ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 11, pp. 2079–2083. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © V.N. Glushko, L.I. Blokhina, N.Yu. Sadovskaya, L.A. Pevtsova, S.K. Belus', 2014, published in Zhurnal Obshchei Khimii, 2014, Vol. 84, No. 11, pp. 1780–1785.

Special Features of Preparing Benzoaza-12-crown-4 by Condensation of *o*-Aminophenol with Triethylene Glycol Dichloride

V. N. Glushko, L. I. Blokhina, N. Yu. Sadovskaya, L. A. Pevtsova, and S. K. Belus'

Scientific-Research Institute of Chemical Reagents and High Pure Chemical Substances "IREA,"
Bogorodskii val 3, Moscow, 107076 Russia
e-mail: tetrazoli@yandex.ru

Received May 29, 2014

Abstract—Preparative method of benzoaza-12-crown-4 preparation via condensation of *o*-aminophenol with trietylene glycol dichloride using sodium hydroxide as the template agent has been studied at elevated temperature in 2-propanol and *n*-butanol. Kinetics of the reaction mixture composition change in the course of the process has been investigated by GLC. Performing the reaction in 2-propanol leads to a higher yield of benzoaza-12-crown-4.

Keywords: crown ether, benzoaza-12-crown-4, condensation, template synthesis, *o*-aminophenol, triethylene glycol dichloride

DOI: 10.1134/S107036321411005X

Pedersen's discovery of synthetic macrocyclic compounds such as crown ethers capable of the *host-guest* complexes formation with metal ions in the 1970th is recognized as foundation of supramolecular chemistry, a branch of science dealing with formation of supramolecular systems via non-covalent intermolecular interactions [1]. Crown ethers form a vast special class of compounds due to ability of metal cations insertion in their cavity enhanced by many of heteroatoms in the macrocycle and orientation of the lone-electron pairs inside the ring [2, 3].

Nowadays crown ether-based supramolecular systems are widely used in sorption and selective catalysis, biology, medicine, and pharmaceutical applications. They are also considered the most promising candidates for extraction of radioactive wastes during their utilization [4].

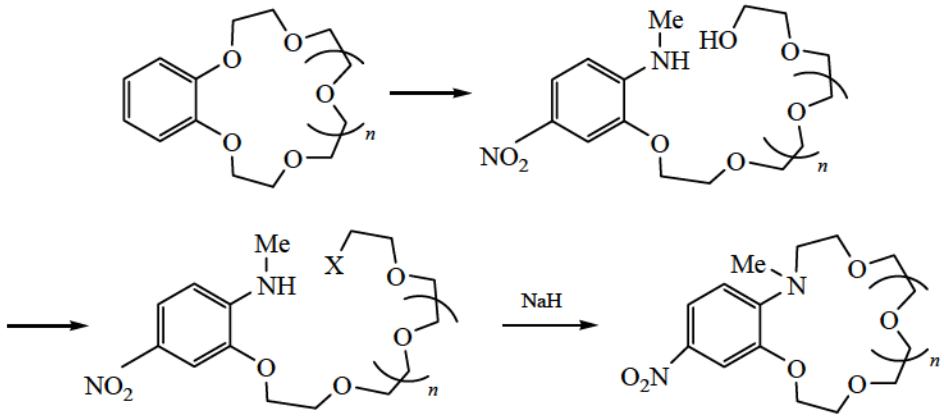
Partial substitution of oxygen atoms with nitrogen ones leads to significant change of the complexing properties of these compounds because aza-group is more rigid, with the lone-electron pair strictly orienttated inside the ring.

Aza-crown compounds exhibit affinity to "soft" cations (those of heavy and transition metals). They are important building blocks of various light-sensitive molecular devices [5–9]. Those of them containing a nitrogen atom of macrocycle conjugated with chromophore as of special interest. Such aza-crown compounds are promising for photometry and fluorescence analysis applications [10], light-induced extraction and the transmembrane ions transportation [11]. Due to synthetic complications accompanying the benzoaza-crown esters preparation, their *N*-phenylaza-analogs are better available, but the complexes of the latter are less stable that these of the corresponding benzoaza-crown compounds.

Chemistry of benzoaza-crown esters has been scarcely studied so far. Preparation of aza-crown compounds from *o*-aminophenol and various polyethylene glycol dichlorides, the latter taken in the ten-fold excess, via stirring in aqueous medium during 48 h was reported in 1973 [12]. The reaction resulted in formation of either of morpholine or aza-crown ether, but the reaction conditions were not reported in detail. Further, benzoaza–crown ethers were synthesized from their oxygen-containing analogs via stepwise transformation according to the following scheme [10, 13] (Scheme 1).

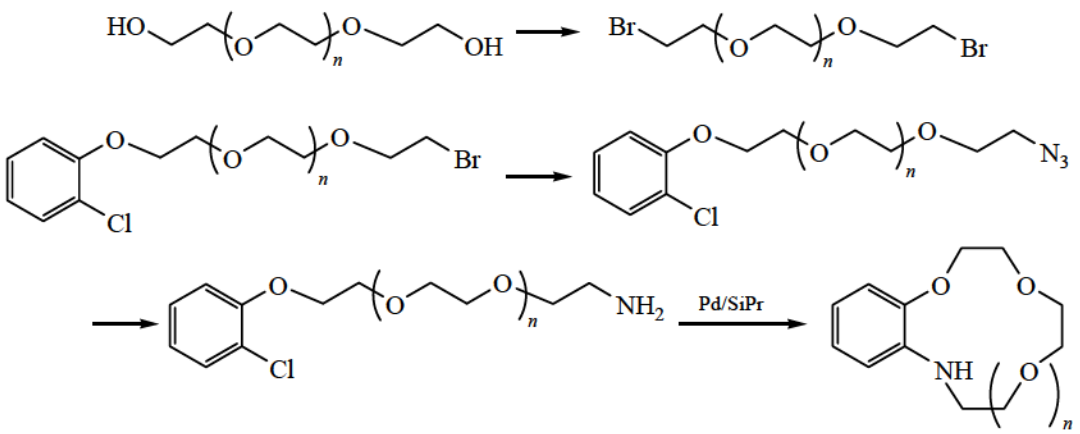
Synthetic protocol for preparation of benzoaza-crown ethers via condensation of *o*-aminophenol with

Scheme 1.

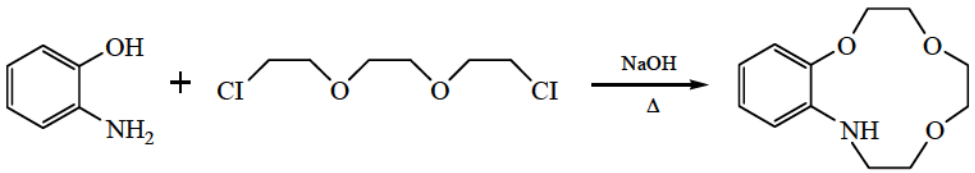


X = Cl, I.

Scheme 2.



Scheme 3.



I

polyethylene glycol ditosylates in the presence of CsF was described in [14].

Preparation of aza-crown ethers from 2-chlorophenol and triethyleneglycol dibromide using palladium catalyst is known [15] (Scheme 2).

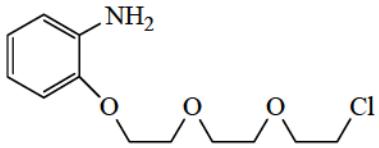
The latter synthesis was performed in micro scale using phosphorus tribromide to obtain triethylene glycol dibromide and sodium azide at the stage of the amine formation. The key stage of cyclization of benzoaza-12-crown-6 proceeded during 26 h. Pd/SIPr [SIPr stands for *N,N*-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidine] was used as catalyst.

Significant drawbacks of all the above-presented methods are high price of the starting substances, long synthesis, and low yield of the target product. That is why it was of practical importance to study kinetics of a scalable method for preparation of benzoaza-crown ethers (benzoaza-12-crown-4 was used as a model) via condensation of *o*-aminophenol with triethylene glycol dichloride taking advantage of the template synthesis.

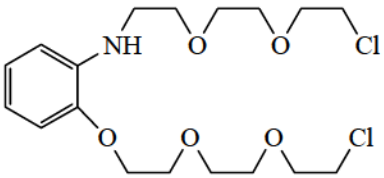
The synthesis of benzoaza-12-crown-4 **I** was based on condensation of *o*-aminophenol with triethylene glycol dichloride using sodium hydroxide as the template agent. 2-Propanol and *n*-butanol were used as solvents (Scheme 3).

In order to elucidate kinetic features of benzoaza-12-crown-4 formation, the reaction mixture was periodically sampled, and the specimen was treated with ethanolic hydrogen chloride solution to stop the reaction (pH 3–4).

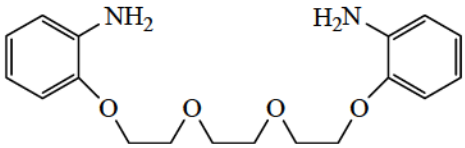
The reaction products were identified by chromato-mass spectrometry. Structures of some of the products identified in the mixtures are given below.



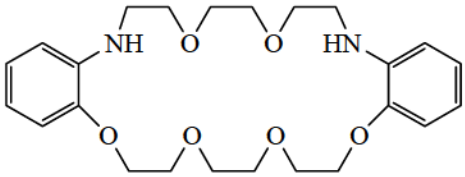
II, *m*/*z* 259.



III, *m*/*z* 409.



IV, *m*/*z* 332.



V, *m*/*z* 446.

To elaborate the optimal reaction conditions (in particular, duration), the sampled reaction mixture composition was studied with GLC (Fig. 1).

The results revealed that at the very beginning of the reaction, in the course of triethylene glycol dichloride addition to the sodium salt of *o*-aminophenol, the chlorine-containing product **II** was accumulated in the mixture. Formation of the product **II**

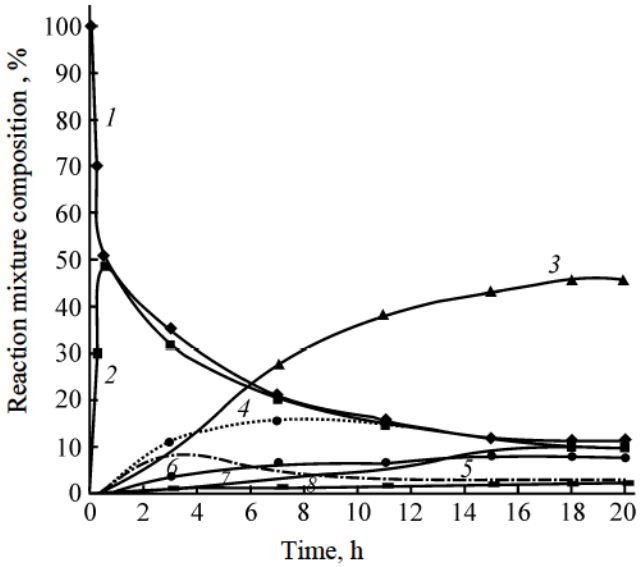


Fig. 1. Evolution of the reaction mixture composition with time. (*1*) *o*-aminophenol, (*2*) triethylene glycol dichloride, (*3*) benzoaza-12-crown-4, (*4*) 2-{2-[2-(2-chloroethoxy)-ethoxy]ethoxy}aniline, (*5*) 2,2'-{2,2'-[ethan-1,2-diylbis(oxy)]-bis[ethan-1,2-diylbis(oxy)]}dianiline, (*6*) etherification products, (*7*) 2{2-[2-(2-chloroethoxy)ethoxy]-*N*-{2-[2-(2-chloro-ethoxy)ethoxy]}aniline, and (*8*) dibenzoaza-24-crown-6.

was significantly faster as compared with formation of the target product, benzoaza-12-crown-4, and of other side products. After addition of triethylene glycol dichloride was complete, concentration of compound **II** continued to grow, and 8 h after the reaction start it reached the highest value of 16.1 wt %. Subsequent refluxing of the mixture was accompanied with monotonous decrease of the content of compound **II** to reach 10.3 wt %. Similar behavior was observed for product **IV**, its content in the reaction mixture reaching the highest value of 8.5 wt % after 3 h from the reaction start, and practically halved over the subsequent 13 h. Hence, the products **II** and **IV** were intermediates that underwent partial cyclization into benzoaza-12-crown-4 **I** and dibenzodiaza-24-crown-8 **V**, respectively.

Noteworthily, the reaction mixture contained another side product, 2{2-[2-(2-chloroethoxy)ethoxy]-*N*-{2-[2-(2-chloroethoxy)ethoxy]}aniline **III**. Its content increased steadily to reach 9.0 wt % by the end of the process. Besides, products of the reaction of 2-propanol with triethylene glycol dichloride and with compounds **II** and **III** were detected in the mixture, their final total amount was 3.2 wt %.

Hence, after 18 h of the reaction the mixture contained the target product, benzoaza-12-crown-4

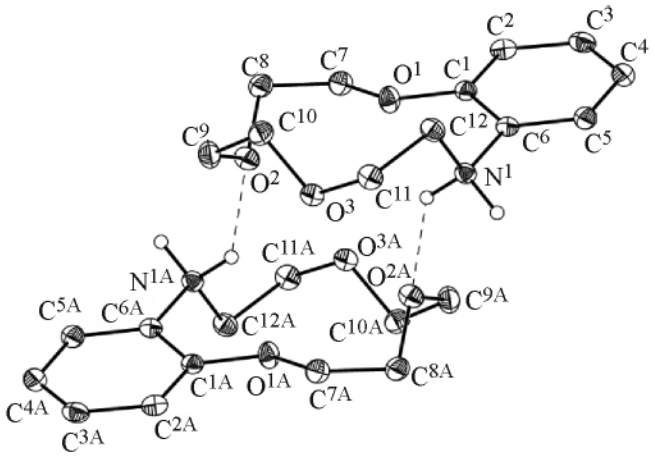


Fig. 2. Centrosymmetric hydrogen-bound dimers of benzoaza-12-crown-4 hydrochloride in the crystal.

(45.9%), the intermediates and the by-products (see the quantities above), and approximately equal amounts of unreacted *o*-aminophenol (11.2%) and triethylene glycol dichloride (9.8%). Longer reaction run (20 h) did change the yield of the target product.

It was reasonable to propose that heating the mixture upon more vigorous stirring would increase the yield of benzoaza-12-crown-4. To check that, *n*-butanol was used as the reaction medium, and ultrasonic mixer (20 kHz) was used instead of mechanical stirrer. The process was carried out similarly to the above-described synthesis in 2-propanol. However, the final mixture contained mainly the etherification products: 1-{2-[2-(2-chloroethoxy)ethoxy]ethoxy}butane (14.1%), 5,8,11,14-tetraoxaoctadecane (26.5%), 2-{2-[2-(butyl)-ethoxy]ethoxy}aniline (3.1%), and product **III** (about twice of its amount as compared to the synthesis in 2-propanol). No dibenzodiaza-24-crown-8 was detected, and yield of the target product, benzoaza-12-crown-4, was significantly decreased. Compositions of the reaction mixture after 20 h refluxing in 2-propanol and in *n*-butanol are compared in the Table.

The reaction mixtures composition (wt %) when performing the reaction in 2-propanol and in *n*-butanol

Component	2-Propanol	1-Butanol
o-Aminophenol	11.1	5.5
Triethylene glycol dichloride	9.9	7.1
Benzoaza-12crown-4	45.8	21.9
II	10.1	3.5
III	7.8	18.4
IV	3.0	–
Dibenzodiaza-24-crown-8 (**V**)	10.1	–
Etherification products	2.2	43.6

It follows that using *n*-butanol and ultrasonic stirring did not increase the target product yield, as side reactions with the solvent turned preferential. The obtained benzoaza-12-crown-4 (Fig. 2) was highly pure, the main substance content was of ≥99% (GLC).

EXPERIMENTAL

The specimens sampled from reaction mixture were quantitatively analyzed by GLC using a Chromatech-Crystall 5000.2 chromatograph equipped with flame ionization detector and a BP-5 quartz capillary column (30 m × 0.32 mm, stationary phase thickness of 0.5 μm), with helium as carrier gas (2.8 mL/min, flow splitting of 1 : 25), column temperature 150–300°C, and temperature program 10°C/min. Concentration of the components was found by square normalization.

Identification of reaction products was carried out using a Chromatech-Crystall 5000.2 chromatograph equipped with thermo ISQ mass spectrometric detector and a TR-5MS quartz capillary column (15 m × 0.25 mm, stationary phase thickness of 0.25 μm), with helium as carrier gas (flow rate 1.2 mL/min, flow splitting of 1 : 25), column temperature 150–280°C, and temperature program 20°C/min.

Electron impact mass spectra were obtained at ionization voltage of 70 eV and ion source temperature of 280°C. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AVANCE III NanoBay spectrometer [300.28 (^{1}H) and 75.50 (^{13}C) MHz) in CD_3Cl at 25°C. Elemental analysis was carried out using an Eurovector EuroEA 3000 CHNS-analyzer. IR absorption spectra (KBr) were registered with a VERTEX 70 IR Fourier spectrometer at 600–3800 cm^{-1} with the resolution of 4 cm^{-1}.

X-ray analysis was carried out using a Bruker APEX IICCD diffractometer at 120 K (MoK_α-radiation). Atomic coordinates, bond lengths, bond angles, and temperature parameters were deposited at the Cambridge bank of structure data (CCDC no. 976857).

Synthesis of benzoaza-12-crown-4 in 2-propanol. A mixture of 17.4 g (0.16 mol) of *o*-aminophenol, 12.6 g (0.32 mol) of sodium hydroxide, and 200 mL of 2-propanol was stirred during 60 min at 60°C, and then 25 mL (0.16 mol) of triethylene glycol dichloride was added. The reaction mixture was refluxed during 20 h,

then cooled, and acidified with hydrochloric acid to pH 3–4; inorganic admixtures were filtered off. The filtrate was treated with 25% ammonia to pH 8–9 and evaporated at a rotor evaporator. The residue was distilled under reduced pressure collecting the fraction with bp of 150°C (6 mmHg). Pure benzoaza-12-crown-6 crystallized while cooling in the collector as a light-yellow powder, mp 173.6–174.2°C. Yield 15.1 g (42%).

IR spectrum (KBr), ν, cm^{-1}: 3433.77, 3125.41 (w), 3091.84 (w), 3027.02 (w), 2963.50 (m), 2922.63 (m), 2877.56 (w), 2672.20 (w), 2612.20 (w), 2563.08 (m), 2529.49 (w), 2485.40 (w), 2429.78 (m), 2365.47 (m), 2318.72 (m), 2291.99 (m), 2065.21 (w), 1615.13 (m), 1564.42 (m), 1501.90 (s), 1470.72 (m), 1448.06 (s), 1405.28 (w), 1381.50 (m), 1347.98 (m), 1296.16 (s), 1271.49 (s), 1249.81 (m), 1149.72 (m), 1101.30 (s), 1069.81 (s), 1047.78 (w), 1025.37 (m), 951.43 (w), 913.17 (m), 823.13 (m), 769.22 (s), 612.54 (s). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 3.45–3.53 m (2H, CH_2), 3.69-3.75 m (2H, CH_2), 3.75–3.81 m (2H, CH_2), 3.81–3.87 m (2H, CH_2), 4.03–4.10 m (2H, CH_2), 4.17–4.24 m (2H, CH_2), 7.09 d.d (1H, Ar, J_{HH} 7.9 Hz, 1.2 Hz), 7.15 t.d (1H, Ar, J_{HH} 7.9 Hz, 1.5 Hz), 7.36 t.d (1H, Ar, J_{HH} 7.9 Hz, 1.5 Hz), 7.79 d.d (1H, Ar, J_{HH} 7.9 Hz, 1.5 Hz). ^{13}C NMR spectrum, (75 MHz, $CDCl_3$), δ_C, ppm: 53.05, 66.81, 70.07, 71.36, 71.62, 72.81, 118.80, 124.57, 127.36, 150.94, 152.09. Mass spectrum, *m/z*: 223.04 $[M]^+$ (For $C_{12}H_{17}NO_3$ calculated: 223.09). Found, %: C 64.50, H 7.66, N 6.24. $C_{12}H_{17}NO_3$. Calculated, %: C 64.57, H 7.62, N 6.28.

Synthesis of benzoaza-12-crown-4 in *n*-butanol. A mixture of 17.4 g (0.16 mol) of *o*-aminophenol, 12.6 g (0.32 mol) of potassium hydroxide, and 200 mL of *n*-butanol was stirred with ultrasonic stirrer (20 kHz) at 80°C during 60 min. Isolation and purification of the target product was carried out as described above. Yield of benzoaza-12-crown-4 7.1 g (20.1%). Characteristics of obtained benzoaza-12 crown-4 were identical to those of the product obtained in 2-propanol.

REFERENCES

1. Len, J-M., *Supramolekylyarnaya khimiya. Kontseptsii i perspektivy* (Supramolecular Chemistry. Concepts and Perspectives) Novosibirsk: Nauka, 1988.
2. Tsivadze, A.Yu., *Russ. Chem. Rev.*, 2004, vol. 73 no. 1, p. 1. DOI: 10.1070/rc2004v073n01ABEH000863.
3. Gromov, S.P. and Alfimov, M.V., *Izv. Akad. Nauk, Ser. Khim.*, 1997, no. 4, p. 641.
4. Yatsimirskii, A.K., *Itogi Nauki i Tekhn., Bioorg. Khim.,* VINITI, Moscow, 1990, no. 17, p. 148.
5. De Silva, A.P., Gunaratne, H.Q.N., Gunalaugsson, A.J., Huxley, M., McCoy, C.P., Rademacher, J.T., and Rice, T.E., *Chem. Rev.*, 1997, no. 97, p. 1515. DOI: 10.1021/cr960386p.
6. *Applied Fluorescence in Chemistry, Biology, and Medicine*, Rettig, W., Stehmel, B., Schrader, S., and Seifert, H., Eds., Springer-Verlag, Berlin, 1999, p. 161.
7. Zhao, Q., Li, F., and Huang, C., *Chem. Soc. Rev.,* 2010, vol. 39. p. 3007. DOI: 10.1038/B915340C.
8. Bekiari, V., Judeinstein, P., and Lianos, P., *J. Luminesce*, 2003, vol. 104, p. 13. DOI: 10.1016/S0022-2313(02)00575-6.
9. *Handbook of Photochemistry and Photobiology*, Nalva, H.S., Ed., Stevenson Ranch: American Scientific Publishers, 2003, p. 271.
10. Ushakov, E.N., Alfimov, M.V., and Gromov, S.P., *Russ. Chem. Rev.*, 2008, vol. 77, no. 1, p. 39. DOI: 10.1070/RC2008v077n01ABEH003757.
11. Gromov, S.P., Dmitrieva, S.N., Vedernikov, A.I., and Churakova, M.V., *Russ. Chem. Bull.*, 2004, vol. 53, no. 7, p. 1417. DOI:10.1023/B;RUCB0000046237.0094.80.
12. Lockhart, C., Robson, A.C., Tompson, M.E., Furtado, S.D., Kaura, S.K., and Allan, A.R., *J. Chem. Soc., Perkin Trans. 1*, 1973, p. 577. DOI: 10.1039/P19730000577.
13. Gromov, S.P., Dmitrieva, S.N., Churakova, M.V., *Russ. Chem. Rev.*, 2005, vol. 74, no. 5, p. 461. DOI: 10.1070/RC2005v074n05ABEH001163.
14. Martin, V.V., Rothe, A., and Gee, K.R., *Bioorg. Med. Chem. Lett.*, 2005, vol. 15, p. 1851. DOI: 10.1016/j.bmcl.2005.02.017.
15. Omar-Amrani, R., Schneider, R., and Fort, Y., *Lett. Org. Chem.*, 2007, vol. 4, no. 5, p. 322. DOI: 10.2174/15701780778121058.