Synthesis of thiaazapodands from 4′-nitrobenzothiacrown ethers*

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A series of thiaazapodands were synthesized from 4′-nitrobenzothiacrown ethers by nucleophilic regioselective opening of the macrocycle on heating with methylamine in up to 94% yield.

Key words: crown compounds, nitrobenzothiacrown ethers, macrocyclic compounds, methylamine, podands, aromatic nucleophilic substitution.

Currently, particular interest in the macroheterocyclic chemistry is attracted by crown compounds containing various combinations of the O, N, and S atoms in the macrocycle,[1] because these compounds are capable of forming strong complexes with transition metal ions (see Ref. 2).

The major approach to the synthesis of macroheterocyclic compounds is based on the reaction of two acyclic fragments (so-called 1+1 condensation).[3—5] Other methods for construction of macrocycles are much less studied.

Previously, we showed that nitro derivatives of benzocrown ethers can undergo nucleophilic ring opening induced by methylamine to give podands (open-chain crown ether analogs).[6] The azapodands thus formed were used to synthesize nitrobenzoazacrown ethers with a nitrogen atom conjugated with the benzene ring in the macrocycle (Scheme 1).[7,8]

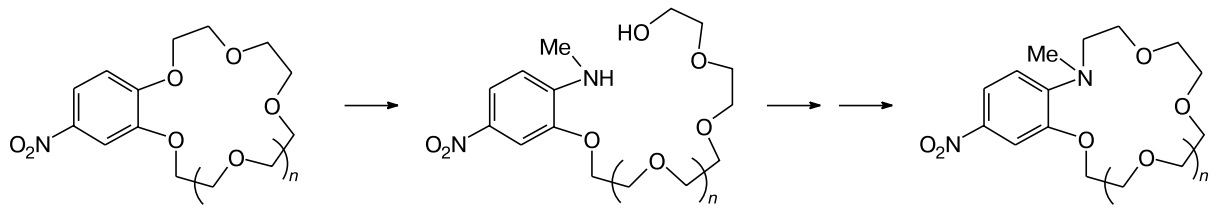
Azacrown compounds having this structure are of particular interest as starting compounds for the preparation of promising light-sensitive crown compounds. Meanwhile, 1-aza-2,3-benzocrown ethers remain a poorly studied type of crown ethers, most of their derivatives being hardly accessible despite the simple structure. The approach to the synthesis of benzoazacrown ethers that we develop appears a promising alternative to the existing methods.[9,10]

In this work we synthesized a series of thiaazapodands from 4′-nitrobenzothiacrown ethers with different macrocycle sizes and different combinations of O and S heteroatoms.

It was found that heating of nitrobenzothiacrown ethers **1a—e** with an ethanol solution of $MeNH_2$ affords podands **2a—e** in yields of up to 94% (Scheme 2, Table 1). Due to the high reactivity of compounds **1a—e**, though differing in macrocycle size, the number and combinations of O and S atoms, the yields of product **2a—e** are almost equal. The nucleophilic substitution in compounds **1a—e** involves the *para*-position relative to the nitro group. This was confirmed by NOE spectroscopy data for podand **2d**. The 2D spectrum of this compound exhibits intense cross-peaks between the methyl group protons and the benzene-ring H(3) proton and between the CH_2OAr methylene protons and the H(6) proton of the benzene ring.

The structures of the obtained compounds were determined by ^1H and ^{13}C NMR and IR spectroscopy and mass spectrometry.

Scheme 1



n = 0—2

* Dedicated to Academician V. A. Tartakovsky on his 75th birthday.

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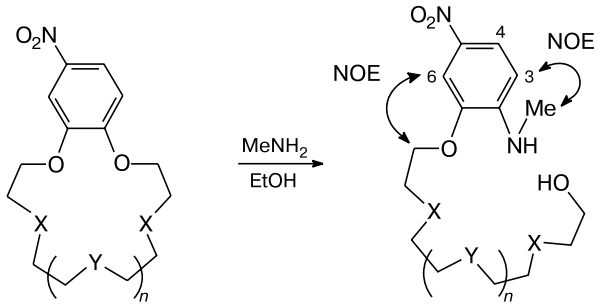
Scheme 2



1, 2: X = S, Y = O, *n* = 0 (**a**), 1 (**b**), 2 (**c**), 3 (**d**); X = O, Y = S, *n* = 1 (**e**)

In the conclusion, the method for the synthesis of azapodands we developed previously was successfully applied to nitro derivatives of benzothia- and benzodithiacrown ethers. The resulting polydentate thiaazapodands may serve as complexing agents for transition and heavy metal ions and as intermediates for the synthesis of various podands and benzothiaazacrown compounds containing a nitrogen atom conjugated to a chromophore.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer (500.13 and 125.76 MHz, respectively) in $CDCl_3$ using the solvent signals as the reference (7.27 ppm for ^{1}H and 77.00 ppm for ^{13}C). The ^{1}H and ^{13}C signals were assigned using 2D homonuclear ^{1}H—^{1}H COSY and NOE spectra and heteronuclear ^{1}H—^{13}C COSY (HSQC and HMBC) spectra. The chemical shifts were measured to an accuracy of 0.01 ppm and spin—spin coupling constants, to an accuracy of 0.1 Hz. Mass spectra were run on Varian MAT 311A and Finnigan MAT-212 instruments with direct sample inlet to the ion source, the ionizing energy was 70 or 60 eV, respectively. High-resolution mass spectra were recorded on a Finnigan MAT-212 instrument (perfluorokerosene as the standard) with direct sample inlet and an ionizing energy of 60 eV. IR spectra were recorded on a Bruker IFS-113v spectrophotmeter in KBr films.

Table 1. Characteristics of compounds **2a—e**

Compound	Yield (%)	R_f[a]	Molecular formula	$[M]^+$ Found / Calculated
2a	87	0.48	$C_{13}H_{20}N_2O_4S_2$	—[b]
2b	89	0.35	$C_{15}H_{24}N_2O_5S_2$	376.1125 / 376.1127
2c	89	0.20	$C_{17}H_{28}N_2O_6S_2$	420.1391 / 420.1389
2d	94	0.26	$C_{19}H_{32}N_2O_7S_2$	464.1656 / 464.1651
2e	94	0.23	$C_{15}H_{24}N_2O_6S$	360.1348 / 360.1355

[a] Elution with benzene—EtOAc (1 : 1) (**2a,b,c**) or EtOAc (**2d,e**).
[b] Found (%): C, 46.88; H, 6.28; N, 8.66. $C_{13}H_{20}N_2O_4S_2$. Calculated (%): C, 46.97; H, 6.06; N, 8.43.

Table 2. IR and ^{1}H NMR spectra of compounds **2a—e**

Compound	IR (KBr), ν/cm^{-1}	^{1}H NMR ($CDCl_3$), δ, *J*/Hz
2a	3411 (NH, OH); 1493, 1321 (NO_2)	2.18 (br.t, 1 H, OH); 2.79 (t, 2 H, CH_2S, *J* = 5.7); 2.84 (m, 4 H, 2 CH_2S); 2.99 (d, 3 H, MeN, *J* = 5.0); 3.01 (t, 2 H, CH_2S, *J* = 6.3); 3.77 (m, 2 H, CH_2O); 4.27 (t, 2 H, C$\underline{H_2}$OAr, *J* = 6.3); 5.19 (br.s, 1 H, NH); 6.51 (d, 1 H, H(3), *J* = 8.9); 7.64 (d, 1 H, H(6), *J* = 1.8); 7.95 (dd, 1 H, H(4), *J* = 8.9, *J* = 1.8)
2b	3412 (NH, OH); 1494, 1321 (NO_2)	2.47 (br.s, 1 H, OH); 2.76 (t, 2 H, CH_2S, *J* = 6.4); 2.78 (t, 2 H, CH_2S, *J* = 5.7); 2.82 (t, 2 H, CH_2S, *J* = 6.4); 2.98 (d, 3 H, MeN, *J* = 5.0); 3.04 (t, 2 H, CH_2S, *J* = 6.4); 3.67 (t, 2 H, CH_2O, *J* = 6.4); 3.71 (t, 2 H, CH_2O, *J* = 6.4); 3.75 (t, 2 H, CH_2O, *J* = 5.7); 4.27 (t, 2 H, C$\underline{H_2}$OAr, *J* = 6.4); 5.24 (br.s, 1 H, NH); 6.50 (d, 1 H, H(3), *J* = 9.1); 7.64 (d, 1 H, H(6), *J* = 2.3); 7.94 (dd, 1 H, H(4), *J* = 9.1, *J* = 2.3)
2c	3410 (NH, OH); 1494, 1321 (NO_2)	2.63 (br.s, 1 H, OH); 2.74 (t, 2 H, CH_2S, *J* = 6.1); 2.77 (t, 2 H, CH_2S, *J* = 5.7); 2.82 (t, 2 H, CH_2S, *J* = 6.4); 2.98 (br.s, 3 H, MeN); 3.03 (t, 2 H, CH_2S, *J* = 6.4); 3.65 (s, 4 H, 2 CH_2O); 3.66 (t, 2 H, CH_2O, *J* = 6.1); 3.72 (t, 2 H, CH_2O, *J* = 6.4); 3.74 (t, 2 H, CH_2O, *J* = 5.7); 4.27 (t, 2 H, C$\underline{H_2}$OAr, *J* = 6.4); 5.26 (br.s, 1 H, NH); 6.49 (d, 1 H, H(3), *J* = 8.8); 7.63 (d, 1 H, H(6), *J* = 2.3); 7.95 (dd, 1 H, H(4), *J* = 8.8, *J* = 2.3)
2d	3410 (NH, OH); 1495, 1322 (NO_2)	2.68 (br.s, 1 H, OH); 2.74 (t, 2 H, CH_2S, *J* = 6.4); 2.77 (t, 2 H, CH_2S, *J* = 5.9); 2.81 (t, 2 H, CH_2S, *J* = 6.6); 2.98 (d, 3 H, MeN, *J* = 5.0); 3.03 (t, 2 H, CH_2S, *J* = 6.4); 3.66 (m, 10 H, 5 CH_2O); 3.72 (t, 2 H, CH_2O, *J* = 6.6); 3.75 (t, 2 H, CH_2O, *J* = 5.9); 4.27 (t, 2 H, C$\underline{H_2}$OAr, *J* = 6.4); 5.25 (br.s, 1 H, NH); 6.49 (d, 1 H, H(3), *J* = 8.9); 7.63 (d, 1 H, H(6), *J* = 2.3); 7.95 (dd, 1 H, H(4), *J* = 8.9, *J* = 2.3)
2e	3400 (NH, OH); 1494, 1322 (NO_2)	2.43 (br.t, 1 H, OH); 2.79 (t, 2 H, CH_2S, *J* = 6.1); 2.83 (t, 2 H, CH_2S, *J* = 6.6); 2.96 (d, 3 H, MeN, *J* = 5.0); 3.58 (m, 2 H, CH_2O); 3.71 (t, 2 H, CH_2O, *J* = 6.1); 3.74 (t, 4 H, 2 CH_2O, *J* = 6.6); 3.86 (m, 2 H, C$\underline{H_2}$$CH_2$OAr); 4.22 (m, 2 H, C$\underline{H_2}$OAr); 5.52 (br.q, 1 H, NH); 6.48 (d, 1 H, H(3), *J* = 8.9); 7.64 (d, 1 H, H(6), *J* = 2.3); 7.94 (dd, 1 H, H(4), *J* = 8.9, *J* = 2.3)

Table 3. ^{13}C NMR and mass spectra of compounds **2a—e**

Compound	^{13}C NMR, δ	MS, m/z (I_{rel} (%))[a,b]
2a	29.64 (MeN); 30.26 (CH_2S); 32.01 (CH_2S); 32.77 (CH_2S); 35.40 (CH_2S); 60.84 (CH_2OH); 68.14 ($\underline{C}H_2OAr$); 105.98 (C(6)); 106.49 (C(3)), 120.40 (C(4)); 136.79 (C(5)); 143.83 (C(1)); 145.37 (C(2))	332 $[M]^+$ (8), 165 (43), 137 (67), 109 (49), 105 (100), 93 (47), 87 (45), 78 (46), 61 (58), 59 (42), 57 (46)
2b	29.63 (MeN); 31.54 (CH_2S); 31.63 (CH_2S); 32.09 (CH_2S); 35.89 (CH_2S); 60.89 (CH_2OH); 68.22 ($\underline{C}H_2OAr$); 70.81 (CH_2O); 70.96 (CH_2O); 105.97 (C(6)); 106.38 (C(3)), 120.35 (C(4)); 136.76 (C(5)); 143.91 (C(1)); 145.44 (C(2))	376 $[M]^+$ (10), 209 (88), 183 (12), 182 (13), 181 (100), 149 (25), 137 (13), 109 (34), 105 (35), 87 (13), 61 (46)
2c	29.66 (MeN); 31.49 (CH_2S); 31.63 (CH_2S); 32.04 (CH_2S); 35.99 (CH_2S); 60.93 (CH_2OH); 68.34 ($\underline{C}H_2OAr$); 70.32 (2 CH_2O); 71.18 (CH_2O); 71.39 (CH_2O); 106.02 (C(6)); 106.38 (C(3)); 120.36 (C(4)); 136.83 (C(5)); 143.96 (C(1)); 145.44 (C(2))	420 $[M]^+$ (12), 255 (25), 254 (28), 253 (100), 225 (93), 149 (44), 109 (27), 105 (94), 87 (49), 61 (92), 60 (29)
2d	29.60 (MeN); 31.39 (CH_2S); 31.51 (CH_2S); 31.93 (CH_2S); 35.80 (CH_2S); 60.93 (CH_2OH); 68.32 ($\underline{C}H_2OAr$); 70.25 (CH_2O); 70.32 (CH_2O); 70.46 (CH_2O); 70.49 (CH_2O); 71.17 (CH_2O); 71.28 (CH_2O), 105.96 (C(6)); 106.30 (C(3)); 120.30 (C(4)); 136.72 (C(5)); 143.91 (C(1)); 145.42 (C(2))	464 $[M]^+$ (8), 299 (12), 298 (20), 297 (97), 269 (31), 193 (13), 105 (100), 89 (28), 87 (34), 61 (51), 60 (17)
2e	29.56 (MeN); 31.95 (CH_2S); 32.08 (CH_2S); 61.71 (CH_2OH); 68.26 ($\underline{C}H_2OAr$); 69.07 (CH_2O); 70.95 (CH_2O); 70.99 (CH_2O); 72.08 (CH_2O); 106.30, 106.36 (C(3), C(6)); 120.44 (C(4)); 136.65 (C(5)); 144.15 (C(1)); 145.73 (C(2))	360 $[M]^+$ (49), 212 (45), 193 (100), 168 (30), 149 (30), 135 (18), 105 (21), 89 (17), 87 (26), 61 (25)

[a] Molecular ion peak and ten most intense peaks.
[b] The spectrum of **2a** was recorded at an ionizing energy of 70 eV and the other spectra were run at 60 eV.

The reactions were monitored by TLC on DC-Alufolien Kieselgel 60 F_{254} plates (Merck). Column chromatography was performed using silica gel (Kieselgel 60, 0.035—0.070 mm, Fluka). The melting point of compound **2a** was determined on a MEL-Temp II device in a capillary. Elemental analysis was done at the M. V. Lomonosov Moscow State Academy of Fine Chemical Technology.

The starting nitro benzothia- and benzodithiacrown ethers **1a—e** were prepared by known methods.[11]

Synthesis of podands 2a—e (general procedure). A mixture of nitrobenzothiacrown ether **1a—e** (0.5 mmol) and a 35% solution of $MeNH_2$ (5 mL) in anhydrous EtOH was heated for 25 h in a sealed tube at 130 °C (oil bath). Then the tube was opened, the reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography on SiO_2, with successive elution by benzene—EtOAc (5 : 1), benzene—EtOAc (1 : 1), and benzene—EtOH (5 : 1) mixtures. Compound **2a** was obtained as yellow crystals, m.p. 77—79 °C (hexane—CH_2Cl_2) and podands **2b—e** were yellow oils. The yields and characteristics of **2a—e** are summarized in Tables 1—3.

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