

Macrocycle opening in crown ethers. Synthesis of thiazapodands from 4'-formylbenzothiacrown ethers

Svetlana N. Dmitrieva, Marina V. Churakova, Artem I. Vedernikov, and Sergey P. Gromov*

Photochemistry Center of the Russian Academy of Sciences, 7A Novatorov str., Moscow 119421, Russia

E-mail: gromov@photonics.ru

Dedicated to Academician Professor Oleg N. Chupakhin on the occasion of his 70th birthday

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Abstract

A method for the synthesis of thiazapodands from 4'-formylbenzothiacrown ethers was developed. It involves nucleophilic regioselective cleavage of the macrocycle by heating with MeNH₂ and MeNH₃⁺Cl⁻.

Keywords: Macrocycle opening, formylbenzothiacrown ethers, methylamine, podands

Introduction

Crown compounds are capable of selective binding of metal ions, organic cations, and neutral molecules. This capability underlies the use of crown compounds as selective ligands for metal cations,¹ including fluorescent and photochromic ones,² for the extraction and separation of metal cations,³ for ion transport through membranes, in ion-selective electrodes,⁴ and so on.

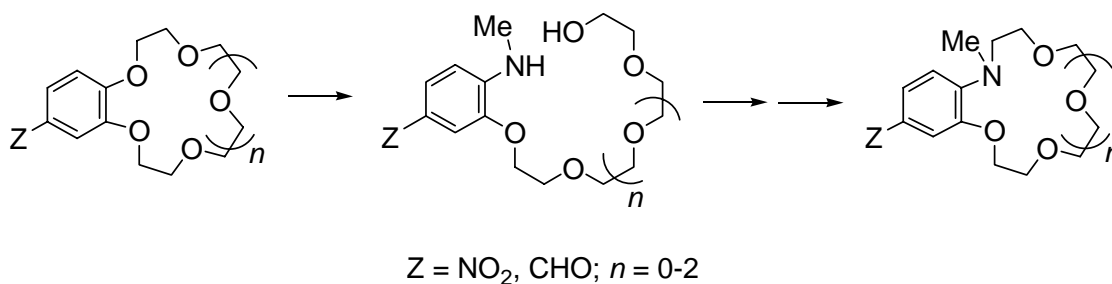
Currently, an intensive search for new types of crown compounds which are capable of efficient and selective complexation in various media is in progress. Crown compounds containing combinations of O-, N-, and S- atoms within the macrocycle attract steady interest, as they are able to form strong complexes with transition and heavy metal ions.⁵

The main approach to the synthesis of macroheterocyclic compounds is based on the reaction of two acyclic fragments (so-called, "1+1 condensation"). Other methods for the construction of macroheterocycles have been much less studied.

We have shown that the formyl- and nitro- derivatives of benzocrown ethers undergo nucleophilic opening of the macrocycle under the action of amines to give open-chain analogs of crown ethers (podands).⁶ The resulting podands were used for the synthesis of benzoazacrown

ethers whose macrocycle contains a nitrogen atom conjugated with the benzene ring⁷ (Scheme 1).

We are developing a new strategy for the synthesis of functional derivatives of azacrown ethers from the nitrogen-containing podands which are formed upon nucleophilic opening by amines of the macrocycle in the available crown ethers used as synthons. This strategy appears a promising alternative to the existing methods for the synthesis of 1-aza-2,3-benzocrown ethers.⁸



Scheme 1. Synthetic route to *N*-methylbenzoazacrown ethers.

Results and Discussion

In this work, we have studied the synthesis of a series of thiazapodands from 4'-formylbenzothiacrown ethers which have various combinations of O- and S- atoms in the macrocycle.

It was found that heating of the formylbenzothiacrown ethers **1a–e** with an ethanolic solution of MeNH₂ and MeNH₃⁺Cl⁻ followed by hydrolysis of the reaction mixture with dilute acid affords the podands **5a–e** in 39–90% yields (Scheme 2).

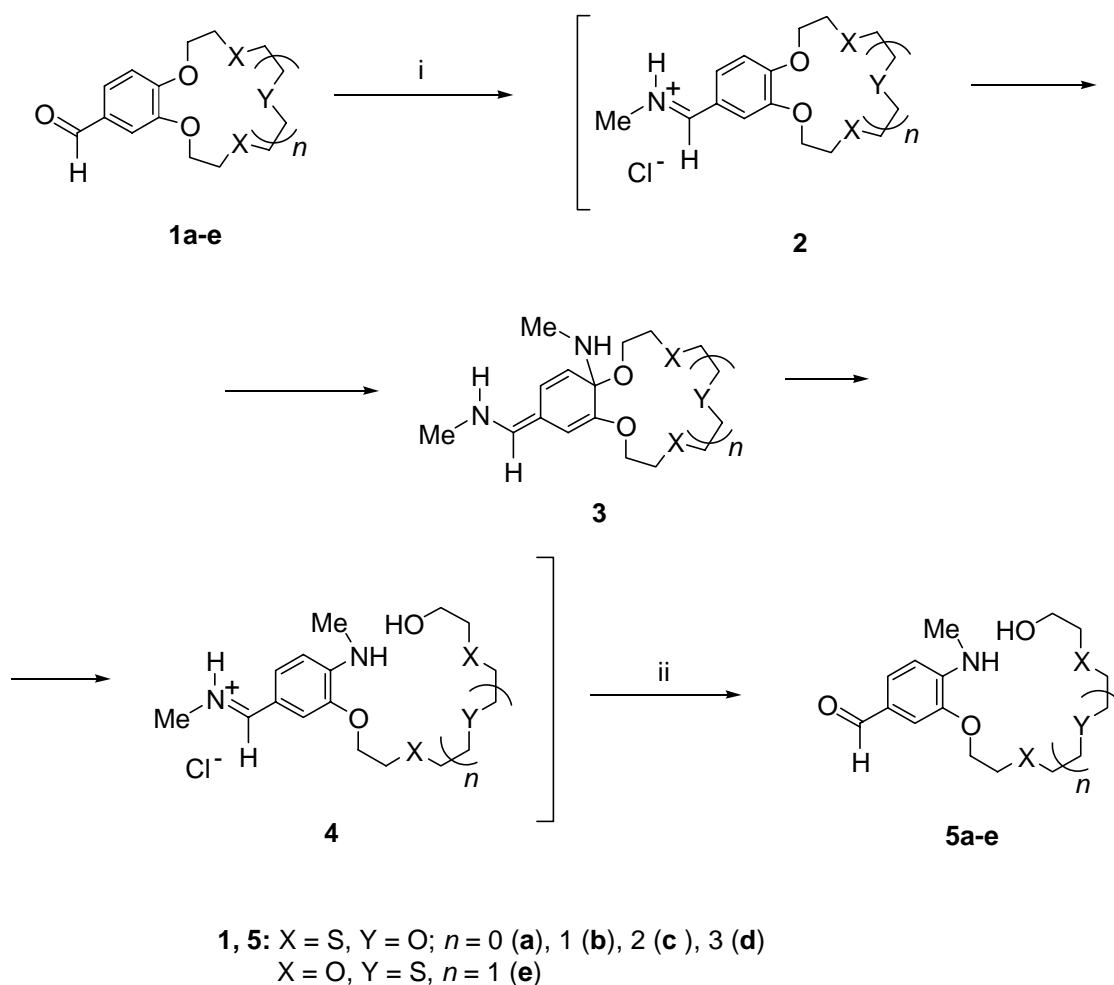
In our opinion, the reaction of methylamine or its hydrochloride with **1** initially gives the iminium derivative of the crown-containing benzaldehyde **2**, which is more activated toward nucleophilic substitution in the *para*- position than the starting compound. This is apparently followed by the addition of MeNH₂ to compound **2** to give σ - complex **3** and elimination of the alkoxy group to give podand **4**. Treatment of **4** with a dilute acid results in hydrolysis of the iminium group, giving rise to the target compounds **5a–e**.

It was found that the yields of the resulting thiazapodands **5a–e** depend on the size of the macrocycle in the initial benzothiacrown ethers, **1a–e**. The highest yields were observed for podands **5b,e** prepared from benzothia-15-crown-5 ethers **1b,e**. However, we found no substantial differences between the reactivities of compounds **1b** and **1e**. Upon a decrease or increase in the size of the benzothiacrown macrocycle in **1a,c,d** the yields of the podands **5a,c,d** diminish.

The structures of the resulting compounds were established by ^1H - and ^{13}C - NMR, IR spectroscopy, and mass spectrometry, including high-resolution mass spectrometry, and confirmed by elemental analysis data.

Conclusions

We have developed a method for the synthesis of thiazapodands based on the nucleophilic regioselective opening by methylamine of the macrocycle in readily available formyl derivatives of benzothia- and benzodithiacrown ethers. The resulting podands may prove promising starting compounds for the synthesis of new benzothiazacrown ethers containing a nitrogen atom conjugated with the benzene ring in the macrocycle.



Scheme 2. Reaction conditions: (i) $\text{MeNH}_3^+\text{Cl}^-$, $\text{MeNH}_2/\text{EtOH}$, sealed tube, 160°C , 120 h; (ii) 1.5% HBr , 25°C , 1 $^{\circ}\text{h}$.

Experimental Section

General Procedures. Melting points [$^{\circ}\text{C}$] were determined with a MEL-Temp II apparatus in a capillary and were not corrected. 1-D- ^1H - and ^{13}C - NMR spectra were recorded on a Bruker DRX500 instrument (500.13 and 125.76 MHz, respectively) in acetone- d_6 or CDCl_3 , using the solvent as internal reference (2.05 and 7.27 ppm for ^1H , and 29.83 and 77.00 ppm for ^{13}C , respectively) at 30°C ; 2D- homonuclear ^1H - ^1H COSY and heteronuclear ^1H - ^{13}C - COSY (HSQC and HMBC) spectra were used to assign the proton and carbon signals. IR spectra were recorded in film on a KBr glass or in KBr pellets on Shimadzu IR-470 and Bruker IFS-113V spectrophotometers. Mass spectra were measured on Varian MAT-311A and Finnigan MAT 8430 instruments, and high-resolution mass spectra were recorded on Finnigan MAT-8430 instrument (perfluoroparaffin as a standard) with direct sample inlet into the ionization zone; the energy of ionizing electrons was 70 eV. Elemental analyses were performed at the microanalytical laboratory of the A. N. Nesmeyanov Institute of Organoelement Compounds in Moscow, Russia. The course of the reactions was monitored by TLC on Merck DC-Alufolien Kieselgel 60 F₂₅₄ plates. Column chromatography was performed with Merck Kieselgel 60 (0.063–0.100 mm).

The starting formyl derivatives of benzothia- and benzodithiacrown ethers **1a–e** were prepared by known methods.⁹

Synthesis of thiazapodands 5a–e. A mixture of benzocrown ether **1a–e** (1 mmol), $\text{MeNH}_3^+\text{Cl}^-$ (10 mmol) and 10 ml of a 35% solution of MeNH_2 in anhydrous EtOH was heated in a sealed tube for 120 h at 160°C (oil bath). The tube was opened, the mixture was concentrated *in vacuo*, 35 ml of a 1.5% aqueous solution of HBr was added to the dry residue, and the mixture was left for 1 h. A 5% aqueous solution of KOH was added to bring the mixture to pH 12, and the reaction products were extracted with EtOAc. The extracts were concentrated *in vacuo* and the residue purified by column chromatography on SiO_2 . Compound **5a** was eluted with a benzene–EtOAc mixture, 5:1; compounds **5b,e** by a benzene–EtOH mixture, 20:1; and compounds **5c,d** by EtOAc.

3-[2-({2-[(2-Hydroxyethyl)sulfanyl]ethyl}sulfanyl)ethoxy]-4-(methylamino)benzaldehyde (5a). Yield 39%, mp $91\text{--}93^{\circ}\text{C}$. R_f 0.46 (C_6H_6 –EtOAc, 1:1). IR (KBr): ν [cm^{-1}] 3494, 3335 (NH, OH), 1655 (CH=O). ^1H NMR (CDCl_3): δ 2.66 (br. s, 1 H, OH), 2.74 (t, $J = 6.1$ Hz, 2 H, CH_2S), 2.79 (m, 4 H, 2 CH_2S), 2.93 (br. s, 3 H, MeN), 2.95 (t, $J = 6.7$ Hz, 2 H, CH_2S), 3.74 (t, $J = 6.1$ Hz, 2 H, CH_2O), 4.22 (t, $J = 6.7$ Hz, 2 H, CH_2OAr), 5.10 (br. s, 1 H, NH), 6.56 (d, $J = 7.9$ Hz, 1 H, H-5), 7.24 (d, $J = 1.2$ Hz, 1 H, H-2), 7.38 (dd, $J = 7.9$, $J = 1.2$ Hz, 1 H, H-6), 9.65 (s, 1 H, CH=O). ^{13}C NMR (CDCl_3): δ 29.53 (MeN), 31.20 (CH_2S), 32.04 (CH_2S), 32.63 (CH_2S), 35.19 (CH_2S), 60.95 (CH_2OH), 67.76 (CH_2OAr), 107.22 (C-5), 107.81 (C-2), 125.33 (C-1), 129.48 (C-6), 145.11 and 145.34 (C-3, C-4), 190.26 (CH=O). MS, m/z , %: 315 [M]⁺ (1), 165 (13), 137 (38), 109 (10), 105 (100), 103 (10), 94 (12), 87 (13), 61 (45), 59 (13), 58 (78). Anal. calcd. for $\text{C}_{14}\text{H}_{21}\text{NO}_3\text{S}_2$ (315.45): C, 53.30; H, 6.71; N, 4.44. Found: C, 53.22; H, 6.70; N, 4.21%.

3-2-[(2-{2-[(2-Hydroxyethyl)sulfanyl]ethoxyethyl)sulfanyl}ethoxy]-4-(methylamino)benzaldehyde

(5b). Yield 90%, yellow oil, R_f 0.55 (C₆H₆-EtOAc, 5:1). IR (KBr): ν [cm⁻¹] 3396 (NH, OH), 1663 (CH=O). ¹H NMR (acetone-d₆): δ 2.68 (t, J = 7.1 Hz, 2 H, CH₂S), 2.71 (t, J = 6.8 Hz, 2 H, CH₂S), 2.80 (t, J = 6.5 Hz, 2 H, CH₂S), 2.87 (br. s, 1 H, OH), 2.94 (d, J = 5.1 Hz, 3 H, MeN), 3.02 (t, J = 6.5 Hz, 2 H, CH₂S), 3.62 (t, J = 6.7 Hz, 2 H, CH₂O), 3.66 (br. t, J = 6.5 Hz, 4 H, 2 CH₂O), 4.27 (t, J = 6.6 Hz, 2 H, CH₂OAr), 5.70 (br. s, 1 H, NH), 6.64 (d, J = 8.1 Hz, 1 H, H-5), 7.27 (d, J = 1.4 Hz, 1 H, H-2), 7.43 (dd, J = 8.1, J = 1.4 Hz, 1 H, H-6), 9.68 (s, 1 H, CH=O). ¹³C-NMR (acetone-d₆): δ 29.55 (MeN), 31.79 (CH₂S), 31.99 (CH₂S), 32.24 (CH₂S), 35.53 (CH₂S), 62.25 (CH₂OH), 69.02 (CH₂OAr), 71.36 (CH₂O), 71.52 (CH₂O), 107.79 (C-5), 108.98 (C-2), 126.20 (C-1), 128.90 (C-6), 146.13 and 146.23 (C-3, C-4), 189.89 (CH=O). MS, m/z , %: 359 [M]⁺ (14), 343 (25), 209 (89), 181 (100), 178 (29), 150 (34), 149 (48), 109 (28), 105 (88), 87 (29), 61 (50). HRMS calcd. for C₁₆H₂₅NO₄S₂ [M]⁺ 359.1225. Found 359.1199.

3-[(14-Hydroxy-6,9-dioxa-3,12-dithiatetradecyl)oxy]-4-(methylamino)benzaldehyde (5c).

Yield 61%, yellow oil. R_f 0.55 (C₆H₆-EtOAc, 5:1). IR (KBr): ν [cm⁻¹] 3388 (NH, OH), 1663 (CH=O). ¹H NMR (acetone-d₆): δ 2.68 (t, J = 6.6 Hz, 2 H, CH₂S), 2.69 (t, J = 6.6 Hz, 2 H, CH₂S), 2.79 (t, J = 6.5 Hz, 2 H, CH₂S), 2.93 (d, J = 5.1 Hz, 3 H, MeN), 3.01 (t, J = 6.5 Hz, 2 H, CH₂CH₂OAr), 3.57 (m, 4 H, 2 CH₂O), 3.60 (t, J = 6.7 Hz, 2 H, CH₂O), 3.66 (t, J = 6.4 Hz, 2 H, CH₂O), 3.67 (t, J = 6.5 Hz, 2 H, CH₂O), 3.83 (br. s, 1 H, OH), 4.26 (t, J = 6.5 Hz, 2 H, CH₂OAr), 5.70 (br. q, 1 H, NH), 6.62 (d, J = 8.2 Hz, 1 H, H-5), 7.27 (d, J = 1.4 Hz, 1 H, H-2), 7.43 (dd, J = 8.2, J = 1.4 Hz, 1 H, H-6), 9.68 (s, 1 H, CH=O). ¹³C NMR (acetone-d₆): δ 29.76 (MeN), 31.92 (CH₂S), 32.13 (CH₂S), 32.38 (CH₂S), 35.70 (CH₂S), 62.37 (CH₂OH), 69.18 (CH₂OAr), 70.81 (CH₂O), 70.87 (CH₂O), 71.80 (CH₂O), 72.01 (CH₂O), 107.94 (C-5), 109.11 (C-2), 126.27 (C-1), 129.12 (C-6), 146.25 and 146.35 (C-3, C-4), 190.13 (CH=O). MS, m/z , %: 403 [M]⁺ (17), 372 (12), 255 (11), 254 (13), 253 (100), 225 (63), 149 (24), 105 (36), 87 (16), 61 (16). HRMS calcd. for C₁₈H₂₉NO₅S₂ [M]⁺ 403.1487. Found 403.1497.

3-[(17-Hydroxy-6,9,12-trioxa-3,15-dithiaheptadecyl)oxy]-4-(methylamino)benzaldehyde

(5d). Yield 49%, yellow oil. R_f 0.30 (EtOAc). IR (KBr): ν [cm⁻¹] 3391 (NH, OH), 1668 (CH=O). ¹H NMR (acetone-d₆): δ 2.69 (m, 4 H, 2 CH₂S), 2.80 (t, J = 6.5 Hz, 2 H, CH₂S), 2.93 (d, J = 5.1 Hz, 3 H, MeN), 3.02 (t, J = 6.5 Hz, 2 H, CH₂S), 3.56 (m, 4 H, 2 CH₂O), 3.58 (s, 4 H, 2 CH₂O), 3.60 (t, J = 6.8 Hz, 2 H, CH₂O), 3.67 (t, J = 6.5 Hz, 4 H, 2 CH₂O), 4.27 (t, J = 6.5 Hz, 2 H, CH₂OAr), 5.71 (br. q, 1 H, NH), 6.63 (d, J = 8.1 Hz, 1 H, H-5), 7.27 (br. s, 1 H, H-2), 7.43 (br. d, J = 8.1 Hz, 1 H, H-6), 9.68 (s, 1 H, CH=O). ¹³C NMR (acetone-d₆): δ 29.94 (MeN), 32.12 (CH₂S), 32.34 (CH₂S), 32.59 (CH₂S), 35.89 (CH₂S), 62.60 (CH₂OH), 69.45 (CH₂OAr), 71.05 (CH₂O), 71.12 (CH₂O), 71.34 (2 CH₂O), 72.06 (CH₂O), 72.26 (CH₂O), 108.15 (C-5), 109.37 (C-2), 126.53 (C-1), 129.26 (C-6), 146.50 and 146.59 (C-3, C-4), 190.29 (CH=O). MS, m/z , %: 447 [M]⁺ (13), 297 (100), 269 (36), 193 (25), 150 (31), 105 (87), 94 (14), 89 (16), 87 (21), 61 (38), 60 (18). HRMS calcd. for C₂₀H₃₃NO₆S₂ [M]⁺ 447.1749. Found 447.1753.

3-[2-(2-{2-(2-Hydroxyethoxy)ethyl}sulfanyl}ethoxy)ethoxy]-4-(methylamino)benzaldehyde

(5e). Yield 76%, yellow oil. R_f 0.41 (C₆H₆-EtOAc, 5:1). IR (KBr): ν [cm⁻¹] 3373 (NH, OH); 1670 (CH=O). ¹H NMR (acetone-d₆): δ 2.74 (t, J = 6.7 Hz, 2 H, CH₂S), 2.77 (t, J = 6.6 Hz, 2 H,

CH₂S), 2.85 (br. s, 1 H, OH), 2.93 (d, $J = 5.1$ Hz, 3 H, MeN), 3.51 (m, 2 H, CH₂O), 3.63 (m, 4 H, 2 CH₂O), 3.71 (t, $J = 6.6$ Hz, 2 H, CH₂O), 3.85 (m, 2 H, CH₂CH₂OAr), 4.22 (m, 2 H, CH₂OAr), 5.74 (br. s, 1 H, NH), 6.64 (d, $J = 8.1$ Hz, 1 H, H-5), 7.28 (d, $J = 1.4$ Hz, 1 H, H-2), 7.43 (dd, $J = 8.1, J = 1.4$ Hz, 1 H, H-6), 9.68 (s, 1 H, CH=O). ¹³C-NMR (acetone-d₆): δ 29.77 (MeN), 32.52 (2 CH₂S), 62.02 (CH₂OH), 69.15 (CH₂OAr), 69.85 (CH₂O), 71.90 (2 CH₂O), 73.23 (CH₂O), 108.02 (C-5), 109.60 (C-2), 126.46 (C-1), 129.16 (C-6), 146.64 and 146.68 (C-3, C-4), 190.09 (CH=O). MS, m/z , %: 343 [M]⁺ (100), 195 (64), 194 (44), 193 (73), 151 (63), 150 (71), 149 (59), 148 (41), 87 (49), 61 (45). HRMS calcd. for C₁₆H₂₅NO₅S, [M]⁺ 343.1453. Found 343.1455.

Acknowledgments

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