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New Method for the Synthesis of Azocrown Compounds Containing Oxygen, Nitrogen and Oxygen, or Sulfur Atoms in the Macroring

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A new method for the synthesis of azocrown ethers with different heteroatoms in macrocycle and of different size of molecular hole has been described. This method consists in reaction of 2,2′-difluoroazobenzene with diols, diamine, aminodiol and dithiol in the presence of base.

Key words: azocrown ethers, azoazacrown ethers, synthesis

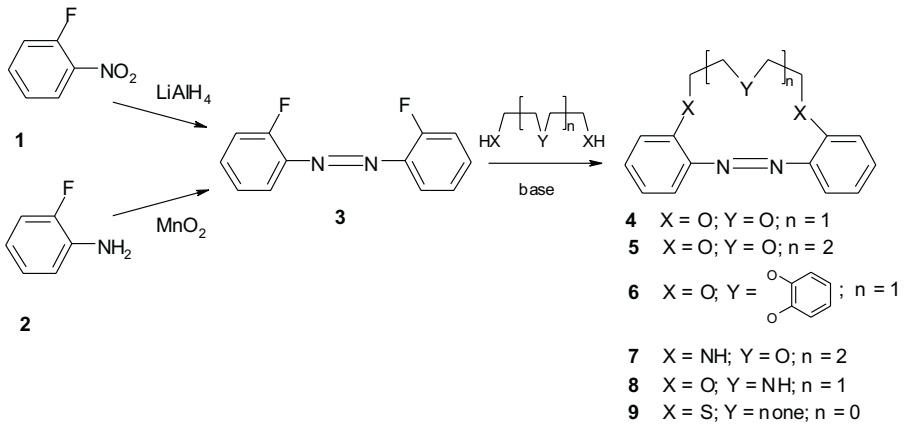
Many compounds are known belonging to crown ethers that selectively complex alkali and alkaline earth metal cations [1]. Some of them contain azo group among typical (poly)oxyethylene residue. 13- and 16-membered azocrown ethers were applied in ion-selective membrane electrodes, in which they play mainly the role of sodium or potassium carriers [2,3]. Insertion of azo group to crown ether macrocycle leads to electroactive compounds, able to photochemical isomerization [4]. These compounds show tendency to complex cations with utilizing nitrogen lone electron pair of azo group [5–8]. Reversible isomerization process could be used for construction of molecular switches or for optical memory storage [9].

At present, search is performed for compounds of high selectivity not only of alkali and alkaline earth cations, but also of transition metal cations. It is generally known, that the replacement of oxygen atoms in crown ethers by nitrogen or sulfur atom(s) causes an effective binding of transition or heavy metal cations [10]. First azocrown ethers with azobenzene unit in macrocycle were obtained by Shiga [11]. The synthesis was based on alkylation of 2,2′-dihydroxyazobenzene with dichloroethers or with the respective ditosylates in the presence of potassium *tert*-butoxide in anhydrous tetrahydrofuran.

Another method, leading to such compounds, consists in reduction of bis(2-nitrophenoxy)-oxaalkanes with sodium or potassium stannite [2,3,12]. By this procedure 10-, 13-, 16-, 20- and 26-membered azocrown ethers and their derivatives substituted in aromatic nuclei were obtained. The last method produces among azocrown ethers also the respective azoxy derivatives and other side products. Thus, isolation of the desired products is troublesome.

RESULTS AND DISCUSSION

The presented method enables the synthesis of azocrown ethers with different heteroatoms in macrocycle and of different size of the molecular hole. The azocrown ethers were prepared according to the following scheme:



The first step was the synthesis of the key 2,2′-difluoroazobenzene **3**. As reduction of 2-fluoronitrobenzene **1** with lithium aluminium hydride in ether solution [13] produces compound **3** with unsatisfactory yield, we applied a method consisting in oxidation of 2-fluoroaniline **2** with active manganese dioxide in benzene solution [14,15]. Compound **3** was subjected to reactions with diols, diamine, aminodiol and dithiol producing azocrown ethers **4–9**. Simultaneous substitution and macrocyclization reactions were performed in the presence of potassium *tert*-butoxide, sodium hydride or potassium carbonate in anhydrous tetrahydrofuran or dimethylformamide. Azocrown ethers **7–9** up to date were not described. As $Z \rightleftarrows E$ isomerization of the obtained compounds occurs fast, chromatography (TLC) always shows two spots corresponding to both isomers. Synthesis of compound **5** was performed in the presence of different bases to reveal their effect on macrocyclization. As large concentration of substrates in reactions leading to macrocycles favor polymeric products, reactions were performed at rather low concentrations. The method described enables synthesis of azocrown ethers of different size and with different heteroatoms in macrocycle with the use of one starting material. The number of side products in this synthesis is smaller as compared with other methods. The yield of compounds **4–6** in relation to other methods is slightly higher.

EXPERIMENTAL

General. All reagents and solvents used were of analytical grade. Silica gel 60 (Fluka) was used for column chromatography. Thin layer chromatography was performed on Alufolien or on preparative glass plates covered with Silica gel 60 F_{254} (Merck). Active manganese dioxide (~85%) was from Aldrich. ^{1}H

NMR spectra were recorded on Varian apparatus at 200 or 500 MHz. Mass spectra (EI) were taken on AMD-604 spectrometer.

Synthesis of 2,2′-difluoroazobenzene (3). Method 1 [13]. To an ice-cooled solution of 5 g 2-fluoronitrobenzene **1** (36 mmol) in 30 mL of dry ethyl ether was added gradually 72 mL of 0.5 mol/dm^3 $LiAlH_4$ solution in ethyl ether with vigorous stirring. When the reaction mixture turned brown it was gently warmed for 1 h and left overnight at room temperature. Then 6 mL water was carefully added and the reaction mixture was filtered, and the solid washed with ethyl ether. The organic solution was evaporated and the product was isolated by column chromatography using hexane and finally hexane/methylene chloride (1:1) mixture. After removal of the solvents, a crystalline red-orange product was obtained. Yield 0.77 g (20%). M.p. 95–97°C; (Lit. 71°C [13]; 102°C [14] or 97–98°C [15]). ^{1}H NMR [$CDCl_3$], δ [ppm]: 7.20–7.33 (4H, m); 7.45–7.53 (2H, m); 7.82 (2H, dt, J_1 = 8.0 Hz, J_2 = 1.8 Hz).

Method 2 [14,15]. A mixture of 2-fluoroaniline **2** (5 g; 45 mmol) and dried active manganese dioxide (16 g) in 250 mL benzene was refluxed for 3 h while water formed was removed with a Dean-Stark water separator. The hot solution was filtered and the manganese dioxide washed with benzene until the filtrate was colorless. The filtrate was evaporated to a small volume, and the residue crystallized from ethanol affording 2.65 g (54%) of azo compound **3** as orange-red crystals. Mp. 100–101°C (isomer *trans*) (Lit. 71°C [13], 102°C [14] and 97–98°C [15]).

Synthesis of macrocyclic azo compounds.

1,2-Azo-3,4,12,13-dibenzo-5,8,11-trioxacyclotridecane (4). To diethylene glycol (0.3 g; 2.8 mmol) a solution of potassium *tert*-butoxide (6.5 mmol) in 30 mL dry tetrahydrofuran was gradually added. After 0.5 h 2,2′-difluoroazobenzene **3** (0.5 g; 2.3 mmol) in a small amount of THF was added and the mixture was heated at 60–65°C for 24 h. Then the mixture was filtered, the solid washed with THF, and the filtrate was evaporated. The residue was diluted with water and the product was three times extracted with chloroform. The combined extracts were evaporated and purified on column using hexane/methylene chloride (1:1) at the beginning and methylene chloride/acetone (10:1) at the end.

Compounds **5–9** were obtained analogously from azocompound **3**. In some cases, the solvent and the base used were changed. Details concerning the syntheses are summarized in Table 1.

Table 1. Summary of the syntheses of azocrown ethers.

Compound	Amount of compound **3** [mmol]	Amount of $HXCH_2(CH_2YCH_2)_nCH_2XH$ [mmol]	Amount of base [mmol]	Solvent	Temperature//time [°C]/[h]	Yield %
4	2.3	Diethylene glycol 2.8	KO-*t*-Bu 6.5	THF	60–65/24	21
5 method a)	2.3	Triethylene glycol 3.3	KO-*t*-Bu 6.5	THF	60/27	26
5 method b)	2.3	Triethylene glycol 3.3	NaH 6.5	THF	60/27	20
6	2.3	1,2-Bis(hydroxyethoxy)-benzene 2.9	KO-*t*-Bu 6.2	THF	65/48	46
7	4.6	1,5-Diamino-3-oxapentane 5.5	K_2CO_3 5.5	DMF	105/26	10
8	2.3	Diethanolamine 2.9	KO-*t*-Bu 6.2	THF	65/29	30
9	2.3	Ethanedithiol 3.5	NaH 7	THF	65/27	7

Isolation of compounds 4–9.

1,2-Azo-3,4,12,13-dibenzo-5,8,11-trioxacyclotridecane (4). The preliminary-isolated product was purified again on column chromatography using methylene chloride/acetone (10:1) mixture. The residue obtained by evaporation of the eluate was crystallized from hexane. Yield 0.14 g (21%) of red crystalline compound, mp. 68–71°C; lit. 69–71°C [11], 70–72°C for isomer *trans* [5]. This compound is identical with an original sample [5].

1,2-Azo-3,4,15,16-dibenzo-5,8,11,14-tetraoxacyclohexadecane (5).

Method a). The respective fraction was rechromatographed using methylene chloride/acetone (4:1) mixture. The crude product was crystallized from *iso*-butyl acetate yielding 0.195 g (26%) of orange-red crystals. M.p. 67–68°C; lit. 67–68°C [6]. This compound by TLC and ^{1}H NMR is identical with original sample.

Method b). In the case of compound **5** isolation was also performed by crystallization of a complex [6]. A mixture of 138 mg of 16-membered azocrown and 70 mg potassium iodide was dissolved in 9 mL 2-propanol and 4 mL methanol. Excess of salt was removed and the solution was evaporated to dryness. The residue was crystallized from a mixture of acetone with tracer amount of 2-propanol. Overall yield 20%; m.p. 198–199°C.

1,2-Azo-3,4,9,10,15,16-tribenzo-5,8,11,14-tetraoxacyclohexadecane (6). Separation was achieved by column chromatography using methylene chloride/acetone (20:1) mixture as an eluent. The main fraction contains *trans* isomer (0.393 g; 46%). M.p. 127–129 °C; lit. 128–129°C [16]. ^{1}H NMR [$CDCl_3$], δ [ppm]: 4.35–4.50 (8H, m); 6.85–6.97 (4H, m); 7.01–7.12 (4H, m); 7.32 (2H, dt, J_1 = 7.8 Hz, J_2 = 1.8 Hz); 7.58 (2H, dd, J_1 = 7.9 Hz, J_2 = 1.9 Hz). This compound by TLC and ^{1}H NMR is identical with original sample [16].

1,2-Azo-3,4,15,16-dibenzo-5,14-diaza-8,11-dioxacyclohexadecane (7). Rechromatography of the crude product on a column using hexane/metylene chloride (2:1 at the beginning, 1:1, and pure methylene chloride at the end) followed by preparative TLC afforded 0.15 g (10%) of a red oily product. ^{1}H NMR [$CDCl_3$], δ [ppm], for isomer *trans*: 3.45–3.54 (4H, m); 3.75 (4H; s); 3.82–3.91 (4H, m); 6.87 (4H, dt, J_1 = 8.1 Hz, J_2 = 1.2 Hz); 7.22–7.34 (2H, m); 7.78 (2H, dd, J_1 = 8.1 Hz, J_2 = 1.3 Hz). MS (EI): found m/z = 326; calcd. m/z = 326. HRMS: 326.17413, for $C_{18}H_{22}N_4O_2$ calculated 326.17428.

1,2-Azo-3,4,12,13-dibenzo-8-aza-5,11-dioxacyclotridecane (8). This compound was chromatographed using methylene chloride/methanol 8:1 as an eluent and then crystallized from methylene chloride/hexane or from 2-propanol. Yield 30%, m.p. 125–127°C (isomer *cis*). ^{1}H NMR [$CDCl_3$], δ [ppm]: 2.8–2.9 (2H, m); 2.95–3.05 (2H, m); 3.98–4.07 (2H, m); 4.1–4.2 (2H, m); 6.74 (2H, d, J = 7.3 Hz); 6.80 (2H, t, J = 7.6 Hz); 6.87 (2H, d, J = 8.3 Hz); 7.10 (2H, t, J = 7.3 Hz). MS (EI): found m/z = 283; calcd. m/z = 283. HRMS: 283.13298, for $C_{16}H_{17}N_3O_2$ calculated 283.13208.

1,2-Azo-3,4,9,10-dibenzo-5,8-dithiacyclodecane (9). This compound was isolated in a manner similar to compound **7** followed by preparative TLC in hexane/ethyl acetate 3:1 mixture. It was obtained 0.044 g (7%) of red oily product. ^{1}H NMR [$CDCl_3$], δ [ppm] for isomer *trans*: 3.36 (4H, s); 7.35 (2H, dt, J_1 = 7.6 Hz, J_2 = 1.5 Hz); 7.47 (2H, dt, J_1 = 7.5, J_2 = 1.5 Hz); 7.73 (2H, dd, J_1 = 7.8, J_2 = 1.5 Hz); 7.88 (2H, dd, J_1 = 7.8, J_2 = 1.5 Hz). MS (EI): found m/z = 272; requires m/z = 272. HRMS: 272.04387, for $C_{14}H_{12}N_2S_2$ calculated 272.04419.

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REFERENCES

1. Gokel G.W., "*Crown Ethers and Cryptands*", The Royal Society of Chemistry, 1991.
2. Luboch E., Biernat J.F., Simonov Yu.A. and Dvorkin A.A., *Tetrahedron*, **54**, 4977 (1998).
3. Luboch E., Biernat J.F., Muszalska E. and Bilewicz R., *Supramol. Chem*., **5**, 201 (1995).
4. Zawisza I., Bilewicz R., Luboch E. and Biernat J.F., *J. Electroanal. Chem*., **471**, 156 (1999).
5. Simonov Yu.A., Luboch E., Biernat J.F., Bolotina N.V. and Zavodnik V.E., *J. Incl. Phenom*., **28**, 17 (1997).
6. Skwierawska A., Luboch E., Biernat J.F., Kravtsov V.Ch., Simonov Yu.A., Dvorkin A.A. and Bel'skii V.K., *J. Incl. Phenom*., **31**, 71 (1998).
7. Luboch E., Biernat J.F., Kravtsov V.Ch. and Simonov Yu.A., *J. Incl. Phenom*., **31**, 109 (1998).

8. Luboch E., Biernat J.F., Simonow Yu.A., Kravtsov V.Ch. and Bel'skii V.K., *Supramol. Chem*., **11**, 109 (1999).
9. Liu Z.F., Hashimoto K. and Fujishima A., *Nature*, **47**, 658 (1990).
10. *Comprehensive Supramolecular Chemistry*, [J.-M. Lehn, J.L. Atwood, J.E.D. Davies, D.D. McNicol, F. Vögtle, Eds] *Pergamon, New York*, 1996; Vol. 1; [G.W. Gokel, Volume Ed], Bradshaw J.S., Izatt R.M., Bordunov A.V., Zhu C.Y., Hathaway J.K., p. 35.
11. Shiga M., Nakamura H. and Takagi M., *Bull. Chem. Soc. Jpn*., **57**, 412 (1984).
12. Biernat J.F., Luboch E., Cygan A., Simonov Yu.A., Dvorkin A.A., Muszalska E. and Bilewicz R., *Tetrahedron*, **48**, 4399 (1992).
13. Olah G., Palath A. and Kuhn J., *Acta Chim. Acad. Sci. Hung.*, **7**, 71 (1956).
14. Banthorpe D.V. and O'Sullivan M., *J. Chem. Soc. (B)*, 616 (1968).
15. Wheeler O.H. and Gonzalez D., *Tetrahedron*, **20**, 189 (1964).
16. Zawisza I., Bilewicz R., Luboch E. and Biernat J.F., *Supramol. Chem.,* **9**, 277 (1998).