reactions of 3-thiapentane-1,5-dithiol (**1**) with 1,3-dichloroacetone (**2a**) or 1,3-dibromopropane (**2b**) under influence of a 5:1 $(i\text{-PrO})_3B/(i\text{-PrO})_3Al$ mixture yielded 1,4,7,11,14,17-hexathia-3,13-diketoeicosane (**6a**) and 1,4,7,11,14,17-hexathiaeicosane (**6b**) respectively^{13a} (Equation 2); only traces (<5%) of the corresponding 1+1 products were present as a contaminant as was established by ^{1}H-NMR spectroscopy.

Reaction of the biscesium salt of **1** with **2b** in DMF^{10} gives exclusively the corresponding 1,5,8-trithia-3-ketocyclodecane (the 1+1 product).

Somewhat in contrast to the results described above reaction of **1** with *ortho*, *meta* and *para*-α,α'-xylylene dibromides, gave exclusively the S_3-cyclophanes (1+1 products) in reasonable yields (20-30%) using the B/Al alkoxo couple. The reaction was improved significantly upon employment of neat boric methoxide ($B(OH)_3$ in MeOH with NaOMe) as template reagent, raising the yields up to 50-85 %.

Although the mechanism of the reaction is unclear, reaction of **1** with

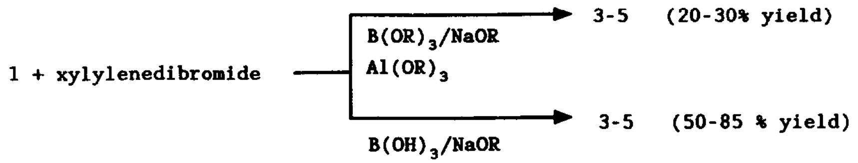
Equation 2

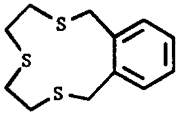


boric alkoxide (Equation 3) probably generates the thioborate[14] *in situ*.

The molecular structure of **5**, as determined by X-ray diffraction[15], is illustrated in Figure 1. The molecule consists of a nearly planar *p*-xylyl unit capped by the thioether fragment. The sulfur atoms are arranged anti and are directed exodentate with respect to the molecular cavity. The sulfur atoms S1 and S3 are slightly twisted with respect to each other, as is clear from the S3-xylyl and S1-xylyl torsion angles.

Equation 3





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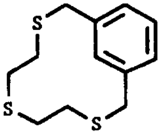

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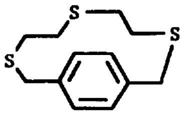


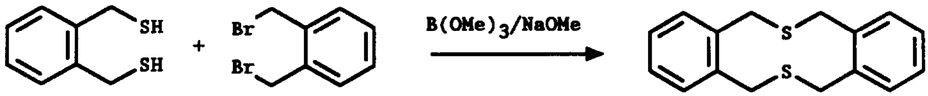
5

The reaction of *ortho*-α,α'-xylylene dibromide with dithiol **7** proceeded essentially in the same fashion as reaction with **1** leading to the formation of **8**[16a] in 73 % yield. Only minor quantities (<3 %) of the 2+2 product were formed.

The molecular structure of **8** is shown in Figure 2. The molecule[16b] is highly symmetrical and possesses an inversion center. The sulfur atoms adopt an overall anti-arrangement with respect to each other and point away from the molecular cavity. This arrangement is quite common and is found also for the substituted analogs of **8**[16d] and in many medium ring and macrocyclic thioethers containing S-C-C-S[1,4-7] and S-C-C-C-S linkages.

The torsional angles between the sulfur atoms and the plane defined by

Equation 4



7

8

the xylyl moiety attain rather large values (S'-C8'-C1a-C6=77.3(3), S-C7-C6-C1=138.2(3), C2-C1-C8a-S=74.5(3), C6-C1-C8'-S=-105.3 (3)°), reflecting the open character of the ligand and are comparable to the values found for a series of ring substituted derivatives of **8**[16d].

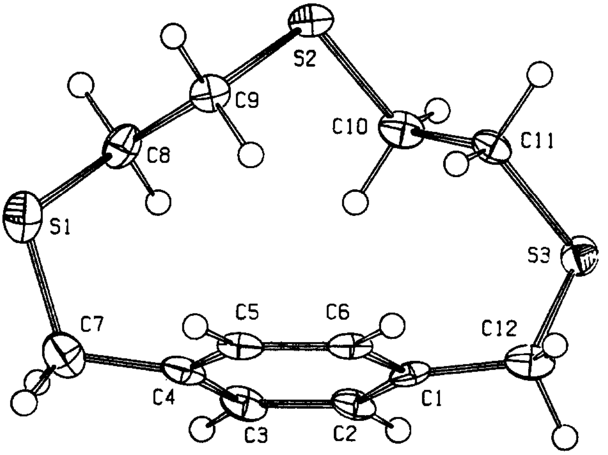


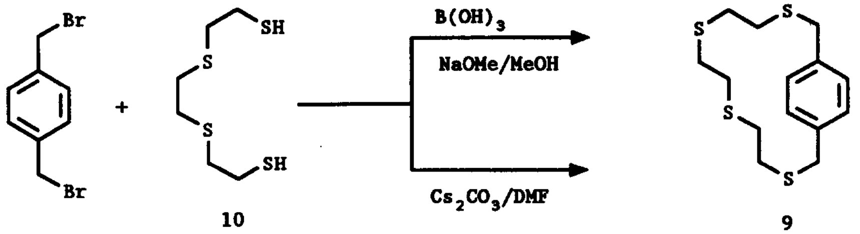
Figure 1. Thermal motion ellipsoid (50% probability) plot of **5**. Selected bond distances (A) and angles (°). S(1)-C(8)-C(9)-S(2)=-179.9(2), S(2)-C(10)-C(11)-S(3)=178.2(3), C(2)-C(1)-C(12)-S(3)=64.3(7), C(6)-C(1)-C(12)-S(3)=-111.3(5), C(3)-C(4)-C(7)-S(1)=113.2(6), S(1)-C(7)-C(4)-C(5)=62.5(7).

TABLE I Crystal data and Structural Analysis Results

Compound	(**8**)	(**5**)
Formula	$C_{16}H_{16}S_2$	$C_{12}H_{16}S_3$
M_w	272.43	256.46
space group	$P2_1/c$	$P2_1/c$
crystal system	monoclinic	monoclinic
Z	2	4
a (A)	8.2745(10)	10.310(1)
b (A)	4.9330(10)	7.430(1)
c (A)	16.5500(12)	17.681(2)
β (°)	100.37(1)	113.27(1)
V (A^3)	664.51(17)	1244.2(3)
D_{calc}, gcm^{-3}	1.3615	1.369
μ (cm^{-1})	3.6	5.4
radiation (MoKα,A)	0.71073	0.71073
T, K	298	150
R_F (R_w)	0.043 (0.045)	0.065 (0.060)

Reaction of para-α,α'-xylylene dibromide with 3,6-dithia-1,8-octanedithiol(**10**) produces the hitherto unknown S4-cyclophane (**9**) in 69 % yield in essentially the same fashion (Equation 5). The identity of **9** was established by comparison of the spectral data with those of a sample of

Equation 5



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9

9[17] prepared via the Cs-thiolate route. The exact molecular structure of **9** has not been established yet since suitable crystals for X-ray analysis of **9** have not yet been obtained.

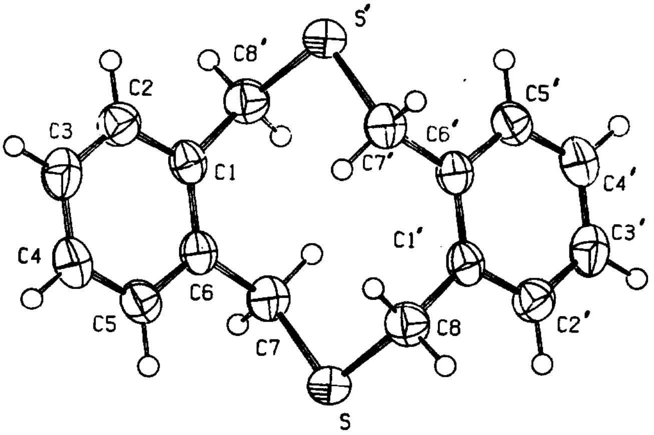

Figure 2. Thermal motion ellipsoid (50% probability) plot of **8**. Selected bond distances (A) and angles (°). S'-C8'-C1a-C6=77.3(3), S-C7-C6-C1=138.2(3), C2-C1-C8'-S=74.5(3), C6-C1-C8'-S=-105.3(3).

In summary, it may be noted that the new method described in this report is a useful alternative for the Cs-based preparation of thiocrown ethers that may be labile under the more basic reaction conditions with Cs_2CO_3 in DMF. This method is furthermore promising since the reactions do not require high dilution techniques or rather expensive cesium carbonate.

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Supplementary material available: Tables listing crystal structure data, structure factors, atomic positional parameters, anisotropic parameters, and complete bond distances for **5** and **8** are available from the Cambridge Crystallographic Data Center.

Experimental Section

All reactions were carried out under inert atmosphere. Solvents were dried and distilled according to standard procedures. Boric acid and 3-thia-1,5-pentanedithiol (**1**) were purchased from Aldrich and used as received. Xylylene dibromides were either purchased from Janssen Chimica or prepared according to methods described in Beilstein. ^{1}H-NMR(200 MHz) and ^{13}C-NMR(50.3 MHz) spectra were recorded on a Varian spectrometer. Infrared data were obtained from a Perkin-Elmer 781 spectrometer. Mass spectra were recorded on an AEI-MS902 mass spectrometer at 70 eV.

Preparation of 3,8-dibenzo-1,6-dithiacyclodecane (**8**) (Representative example). Sodium (0.46 g, 20 mmol) was dissolved in dry methanol. The solution was cooled to 10°C and dithiol (10 mmol) was introduced dropwise. After addition, the mixture was refluxed and stirred for 1.5 h. The solution was cooled to 20°C and boric acid (0.30 g, 5 mmol) was added portion-wise. The mixture was refluxed for 2h. whereafter the dihalide (10 mmol) was added within 3h. The refluxing was continued for 16 h after which the solvent was removed *in vacuo*. The residue was redissolved in CH_2Cl_2 and washed with water to remove the inorganic salts. The organic layer was evaporated and the residue was chromatographed over silica gel using CH_2Cl_2 as eluent; yield 67% of white crystals. ^{1}H-NMR($CDCl_3$) 3.46 (s,8H), 7.23(m,4H,AB system), 7.55(m,4H,AB system); anal. calcd. (found) for $C_{16}H_{16}S_2$: S 23.54(23.52), H 5.92 (5.81), C 70.54(70.82); mass spectrum (M/e) 271.91, 167.91, 134.99, 104.04, 90.97; HRMS M/e$^+$=272.068 (calcd for $C_{16}H_{16}S_2$ 272.069).

2,5,8-trithia-(9)-o-benzenophane (**2**)

Yield 71%; ^{1}H-NMR($CDCl_3$) 2.66(m,8H,AB system), 3.91(s,4H), 7.42(m,4H); ^{13}C-NMR($CDCl_3$) 31.84(t), 32.11(t), 32.25(d), 127.26(d), 130.25(d), 136.93 (s); anal. calcd. (found) for $C_{12}H_{16}S_3$: S 37.51(37.59), H 6.19 (6.23), C

56.20(56.13); mass spectrum (M/e) 255.93, 195.95, 167.93, 137.01, 136.01, 118.92, 105.06, 104.03, 90.96; HRMS M/e$^+$=256.042 (calcd. for $C_{12}H_{16}S_3$ 256.041).

2,5,8-trithia-(9)-m-benzenophane (4)

Yield 73 %; ^{1}H-NMR($CDCl_3$) 2.26(m,4H,AB system), 2.39(m,4H,AB system), 3.79(s,4H), 7.03(s,1H), 7.43(m,3H); ^{13}C-NMR($CDCl_3$) 30.84(t), 30.95 (t), 35.51(d), 130.62(d), 130.71(d), 137.09(s); anal. calcd. (found) for $C_{12}H_{16}S_3$: S 37.51(37.59), H 6.19(6.23), C 56.20(56.13); mass spectrum (M/e) 255.95, 195.94, 167.93, 151.91, 137.01, 136.01, 120.94, 118.91, 105.03, 104.04, 90.96; HRMS M/e$^+$=256.041 (calcd. for $C_{12}H_{16}S_3$ 256.041).

2,5,8-trithia-(9)-p-benzenophane (3)

Yield 86 %; ^{1}H-NMR($CDCl_3$) 1.88(m,4H,AB system), 2.27(m,4H,AB system), 3.85(s,4H), 7.38(s,4H); ^{13}C-NMR($CDCl_3$) 30.70(t), 33.00(t), 36.27(t), 130.75(d), 136.10(s); anal. calcd. (found) for $C_{22}H_{16}S_3$: S 37.51 (37.64), H 6.19(6.34), C 56.20(55.96); mass spectrum (M/e) 256.77, 255.74, 135.97, 134.96, 120.90, 104.99, 103.99; HRMS M/e$^+$=256.041 (calcd. for $C_{12}H_{16}S_3$ 256.041).

2,5,8,11-tetrathia-(12)-p-benzenophane (9)

Yield 69 %; ^{1}H-NMR($CDCl_3$) 2.65(m,4H), 2.71(m,4H), 2.76(m,4H), 3.74(m, 4H), 7.27(s,4H); ^{13}C-NMR($CDCl_3$) 31.39(t), 32.31(t), 36.05(t), 43.86(t), 66.96(t), 129.08(d), 136.63(s); mass spectrum (M/e) 315.55, 256.68, 255.72, 216.90, 202.95, 196.92, 184.92; HRMS M/e$^+$=316.044 (calcd. for $C_{14}H_{20}S_4$ 316.044).

X-ray data collection and refinement (general)

All calculations were performed on a DEC-5000 system. Scattering factors were taken from Cromer and Mann[18] and data were corrected for anomalous dispersion (Cromer and Liberman[19]). Illustrations were done with PLATON[20].

X-ray data for (8) were collected on an ENRAF-NONIUS CAD4 (Mo-Kα, Zr-filtered) for a transparent colorless crystal. Unit cell dimensions were derived from the SET4 setting angles of 25 reflections in the range $8<\vartheta<18°$. A total of 2579 reflections were scanned and averaged in a unique set of 949 reflections with ($I>2.5\sigma(I)$). No decay was observed during data collection. The structure was solved with SHELXS86/TREF[21] and refined on F by full-matrix least-squares techniques (SHELX76)[22] to a final R=0.043. Hydrogen atoms were located at calculated positions (C-H=0.89 A) and refined with one isotropic thermal parameter. There was no residual electron density outside -0.22 and 0.22 eA^{-3}.

X-ray data for (3) were collected on an ENRAF-NONIUS CAD 4T/Rotating Anode (Mo-Kα, graphite monochromator, 150 K) for a transparent colorless crystal. Unit cell dimensions were derived from the SET4 setting angles of 25 reflections in the range $10<\theta<16°$. A total of 4196 reflections were scanned and averaged in a unique set of 1980 reflections with ($I>2.5\sigma(I)$). No decay was observed during data collection. The structure was solved with DIRDIF-92[23] and refined on F by full-matrix least-squares techniques (SHELX76)[22] to a final R=0.065. H-atoms were take into account at calculated positions (C-H=1.08 A) with one common isotropic temperature parameters. There was no residual electron density outside -0.55 and 0.55 eA^{-3}.

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