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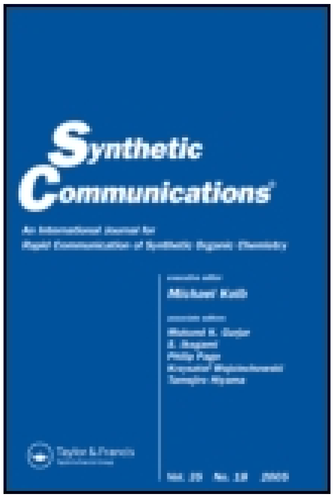

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A FACILE METHOD FOR THE SYNTHESIS OF BENZOTHIACROWN ETHER FORMYL DERIVATIVES

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A FACILE METHOD FOR THE SYNTHESIS OF BENZOTHIACROWN ETHER FORMYL DERIVATIVES

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ABSTRACT

A facile route to the formyl derivatives of benzothiacrown ethers with different combinations of O and S heteroatoms in the macrocycle involving ring closure reactions of substituted benzaldehydes with dithiols was developed. The effects of alkali metal cations and solvent were studied.

There exist lots of macrocycles containing one or more sulfur atoms including crown ethers,[1] cryptates,[2] cyclophanes,[3] and ligands of a definite shape.[4] Macrocyclic sulfur compounds present considerable interest due to their ability to bind selectively heavy and transition metal cation.[5] A wide range of macrocyclic polythioethers are known; they are prepared by the route developed by Ochrymowycs and coworkers.[6] The formation of macrocycles from thiolates was found to proceed in remarkably good yields

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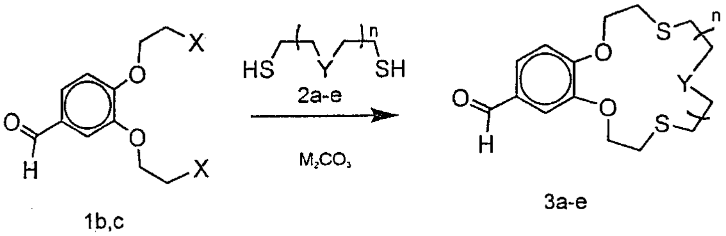
when cesium is used as the counterion in the nucleophile and DMF is used as the solvent.[7] However, only a few macrocyclic polythioethers have been prepared using another alkali metal cation to coordinate the sulfur atoms in the reaction of thiols with dihalides;[8] the template requirement has not been established.[9]

A number of O,S-mixed benzocrown ethers have been prepared.[10] Substitution is considered to be of great importance because it provides reactive sites for the attachment of other functions[11a–c] or polymer supports.[12] Syntheses of the substituted benzothiacrown ethers have not been well developed by now, although some of the possible methods have been presented in our publications. [13a,b] The methods described are multistep procedures relatively difficult to perform in practice (low temperatures, anhydrous solvents, inert atmosphere).

Here we propose a facile process for the preparation of macrocyclic benzopolythiacrown ethers. Compounds **3a–e** were obtained in 42–90% yields by refluxing substituted benzaldehydes **1b, c** and dithiols **2a–e** in organic or aqueous organic solvents in the presence of alkali metal carbonates (Scheme 1). The roles of the alkali metal cation and the solvent in the synthesis of the crown ethers **3a–e** were studied.

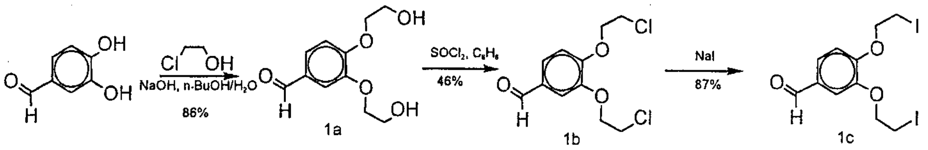
The dithiols **2a–c** required for the experiments were commercially available, compounds **2d, e** were prepared according to known methods. [14a,b] The substituted benzaldehyde **1b, c** were prepared according Scheme 2 (see Experimental).

The results obtained demonstrate that various organic solvents and their mixtures with water (organic solvent/water = 1/1) are suitable for the synthesis of the macrocycles **3a–e**. Thus the yields of **3c** in the condensation reaction between **1b** and **2c** in the presence of Cs_2CO_3 were: 61% ($EtOH/H_2O$); 88% (MeCN); 81% ($MeCN/H_2O$); 90% (DMF); and 90% (DMF/H_2O). The aliphatic components **2b–d** containing O and S atoms



1 : b, X = Cl; c, X = I; 2, 3: a, $n = 0$; b, Y = O, $n = 1$; c, Y = O, $n = 2$; d, Y = O, $n = 3$; e, Y = S, $n = 2$, M = Li, Na, K, Cs.

Scheme 1.



Scheme 2.

are reactive towards both dichloro (**1b**) and diiodo (**1c**) substituted benzaldehydes. However, aliphatic oxygen-free components **2a, e** are able to react only with diiodide **1c**.

All the alkali metal carbonates studied can be used effectively in the synthesis of the formyl derivatives of the benzothiacrown ethers. The Li^+, Na^+ and K^+ cations demonstrated the template effect, which implies that the yield of the product reaches its maximum when the cation perfectly fits into the cavity of the crown ether: **3b**—81% (Li^+); **3c**—75% (Na^+); **3d**—74% (K^+) (see Table 1).

In the presence of cesium carbonate, all the prepared compounds underwent successfully the ring-closure reaction; the yields of the products did not depend on the size or composition of the macrocycle formed, for instance, **3b**—61%, **3c**—61%, **3d**—53%, **3e**—68% (solvent $EtOH/H_2O$). As has been shown previously,[15] intramolecular cyclization does not involve the formation of template complex but occurs on the surface of the highly polarizable cesium ion. A detailed mechanistic study will be reported in full paper.

The methodology described herein provides an acceptable synthetic basis for the preparation of a large variety of sulfur-containing formyl derivatives of the benzocrown ethers otherwise difficulty accessible. A wide range of structural types have been prepared in this way in good to excellent yields.

Table 1. The Yield (in %) of **3a–e** in Reaction Condensation of **1b, c** with **2a–e** in $EtOH/H_2O$

Crown Ether	**3a** (From **1c**)	**3b** (From **1b**)	**3c** (From **1b**)	**3d** (From **1b**)	**3e** (From **1c**)
Li^+	42	81	69	58	62
Na^+	0	30	75	67	33
K^+	–	30	41	74	–
Cs^+	44	61	61	53	68

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer in $CDCl_3$ using tetramethylsilane as the internal standard. Chemical shifts were measured with an accuracy of 0.01 ppm and spin–spin coupling constants were determined with an accuracy of 0.1 Hz. Mass spectra were run on a Varian MAT 311A instrument at an ionization energy of 70 eV with direct sample injection into the ionization area. IR spectra were measured on Shimadzu IR-435 and Bruker IFS-113v spectrophotometers in thin films or in pellets with KBr. The reactions were monitored by TLC on DC-Alufolien Kieselgel 60 F_{254}, plates (Merck). Dehydration of DMF needed for the reactions was performed by distilling the solvent from BaO in vacuo. Commercial anhydrous ethanol (Aldrich), MeCN (Aldrich), 1,2-*bis*(2-hydroxyethoxy)benzene (Aldrich), and 3,4-dihydroxybenzaldehyde (Merck) were used.

3,4-*bis*(2-Hydroxyethoxy)benzaldehyde (1a). A solution of 2-chloroethanol (21.7 ml, 0.33 mol) in 60 ml of *n*-BuOH was added over a period of 1 h to a boiling solution of 3,4-dihydroxybenzaldehyde (15.0 g, 0.109 mol) and NaOH (13.2 g, 0.33 mol) in a mixture of 300 ml of *n*-BuOH and 25 ml of water. The reaction mixture was refluxed for an additional 12 h, the solvent was evaporated in vacuo, and the residue was chromatographed on a column with silica gel (Kieselgel 60, 0.063–0.100 mm, elution with benzene–EtOH, 20 : 1) to give 20.4 g of product **1a** (86%). ^{1}H NMR (500 MHz, $CDCl_3$–CCl_4) δ 2.79 (br, s, 2H, 2OH), 3.95 (m, 4H, $2\underline{CH_2}OH$), 4.19 (m, 4H, $2CH_2O$), 7.02 (d, 1H, H-6, $J = 8.1$ Hz), 7.45 (m, 2H, $\underline{\text{H-3}}$, H-5), 9.85 (s, 1H, CH=O); Anal. calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.13; H, 6.19.

3,4-*bis*(2-Chloroethoxy)benzaldehyde (1b). A solution of $SOCl_2$ (19.7 ml, 0.27 mol) in 30 ml of dry benzene was added with vigorous stirring over a period of 1 h to a boiling solution of **1a** (20.4 g, 0.09 mol) and anhydrous pyridine (21.8 ml, 0.27 mol) in 120 ml of anhydrous benzene. The reaction mixture was refluxed for 5 h and cooled, and 100 ml of 15% HCl was added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 50 ml). The extracts were combined, the solvent was evaporated in vacuo, and the residue was chromatographed on silica gel (Kieselgel 60, 0.063–0.200 mm, elution with benzene–$MeCO_2Et$, 10 : 1) to give 1.26 g of dichloride **1b** (53%). ^{1}H NMR (500 MHz, $CDCl_3$–CCl_4) δ 3.86 (m, 4H, $2CH_2Cl$), 4.35 (m, 4H, $2CH_2O$), 7.02 (d, 1H, H-6, $J =$ 8.1 Hz), 7.43 (s, 1H, H-3), 7.47 (d, 1H, H-5, $J = 8.1$ Hz), 9.85 (s, 1H, CH=O); Anal. calcd for $C_{11}H_{12}Cl_2O_3$: C, 50.21; H, 4.60. Found: C, 50.72; H, 4.61.

3,4-*bis*(2-Iodoethoxy)benzaldehyde (1c). A mixture of dichloride **1b** (5.8 g, 0.022 mol), anhydrous NaI (12.3 g, 0.082 mol), and 30 ml of anhydrous acetone was refluxed with vigorous stirring for 120 h. The precipitate was filtered off, the mother liquor was concentrated in vacuo, and the residue was dissolved in 50 ml of ethyl acetate and washed successively with 5% aqueous solutions of Na_2SO_3 and Na_2CO_3 and with water. The solvent was evaporated in vacuo and the residue was chromatographed on a column with silica gel (Kieselgel 60, 0.063–0.100 mm, elution with benzene–$MeCO_2Et$, 20 : 1) to give 8.3 g of diiodide **1c** (85%). ^{1}H NMR (500 MHz, $CDCl_3$–CCl_4): δ 3.49 (m, 4H, $2CH_2I$), 4.38 (m, 4H, $2CH_2O$), 7.00 (d, 1H, H-6, $J = 8.1$ Hz), 7.43 (s, 1H, H-3), 7.47 (d, 1H, H-5, $J = 8.1$ Hz), 9.86 (s, 1H, CH=O); Anal. calcd for $C_{11}H_{12}I_2O_3$: C, 29.62; H, 2.71. Found: C, 30.07; H, 2.69.

Preparation of crown compounds 3a–e (General procedure). At 75–85°C, solutions of dihalide **1b,c** (4.24 mmol) and dithiol **2a–e** (4.66 mmol), each in 10 ml of a solvent (EtOH/H_2O, MeCN, MeCN/H_2O, DMF, DMF/H_2O), were added simultaneously with stirring over a period of 1 h to a mixture of M_2CO_3 (M = Li, Na, K, Cs) (21.2 mmol) in 200 ml of a solvent. The reaction mixture was kept at the specified temperature for 13–20 h, the solvent was evaporated, 100 ml of water was added to the residue, and the products were extracted with a benzene–$CHCl_3$ mixture (10 : 1). The extracts were concentrated in vacuo and the residue was chromatographed on a column with silica gel (Kieselgel 60, 0.063–0.100 mm); the products were eluted successively with benzene and a benzene–$MeCO_2Et$ mixture (20 : 1).

3a: ^{1}H NMR: δ 2.98 (m, 4H, $2CH_2S$), 3.07 (s, 4H, $2CH_2S$), 4.42 (m, 4H, $2CH_2O$), 6.92 (d, 1H, H-6, $J = 8.1$ Hz), 7.36 (s, 1H, H-3), 7.47 (d, 1H, H-5, $J = 8.1$ Hz), 9.85 (s, 1H, CH=O); Anal. calcd for $C_{13}H_{16}O_3S_2$: C, 54.90; H, 5.67. Found: C, 54.78; H, 5.61; b) **3b**, **3c** were published in Ref. [13]; c) **3d:** ^{1}H NMR, δ 2.95 (m, 4H, $2CH_2S$), 3.05 (s, 4H, $2CH_2S$), 3.66 (m, 8H, $4CH_2O$), 3.78 (m, 4H, $2CH_2O$), 4.27 (m, 4H, $2CH_2O$), 6.96 (d, 1H, H-6, $J = 8.2$ Hz), 7.39 (s, 1H, H-3), 7.45 (d, 1H, H-5, $J = 8.2$ Hz), 9.85 (s, 1H, CH=O); Anal. calcd for $C_{19}H_{28}O_6S_2$: C, 54.78; H, 6.78. Found: C, 54.56; H, 6.81; d) **3e:** ^{1}H NMR δ 2.81–2.94 (m, 6H, $3CH_2S$), 2.97–3.15 (m, 10H, $5CH_2S$), 4.27–4.39 (m, 4H, $2CH_2O$), 6.98 (d, 1H, H-6, $J = 8.2$ Hz), 7.41 (s, 1H, H-3), 7.47 (d, 1H, H-5, $J = 8.2$ Hz), 9.86 (s, 1H, CH=O); Anal. calcd for $C_{17}H_{24}O_3S_4$: C, 50.46; H, 5.98. Found: C, 50.65; H, 6.04.

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