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ANOMALOUS BEHAVIOR OF THE AMIDES OF BENZO- AND DIBENZOCROWN THIOCARBOXYLIC ACIDS UNDER THE CONDITIONS OF METHYLATION

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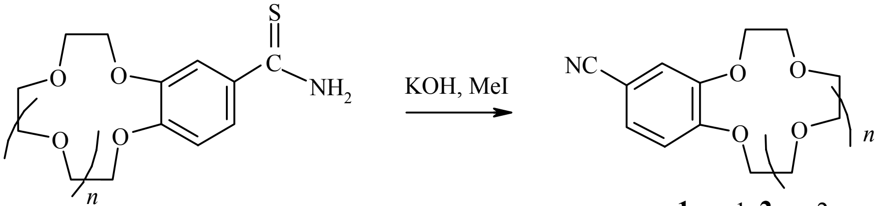
During the reaction of the amides of benzo- and dibenzocrown thiocarboxylic acids with methyl iodide in the presence of potassium hydroxide they exhibit anomalous behavior leading to the nitriles of benzo- and dibenzocrown carboxylic acids. The nitriles of benzo-15-crown-5-, benzo-12-crown-4-, and dibenzo-18-crown-6-4'-carboxylic acids and the dinitriles of dibenzo-18-crown-6- and dibenzo-24-8-4',4"(5")-dicarboxylic acids were obtained.

Keywords: benzocrown ethers, nitriles, complexing, methylation, thioamidation.

Earlier we developed a method for the production of thioamide derivatives of benzocrown ethers by reaction with potassium thiocyanate in polyphosphoric acid [1]. In order to produce the more reactive S-alkyl derivatives, which could be used as starting compounds for the synthesis of benzocrown ethers with various functional groups or condensed heterocyclic systems, we studied the methylation of benzo-15-crown-5-4'-thiocarboxamide. We found that benzo-15-crown-5-4'-carbonitrile (**2**) was formed instead of the expected S-methylthioimidic ester. We explained such a reaction path by the influence of the macrocycle in the crown ethers. By selecting the reaction conditions we found that increase of the reaction temperature from 20 to 70-75°C reduced the yield by half. Curtailment of the reaction time and halving the amount of methyl iodide did not affect the yield of the reaction product. The course of the reaction was also not affected by the replacement of ethanol by dioxane in order to improve the dissolution of the initial compound.



1 $n = 1$, **2** $n = 2$

It should be noted that if the order in which the reagents are added (KOH, crown ether, methyl iodide) is changed benzo-15-crown-5-4'-carboxylic acid, melting at 180-185°C (mp 184-186°C [2]), is formed instead of nitrile.

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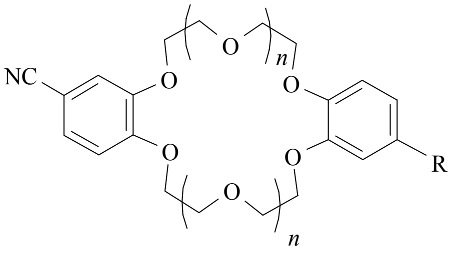
Thus, it was found that the best yields of the nitriles are obtained with the thioamide, methyl iodide, and potassium hydroxide reagents in ratios of 1:2:4 at room temperature for 1 h in dioxane solution. The reactions with the thioamides of other crown ethers under these conditions also lead to the formation of the nitriles of benzocrown carboxylic acids.

In the reaction of dibenzo-18-crown-6- and dibenzo-24-crown-8-4',4"(5")-dithiocarboxamides under similar conditions the dibenzo-18-crown-6- and dibenzo-24-crown-8-4',4"(5")-dicarbonitriles (**3**, **4**) are formed smoothly. The 4'-nitrile of dibenzo-18-crown-6-carboxylic acid (**5**) was obtained from the monosubstituted derivative of dibenzo-18-crown-6.

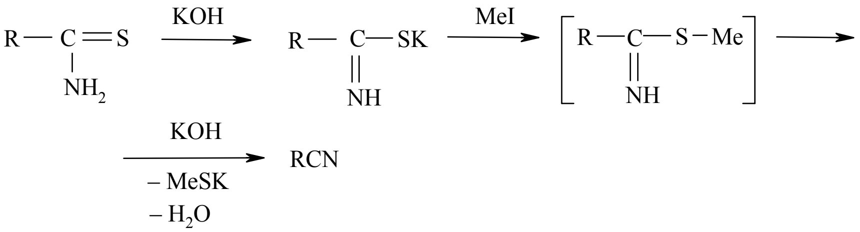


3–5

3 R = CN, *n* = 1, **4** R = CN, *n* = 2, **5** R = H, *n* = 1

The transformation of the thioamides into the nitriles takes place in two stages: alkylation at the sulfur atom with the formation of S-methylthioimidic esters and subsequent elimination of methylthiol.

The thioamides contain two reaction centers – the sulfur and nitrogen atoms. It is known that in such systems even the simplest electrophile, the proton, adds at the more polarized sulfur atom with the formation mainly of the thioimidic esters [3]. They react in the same way with alkyl halides. In the case of thioamides the mercaptide is formed at the first stage, alkylation takes place at the sulfur atom, and the obtained S-methylthioimidic ester then eliminates methylmercaptan under the influence of the potassium hydroxide.



$$\underset{NH_2}{R-C{=}S} \xrightarrow{KOH} \underset{NH}{R-C{-}SK} \xrightarrow{MeI} \left[\underset{NH}{R-C-S-Me}\right] \longrightarrow \xrightarrow[\substack{-\,MeSK \\ -\,H_2O}]{KOH} RCN$$

R = dibenzocrown

Crown ethers, which are complexones, have strong solvating properties [4, 5]. In the present case, as a result of these properties, they promote polarization of the S–K bond. As a result of the complexing of the potassium with the crown ethers the S–K bond acquires ionic character, and methylation therefore takes place at the sulfur atom. The obtained S-methylthioimidic ester is destabilized, first, by attack of the active OH anion formed as a result of complexing between the crown ether and the KOH and, second, by the possibility of complexing between the crown ether and the methylthiol, promoting elimination of the latter. As a result the reaction does not stop at the methylation stage but goes on to the formation of the nitrile. This explains the need for an excess of KOH and the role of the benzocrown ether in this reaction.

The occurrence of the reaction in the other direction in the case where the reagents are added in the reverse order is due to the hydrolysis of the thioamide to the acid, which competes with nitration. This can also explain the decrease in the yield of the nitriles with increase in the reaction temperature.

The structure of the obtained compounds was established by ^{1}H NMR and IR spectroscopy and mass spectrometry. In the ^{1}H NMR spectrum of the nitriles there are signals for the protons of the benzene ring in the form of a doublet, a singlet, and a doublet in the region of 6.8-7.2 ppm, characteristic of 1',2',4'-trisubstituted benzene, and a multiplet for the macrocycle in the region of 3.7-4.2 ppm. The IR spectra of these compounds contain an absorption band at 2230 cm^{-1}, characteristic of the CN group. The mass spectrum of compound **1** contains a molecular ion peak at *m*/*z* 249. The strongest peak for an ion with *m*/*z* 160 is produced as a result of the abstraction of a hydrogen atom from the radical-ion with *m*/*z* 161 to form a cation with the charge at the oxygen atom. As a result of the elimination of a CH_3 group the last ion gives a fragment with *m*/*z* 145. Such fragmentation is typical of crown ethers, and we have observed it before in other derivatives [6, 7]. The molecular ion of the nitrile **2** with *m*/*z* 293 disintegrates with the removal of two and three molecules of ethylene oxide and the formation of ions with *m*/*z* 205 and 161. The fragment with *m*/*z* 146 is formed as a result of the removal of a CH_3 group. The dissociation of the molecular ions of compounds **3-5** with *m*/*z* 410, 498, and 385 respectively takes place with the elimination of ethylene oxide molecules and the formation of a fragment with *m*/*z* 160, which is characterized by the removal of a CH_3 group and the formation of an ion with *m*/*z* 145.

A single crystal was grown by the crystallization of compound **2** from a dilute solution in a mixture of hexane and acetone, and the formation of the nitrile in this reaction was also confirmed by X-ray crystallographic analysis [8].

EXPERIMENTAL

The IR spectra were obtained on a Perkin-Elmer 200 Fourier spectrometer in KBr tablets. The ^{1}H NMR spectra were recorded on a Tesla BS-567 instrument (100 MHz) in deuterochloroform with HMDS as internal standard (δ 0.05 ppm).

Benzo-12-crown-4-4'-carbonitrile (1). While stirring on a magnetic stirrer at room temperature benzo-12-crown-4-4'-thiocarboxamide (0.28 g, 1 mmol) was dissolved in dioxane (5 ml). Methyl iodide (0.13 ml, 2 mmol) and then a solution of KOH (0.22 g, 4 mmol) in water (1 ml) were added to the solution obtained. The reaction mixture became colorless, and a white precipitate separated. Stirring was continued for 1 h, and the mixture was diluted with water to dissolve the KI and extracted with chloroform. After removal of the chloroform the product was isolated by crystallization from hexane with the addition of acetone; mp 99-102°C, yield 0.15 g (62%). IR spectrum, ν, cm^{-1}: 2230 (CN), 2920-2880, 1120 (COC), 1600, 1520 (=CH), 880, 850, 820 (1-, 2-, 4-substituted benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.30 (H, dd, *J* = 2.5, H-5'$_{Ar}$); 7.18 (H, d, *J* = 2.5, H-3'$_{Ar}$); 6.90 (H, dd, *J* = 2.5, H-6'$_{Ar}$); 4.00-4.25 (4H, m, α-OCH_2); 3.75-3.92 (4H, m, β-OCH_2); 3.70 (4H, s, γ-OCH_2). Found: $[M]^+$ 249.1001. $C_{13}H_{15}NO_4$. Calculated: M 249.2648.

Benzo-15-crown-5-4'-carbonitrile (2). This compound was obtained similarly to compound **1** from benzo-15-crown-5-thiocarboxamide (0.34 g, 1 mmol), methyl iodide (2 mmol), and potassium hydroxide (4 mmol). The product was isolated in the pure form by crystallization from hexane; mp 86-87°C, yield 0.2 g (70%). IR spectrum, ν, cm^{-1}: 2230 (CN), 2920-2880, 1120 (COC), 1600, 1520 (=CH), 880, 850, 820 (1-, 2-, 4-substituted benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.20 (1H, dd, *J* = 2.5, H-5'); 7.00 (1H, d, *J* = 2.5, H-3'); 6.80 (1H, dd, *J* = 2.5, H-6'$_{Ar}$); 3.60-4.17 (16H, m, OCH_2). Found: $[M]^+$ 293. $C_{15}H_{19}NO_5$. Calculated: M 293.3037.

Dibenzo-18-crown-6-4'-carbonitrile (5). This compound was obtained similarly to the acid **1** from dibenzo-18-crown-6-4'-thiocarboxamide (0.4 g, 4 mmol), methyl iodide (0.13 ml, 2 mmol), and potassium hydroxide (0.22 g, 4 mmol). We isolated 0.15 g (28%) of the product; mp 138-142°C. IR spectrum, ν, cm^{-1}: 2230 (CN), 2930-2880, 1140 (COC), 1600, 1520 (=CH), 880, 860, 820 (1-, 2-, 4-substituted benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.20 (1H, dd, *J* = 2.5, H-5'); 7.00 (1H, d, *J* = 2.5, H-3'); 6.80 (1H, dd, *J* = 2.5, H-6'); 6.85 (4H, s, H-3",4",5",6"$_{Ar}$); 4.05-4.25 (8H, m, α-OCH_2); 3.88-4.05 (8H, m, β-OCH_2). Found: $[M]^+$ 385.1525. $C_{21}H_{23}NO_6$. Calculated: M 385.4746.

Dibenzo-18-crown-6-4',4"(5")-dicarbonitrile (3). This compound was obtained by the procedure described above from dibenzo-18-crown-6-4',4"(5")-dithiocarboxamide (0.4 g, 0.8 mmol), methyl iodide(0.2 ml, 3.2 mmol), and potassium hydroxide (0.36 g, 6.4 mmol) with a yield of 0.12 g (35%); mp 195-203°C. IR spectrum, ν, cm^{-1}: 2230 (CN), 2930–2870, 1140 (COC), 1600, 1520 (=CH), 890, 860, 815 (1-, 2-, 4-substituted benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.20 (2H, dd, *J* = 2.5, H-5',5"); 6.80 (2H, d, *J* = 2.5, H-3',3"); 6.77 (2H, d, H-6',6"$_{Ar}$); 4.02-4.20 (8H, m, 4-α-OCH$_2$); 3.80–4.00 (8H, m, 4-β-OCH$_2$). Found: [M]$^+$ 410.1478. $C_{22}H_{22}N_2O_6$. Calculated: M 410.4241.

Dibenzo-24-crown-8-4',4"(5")-dicarbonitrile (4). This compound was obtained by the procedure described above from dibenzo-24-crown-8-4',4"(5")-dithiocarboxamide (0.2 g, 0.35 mmol), methyl iodide (0.1 ml, 1.2 mmol), and potassium hydroxide (0.13 g, 2.4 mmol) with a yield of 0.15 g (85%); mp 104-106°C. IR spectrum, ν, cm^{-1}: 2230 (CN), 2920-2880, 1120 (COC), 1600, 1520 (=CH), 880, 860, 810 (1-, 2-, 4-substituted benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.17 (2H, dd, *J* = 2.5, H-5',5"; 7.00 (2H, d, *J* = 2.5, 3'-,3"H); 6.82 (2H, d, H-6',6"$_{Ar}$); 4.00-4.20 (8H, m, α-OCH$_2$); 3.80-4.20 (8H, m, β-OCH$_2$); 3.75 (8H, s, γ-OCH$_2$). Found: [M]$^+$ 498.2002. $C_{26}H_{30}N_2O_8$. Calculated: M 498.5296.

REFERENCES

1. N. J. Sayfullina, A. D. Grebenyuk, K. A. Ibragimzhanov, and A. K. Tashmukhamedova, *Uzb. Khim. Zh.,* **1**, 29 (1999).
2. R. Ungaro, B. El Haj, and J. Smid, *J. Am. Chem. Soc.*, **98**, 5198 (1976).
3. W. Walter, M. F. Sieveking, and E. Schaumann, *Tetrahedron Lett.*, 839 (1974).
4. Yu. Sh. Goldberg, *Selected Chapters on Phase-Transfer Catalysis* [in Russian], Zinatne, Riga (1989), p. 12.
5. A. V. Bogatskii, *Meso- and Macroheterocycles* [in Russian], Naukova Dumka, Kiev (1986), p. 171.
6. D. Aslanova, A. K. Tashmukhamedova, and R. Razakov, *Khim. Geterotsikl. Soedin.*, 898 (1987). [*Chem. Heterocycl. Comp.*, **23**, 737 (1987)].
7. N. J. Sayfullina, K. A. Ibragimzhanov, A. K. Tashmukhamedova, and Kh. M. Shakhidoyatov, *Khim. Geterotsikl. Soedin.*, 937 (1999). [*Chem. Heterocycl. Comp.*, **35**, 821 (1999)].
8. S. A. Talipov, Z. Karimov, B. T. Ibragimov, A. K. Tashmukhamedova, H. J. Sayfullina, and T. F. Aripov, *Kristallografiya,* **45**, 492 (2000).