

## New Synthesis of Formylbenzoazacrown Ethers

S. N. Dmitrieva, O. V. Tikhonova, and S. P. Gromov

Photochemistry Center, Russian Academy of Sciences, ul. Novatorov 7A, Moscow, 119421 Russia  
e-mail: gromov@photonics.ru

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**Abstract**—A new procedure has been developed for the synthesis of formyl-substituted benzoazacrown ethers via cyclization of halogen derivatives of aza podands by the action of sodium hydride.

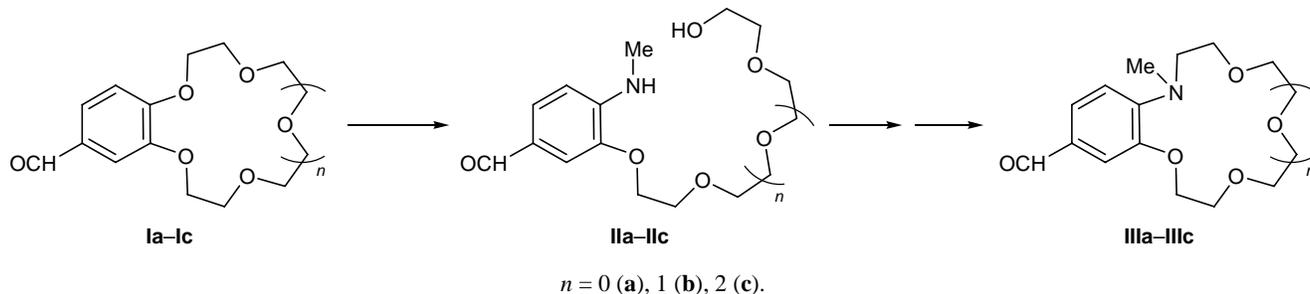
Crown compounds possess a unique ability to form stable complexes with metal ions, organic cations, and polar neutral molecules. Therefore, crown compounds attract attention of researchers in many fields of chemistry [1–11]. Extensive search for new crown compounds capable of effectively and selectively binding various species in different media is now in progress. From the viewpoint of using fragments of crown compounds as components of light-sensitive ligands, of specific interest are those derivatives in which a nitrogen atom is conjugated with a chromophore. Such ligands can be used as a basis for building up optical sensors for metal and ammonium ions, optical data storage systems, photocontrolled molecular devices, molecular machines for molecular electronics, carriers of metal cations for photocontrolled transport through membranes, etc. At present, derivatives of phenylazacrown ethers are used most widely for the above purposes. A strong disadvantage of these compounds is low complex formation constant with metal ions. In this respect, benzo-fused azacrown ethers may be considerably more advantageous.

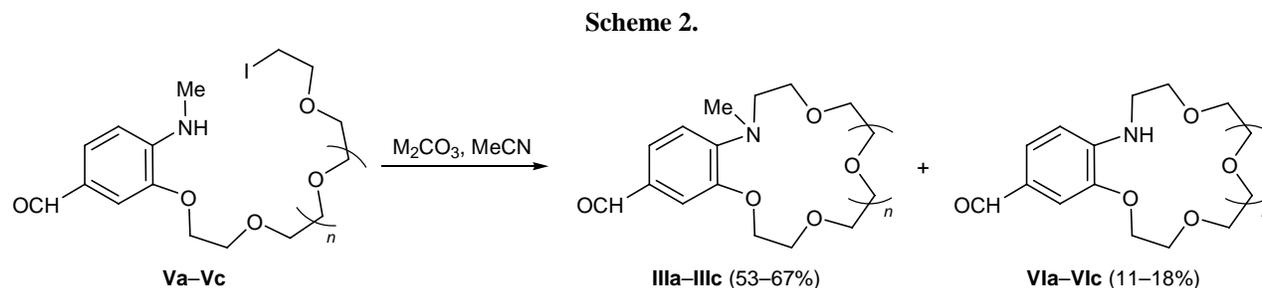
Until recently, the chemistry of 1-aza-2,3-benzo-crown ethers has poorly been developed due to dif-

iculties in their synthesis by condensation of two fragments and inaccessibility of podands necessary for intramolecular cyclization [12]. We proposed a new method for the synthesis of functionalized benzoazacrown ethers in which the nitrogen atom is conjugated with the benzene ring via stepwise transformations of readily accessible benzocrown ethers. The proposed method seems to be a promising alternative to the existing synthetic procedures [13].

Formyl-substituted derivatives of benzoazacrown ethers are the most promising for the synthesis of light-sensitive compounds (Scheme 1). We previously showed [14, 15] that heating of formylbenzocrown ethers **Ia–Ic** (which were prepared by known methods [16, 17]) with an alcoholic solution of MeNH<sub>2</sub> and MeNH<sub>3</sub><sup>+</sup>Cl<sup>−</sup> leads to formation of nitrogen-containing podands **IIa–IIc** in 66–80% yield. The cyclization of **IIa–IIc** to benzoazacrown ethers **IIIa–IIIc** was effected via replacement of the terminal hydroxy group in **IIa–IIc** by chlorine or iodine [18–20], i.e., readily departing groups. As a result, we obtained up to 97% of chloro and iodo derivatives **IVa–IVc** and **Va–Vc**. Iodo derivatives **Va–Vc** were brought into cyclization in the absence of a base and by the action of such weak

Scheme 1.





M = Li, Na, K, Rb, Cs;  $n = 0$  (a), 1 (b), 2 (c).

bases as alkali metal carbonates [18–20]. In the presence of weak bases, mixtures of benzoazacrown ethers **IIIa–IIIc** and **VIa–VIc** were formed, *N*-methyl derivatives **IIIa–IIIc** prevailing (Scheme 2). When the reaction was carried out in the absence of a base, compounds **VIa–VIc** were obtained as the major or only product [20].

Despite fairly high yields of target products **IIIa–IIIc** in the cyclization of iodides **Va–Vc** in the presence of alkali metal carbonates, a considerable disadvantage of this procedure is very long reaction time. Even after 150 h, the reaction was not complete. Further increase of the reaction time leads to appreciable loss in the yield of **IIIa–IIIc** (especially of 18-membered compound **IIIc**) because of strong tarring. Moreover, it is difficult to separate *N*-methyl derivatives **IIIa–IIIc** from their NH analogs **VIa–VIc** by chromatography.

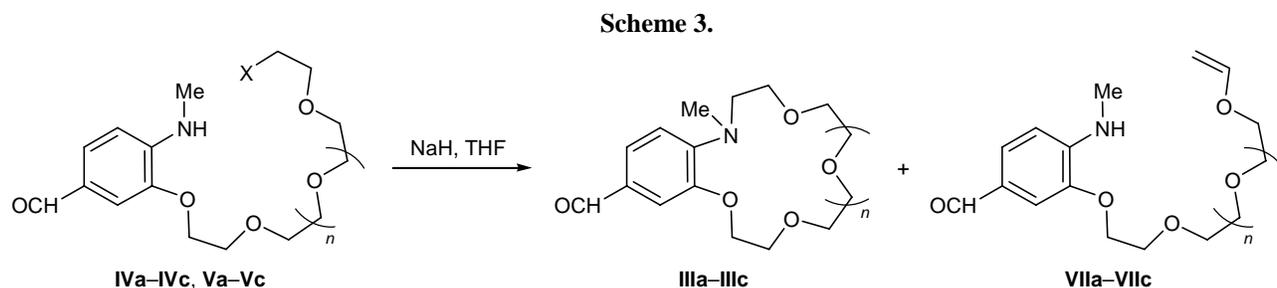
On the other hand, we showed that *N*-methylbenzoazacrown ethers **IIIa–IIIc** are clearly superior to widely used *N*-phenylazacrown ethers with the same size of the macroring [20, 21] in the complexing ability toward  $\text{Ca}^{2+}$  ions. Benzoazacrown ethers **IIIa–IIIc** may be promising from the viewpoint of synthesis of light-sensitive compounds on their basis. Therefore, we tried to find alternative synthetic routes to formyl derivatives of *N*-methylbenzoazacrown ethers. For this purpose, we examined the reactivity of chloro and iodoaza podands **IVa–IVc** and **Va–Vc** in the presence of

such strong bases as alkali metal hydroxides and sodium hydride (Scheme 3).

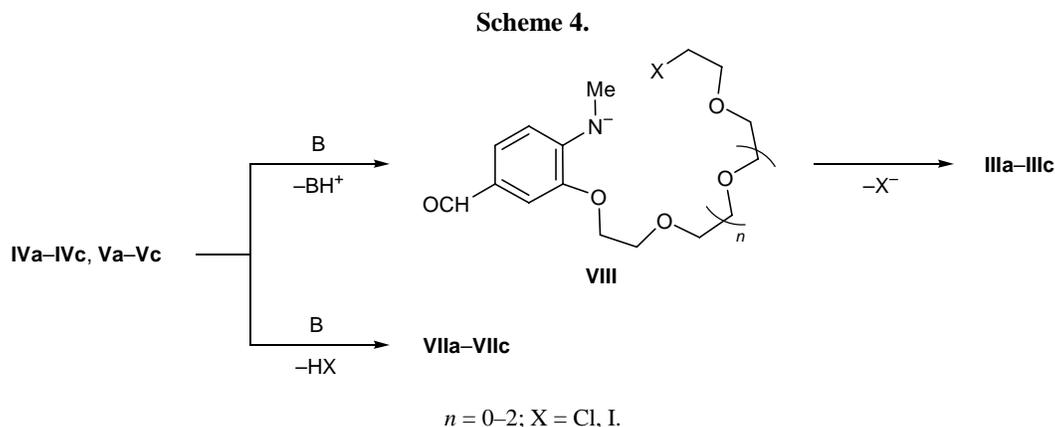
By reactions of compounds **IVa–IVc** and **Va–Vc** with alkali metal hydroxides in dioxane we obtained aldehydes **IIIa–IIIc** in a considerably shorter time than in reactions with metal carbonates, but the yields of the target products were poor. The reaction was accompanied by elimination of hydrogen halide HX (X = Cl, I) from the initial halogen derivative to produce an appreciable amount of the corresponding vinyl ether **VIIa–VIIc**. The maximal yield (33%) was obtained in the synthesis of benzoazacrown ether **IIIb** from chloride **IVb**.

We succeeded in effecting cyclization of compounds **IVa–IVc** and **Va–Vc** and selectively obtaining *N*-methylbenzoazacrown ethers **IIIa–IIIc** in high yields and in short time by carrying out the reaction with sodium hydride in tetrahydrofuran (Scheme 3, see table). In this case, the reaction was also accompanied by formation of vinyl ethers **VIIa–VIIc**, but their fraction was much smaller than with the use of alkali metal hydroxides.

The cyclization of chloro derivatives **IVb** and **IVc** by the action of sodium hydride in anhydrous tetrahydrofuran on heating afforded *N*-methylbenzoazacrown ethers **IIIb** and **IIIc** in 59 and 27% yield (5.5 and 17 h, respectively). Compound **IVa** almost failed to react under analogous conditions: even after prolonged heating (100 h), the yield of **IIIa** was as low as



IV, X = Cl; V, X = I;  $n = 0$  (a), 1 (b), 2 (c).



5%. Iodides **Va–Vc** were thus converted into **IIIa–IIIc** in a much shorter time (0.5 h on heating), and the yields were fairly good (57–68%), regardless of the macroring size. Iodides **Va–Vc** underwent cyclization even at room temperature, but in this case the reaction time was longer, and the yields were lower (51–61%).

Our results suggest that the cyclization of halogen derivatives **IVa–IVc** and **Va–Vc** by the action of sodium hydride involves formation of reactive arylamide ion **VIII** (Scheme 4). This follows from the much shorter reaction time, as compared to the reaction with alkali metal carbonates in acetonitrile. As shown previously [20], in the latter case the cyclization occurs via intramolecular N-alkylation with formation of macrocyclic ammonium salt. The yields of vinyl ethers **VIIa–VIIc** depend only slightly on the length of the polyether chain, indicating intermolecular mechanism of hydrogen halide elimination; i.e., compounds **VIIa–VIIc** are formed directly from halides **IVa–IVc** and **Va–Vc** rather than via intramolecular transformation of anion **VIII**. The structure of the isolated compounds was determined on the basis of their  $^1\text{H}$  NMR, IR, and mass spectra (including high-resolution mass spectra).

Thus we have developed a new effective procedure for the synthesis of formyl-substituted *N*-methylbenzoazacrown ethers from halogen derivatives of aza podands by the action of sodium hydride. The procedure is advantageous due to good yields of the target products, short reaction time, and the possibility for preparing *N*-methylbenzoazacrown ether **IIIb** from chloro derivative **IVb** in a fewer number of steps.

#### EXPERIMENTAL

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 30°C on a Bruker DRX-500 spectrometer from solutions in  $\text{C}_6\text{D}_6$  or  $\text{CDCl}_3$  using the solvent as internal

reference. The chemical shifts were measured with an accuracy of  $\pm 0.01$  ppm, and coupling constants, with an accuracy of  $\pm 0.1$  Hz. The IR spectra were obtained on a Bruker IFS-113V spectrophotometer. The mass spectra were run on a Varian MAT-311A instrument, and the high-resolution mass spectra were recorded on a Finnigan MAT-8430 spectrometer using perfluorokerosene as reference (electron impact, 70 eV; direct sample admission into the ion source). Kieselgel 60 silica gel (0.063–0.100 mm, Merck) and  $\text{Al}_2\text{O}_3$  (0.063–0.200 mm, neutral, type E, Merck) were used for column chromatography. The progress of reactions was monitored by TLC on DC-Alufolien Kieselgel 60 F<sub>254</sub> plates (Merck).

#### Benzoazacrown ethers **IIIa–IIIc** and vinyl ethers **VIIa–VIIc** (general procedure). a.

Cyclization of halogen derivatives **IVa–IVc** and **Va–Vc** into formylbenzoazacrown ethers **IIIa–IIIc** and vinyl ethers **VIIa–VIIc** by the action of NaH in THF

Initial halide no.	Reaction time, <sup>a</sup> h	Yield (%)
<b>IVa</b>	100	<b>IIIa</b> (5), <sup>c,d</sup> <b>VIIa</b> (11), <sup>c,d</sup> <b>IVa</b> (9) <sup>d</sup>
<b>IVb</b>	5.5	<b>IIIb</b> (59), <b>VIIb</b> (16)
<b>IVc</b>	17	<b>IIIc</b> (27), <b>VIIc</b> (9)
<b>Va</b>	0.5	<b>IIIa</b> (68), <b>VIIa</b> (8)
	72 <sup>b</sup>	<b>IIIa</b> (61), <b>VIIa</b> (19)
<b>Vb</b>	0.5	<b>IIIb</b> (63), <b>VIIb</b> (10)
	24 <sup>b</sup>	<b>IIIb</b> (61), <b>VIIb</b> (13)
<b>Vc</b>	0.5	<b>IIIc</b> (57), <b>VIIc</b> (23)
	19 <sup>b</sup>	<b>IIIc</b> (51), <b>VIIc</b> (20)

<sup>a</sup> Heating under reflux.

<sup>b</sup> At room temperature.

<sup>c</sup> Calculated from the  $^1\text{H}$  NMR spectrum of a mixture of **IIIa**, **VIIa**, and **IVa**.

<sup>d</sup> Calculated on the reacted chloride **IVa**.

0.1 mmol of iodide **Va–Vc**, 7 ml of anhydrous THF, and 40 mg (1 mmol) of 60% NaH (in paraffin) was heated for 30 min under reflux with stirring. The mixture was cooled, diluted with water, and extracted with benzene. The extract was washed with water and evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel [successive elution with benzene–EtOAc (1:1) and EtOAc]. Benzoazacrown ethers **IIIa–IIIc** and vinyl ethers **VIIa–VIIc** were isolated as light yellow oily liquids; compounds **IIIa** and **IIIb** crystallized on storage. The yields are given in table.

*b.* A mixture of 0.1 mmol of iodide **Va–Vc**, 7 ml of anhydrous THF, and 40 mg (1 mmol) of 60% NaH (in paraffin) was stirred for 3 days (**Va**), 24 h (**Vb**), or 19 h (**Vc**) at room temperature. The mixture was then treated as described above in *a*. The yields of products **IIIa–IIIc** and **VIIa–VIIc** are given in table.

*c.* A mixture of 0.1 mmol of chloride **IVb** or **IVc**, 7 ml of anhydrous THF, and 40 mg (1 mmol) of 60% NaH (in paraffin) was heated under reflux with stirring for 5.5 (**IVb**) or 17 h (**IVc**). The mixture was then treated as described above in *a*. The yields of **IIIb**, **IIIc**, **VIIb**, and **VIIc** are given in table.

**14-Methyl-6,7,9,10,13,14-hexahydro-12H-5,8,11-trioxa-14-azabenzocyclododecene-3-carbaldehyde (IIIa).** Yield 68% (*a*), mp 71–72°C (from hexane) [20],  $R_f$  0.38 (C<sub>6</sub>H<sub>6</sub>–AcOEt, 1:1).

**4-Methylamino-3-{2-[2-(vinylloxy)ethoxy]ethoxy}benzaldehyde (VIIa).** Yield 19% (*b*),  $R_f$  0.73 (C<sub>6</sub>H<sub>6</sub>–AcOEt, 1:1). Light yellow oily substance. IR spectrum (KBr),  $\nu$ , cm<sup>-1</sup>: 3392 (NH), 1671 (C=O). <sup>1</sup>H NMR spectrum (C<sub>6</sub>D<sub>6</sub>),  $\delta$ , ppm: 2.22 d (3H, MeN,  $J = 5.2$  Hz), 3.28 m (4H, CH<sub>2</sub>O), 3.48 m (2H, CH<sub>2</sub>CH<sub>2</sub>OAr), 3.60 m (2H, CH<sub>2</sub>OAr), 3.91 d.d (1H, OCH=CH-*cis*,  $J = 6.8, 1.9$  Hz), 4.12 d.d (1H, OCH=CH-*trans*,  $J = 14.3, 1.9$  Hz), 4.78 br.s (1H, NH), 6.21 d (1H, 5-H,  $J = 8.1$  Hz), 6.35 d.d (1H, OCH=CH<sub>2</sub>,  $J = 14.3, 6.8$  Hz), 7.22 d.d (1H, 6-H,  $J = 8.1, 1.4$  Hz), 7.40 d (1H, 2-H,  $J = 1.4$  Hz), 9.83 s (1H, CHO). Mass spectrum,  $m/z$  ( $I_{rel}$ , %): 265 (63) [M]<sup>+</sup>, 151 (83), 150 (100), 122 (40), 94 (50), 78 (40), 77 (45), 73 (68), 71 (67), 65 (42). High-resolution mass spectrum,  $m/z$ : Found: [M]<sup>+</sup> 265.1307. C<sub>14</sub>H<sub>19</sub>NO<sub>4</sub>. Calculated:  $M$  265.1314.

**17-Methyl-6,7,9,10,12,13,16,17-octahydro-15H-5,8,11,14-tetraoxa-17-azabenzocyclopentadecene-3-carbaldehyde (IIIb).** Yield 59% (*c*), mp 50–51°C (from hexane) [20],  $R_f$  0.34 (AcOEt).

**4-Methylamino-3-(2-[2-(vinylloxy)ethoxy]ethoxy)benzaldehyde (VIIb).** Yield 16% (*c*),  $R_f$  0.75 (AcOEt). Light yellow oily substance. IR spectrum (KBr),  $\nu$ , cm<sup>-1</sup>: 3441, 3385 (NH); 1667 (C=O). <sup>1</sup>H NMR spectrum (C<sub>6</sub>D<sub>6</sub>),  $\delta$ , ppm: 2.25 d (3H, MeN,  $J = 5.2$  Hz), 3.34 m (8H, CH<sub>2</sub>O), 3.52 m (2H, CH<sub>2</sub>CH<sub>2</sub>OAr), 3.64 m (2H, CH<sub>2</sub>OAr), 3.91 d.d (1H, OCH=CH-*cis*,  $J = 6.8, 1.8$  Hz), 4.12 d.d (1H, OCH=CH-*trans*,  $J = 14.3, 1.8$  Hz), 4.85 br.s (1H, NH), 6.21 d (1H, 5-H,  $J = 8.0$  Hz), 6.37 d.d (1H, OCH=CH<sub>2</sub>,  $J = 14.3, 6.8$  Hz), 7.22 br.d (1H, 6-H,  $J = 8.0$  Hz), 7.42 br.s (1H, 2-H), 9.83 s (1H, CHO). Mass spectrum,  $m/z$  ( $I_{rel}$ , %): 309 (24) [M]<sup>+</sup>, 283 (41), 162 (31), 150 (81), 149 (79), 88 (61), 73 (32), 71 (57), 58 (100), 57 (38). High-resolution mass spectrum,  $m/z$ : Found: [M]<sup>+</sup> 309.1589. C<sub>16</sub>H<sub>23</sub>NO<sub>5</sub>. Calculated:  $M$  309.1576.

**20-Methyl-6,7,9,10,12,13,15,16,19,20-decahydro-18H-5,8,11,14,17-pentaoxa-20-azabenzocyclooctadecene-3-carbaldehyde (IIIc).** Yield 57% (*a*),  $R_f$  0.15 (AcOEt). Light yellow oily substance. <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>),  $\delta$ , ppm: 3.02 s (3H, MeN), 3.59 t (2H, CH<sub>2</sub>N,  $J = 6.0$  Hz), 3.62–3.68 m (8H, CH<sub>2</sub>O), 3.71 m (4H, CH<sub>2</sub>O), 3.83 t (2H, CH<sub>2</sub>CH<sub>2</sub>N,  $J = 6.0$  Hz), 3.93 m (2H, CH<sub>2</sub>CH<sub>2</sub>OAr), 4.21 m (2H, CH<sub>2</sub>OAr), 6.85 d (1H, 1-H,  $J = 8.2$  Hz), 7.32 d (1H, 4-H,  $J = 1.7$  Hz), 7.37 d.d (1H, 2-H,  $J = 8.2, 1.7$  Hz), 9.76 s (1H, CHO) [20].

**4-Methylamino-3-(3,6,9,12-tetraoxa-13-tetra-decenyloxy)benzaldehyde (VIIc).** Yield 23% (*a*),  $R_f$  0.54 (AcOEt). Light yellow oily substance. IR spectrum (KBr),  $\nu$ , cm<sup>-1</sup>: 3394 (NH), 1670 (C=O). <sup>1</sup>H NMR spectrum (C<sub>6</sub>D<sub>6</sub>),  $\delta$ , ppm: 2.27 d (3H, MeN,  $J = 5.2$  Hz), 3.34 m (4H, CH<sub>2</sub>O), 3.38 m (8H, CH<sub>2</sub>O), 3.53 m (2H, CH<sub>2</sub>CH<sub>2</sub>OAr), 3.65 m (2H, CH<sub>2</sub>OAr), 3.91 d.d (1H, OCH=CH-*cis*,  $J = 6.8, 1.9$  Hz), 4.13 d.d (1H, OCH=CH-*trans*,  $J = 14.3, 1.9$  Hz), 4.91 br.s (1H, NH), 6.22 d (1H, 5-H,  $J = 8.1$  Hz), 6.38 d.d (1H, OCH=CH<sub>2</sub>,  $J = 14.3, 6.8$  Hz), 7.22 d.d (1H, 6-H,  $J = 8.1, 1.4$  Hz), 7.42 d (1H, 2-H,  $J = 1.4$  Hz), 9.83 s (1H, CHO). Mass spectrum,  $m/z$  ( $I_{rel}$ , %): 353 (34) [M]<sup>+</sup>, 178 (28), 162 (28), 151 (100), 150 (94), 149 (27), 122 (28), 94 (32), 89 (32), 73 (32). High-resolution mass spectrum,  $m/z$ : Found: [M]<sup>+</sup> 353.1830. C<sub>18</sub>H<sub>27</sub>NO<sub>6</sub>. Calculated:  $M$  353.1838.

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