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SYNTHESIS OF BIS(2,2-BENZ-IMIDAZOLYL)DIBENZO-18-CROWN-6

N. Zh. Saifullina, E. B. Galieva, and A. K. Tashmukhamedova

A method has been developed for the introduction of benzimidazole substituents into the dibenzo-18-crown-6 molecule by condensation of its 4',4"(5")-diacetyl derivative with ortho-phenylenediamine. Increasing the length of the hydrocarbon chain of the acyl substituent or replacing Ac by $CSNH_2$ led to a decrease in the yield of the desired product. No product was formed when Ac was replaced by COOH or CN.

Keywords: acylation, benzimidazoles, dibenzo-18-crown-6, condensation with *ortho*-phenylenediamine.

Many derivatives of benzimidazole possess biological activity [1]. The addition of benzimidazole residues to the molecule of an ionophore which readily passes into a bacterium is an interesting and promising direction of research aimed at the creation of new biologically active compounds.

The objective of the present work includes the development of a method for the introduction of benzimidazole substituents into the molecule of the crown ether dibenzo-18-crown-6 (DB-18-C6). It is known that the condensation of acids or carbonyl compounds with *o*-phenylenediamine (**1**) is the simplest method for the preparation of benzimidazoles [1, 2]. It is carried out in the presence of HCl, polyphosphoric acid, or polyphosphoric acid ester or by simply fusing the reagents together [1-3]. We chose as the carbonyl compound 4',4"(5")-diacetyl-DB-18-C6 (**2a**), which we had synthesized earlier [4], since its condensation with the diamine **1** should permit preparation of the required product in a single step. We did not succeed in carrying out the reaction of diamine **1** with the diacetyl derivative in the presence of the condensing agents mentioned above. We obtained the desired product – 4',4"(5")-bis(2,2-benzimidazolyl)dibenzo-18-crown-6 (**3**) – in 50% yield by heating compound **2a** with a three-fold excess of diamine **1** at 180-200°C for 5 h. The structure of compound **3** was confirmed by ^{1}H NMR, IR, and mass spectroscopy. For example, the ^{1}H NMR spectrum contains a multiplet in the 3.5-4.5 ppm range with an intensity corresponding to the 16 protons of the macrocycle. This signal is shifted to weaker field in comparison with the corresponding signal in the diacetyl-DB-18-C6 starting material. The multiplet at 6.5-7.8 ppm corresponds to the 14 aromatic protons. In contrast to the starting material **2a**, it was not possible to assign these protons.

In the IR spectrum there is broad N–H absorption band at 3660-3300 cm^{-1}. The absorption at 1660 cm^{-1} indicates the presence of the C=N bond, while the bands at 1590 and 1515 cm^{-1} are assigned to C–H bonds of the benzene ring. Absorptions in the 3000-2880 and 1270-1200 cm^{-1} regions are characteristic of the C–O–C bonds of the macrocycle, while the intense multiple bands in the regions of 869, 794, and 766 cm^{-1} are linked to the presence of the benzimidazole unit.

M. Ulugbek National University of Uzbekistan, Tashkent 700095; e-mail: sayfullin@mail.tps.uz.
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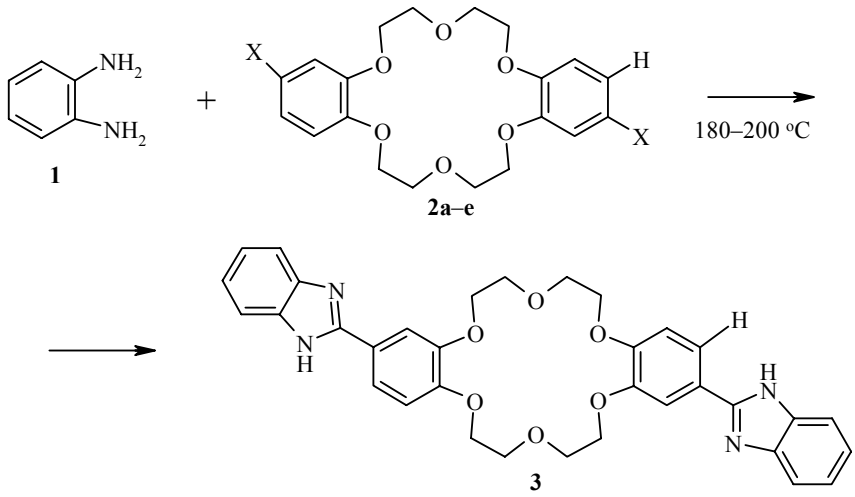
In the mass spectrum of the product decomposition of the molecule occurs in the direction of contraction of the macrocycle with the formation of fragments with *m/z* 340, 296, and 252. In addition there are peaks of ions explained by splitting of the substituent from the basic molecule and its decomposition. We previously observed analogous decomposition for derivatives of DB-18-C6 [5]. The molecular ion M^+ 592 corresponds to the molecular mass of 4',4"(5")-bis(2,2-benzimidazolyl)-DB-18-C6.

We used the conditions found for the synthesis of compound **3** for the reaction of diamine **1** with the known dipropionyl- (**2b**), dibutyryl- (**2c**), and divaleryl-DB-18-C6 (**2d**) [3] and derivatives containing thioamide (**2e**) [6], carboxyl (**2f**) [7], and nitrile (**2g**) [8] in place of the acyl substituents.



2 a X = COMe, **b** X = COEt, **c** X = COPr, **d** X = COC_4H_9, **e** X = $CSNH_2$

The yield of compound **3** decreased with increasing length of the acyl substituent: for the divaleryl-substituted **2d** the yield was only 3%. Interaction of the dithiocarbonic acid **2e** with the diamide gave compound **3**. The samples of compound **3** obtained were identical in all cases (IR, TLC). Reaction with the dicarboxylic acid was unsuccessful because it melted above 200°C. Increasing the temperature to 240-250°C led to complete charring of the reaction mixture. No condensation product was isolated in the case of the dinitrile **2g**. The characteristic garlic smell and the TLC data suggested that isomerization of the nitrile starting material into the isonitrile occurred under the reaction conditions.

Thus a method has been developed for the insertion of the benzimidazole unit into the DB-18-C6 molecule. It is shown that the nature of the substituents on the DB-18-C6 starting material, the length of the hydrocarbon chains of the acyl substituents, and the thermal stabilities of the molecules affect the condensation process.

EXPERIMENTAL

The ^{1}H NMR spectrum of compound **3** in CD_3OD with HMDS (δ 0.05 ppm) as internal standard was recorded on a Tesla BS-567 (100 MHz) spectrometer. Mass spectra were recorded with a Kratos MS 25 RF machine. IR spectra of KBr disks were recorded with Perkin-Elmer 2000 Fourier spectrometer. Composition of the reaction mixture was controlled by TLC on Merck plates with 1:20:20:1 hexane–chloroform–acetone–ethanol as solvent. The starting materials **2a-d** were synthesized as we described previously [4]. Compounds **2e,f,g** were prepared by the methods of papers [6-8] respectively.

4',4"(5")-Bis(2,2-benzimidazolyl)-DB-18-C6 (3). A mixture of the diacetyl derivative **2a** (0.44 g, 1 mmol) and diamine **1** (0.3 g, 3 mmol) was ground in a mortar and heated at 180-200°C for 5 h. The glass-like mass was triturated with water (15 ml), the solid was filtered off, washed on the filter with dilute HCl, then $CHCl_3$, dissolved in acetone and the product **3** was precipitated with water. Yield 0.37 g (50%); mp 138-145°C, R_f 0.31. IR spectrum, ν, cm^{-1}: 3660-3300 (NH-assoc.), 1660 (C=N), 1590, 1515 (=CH), 3000-2820, 1270-1200 (C–O–C), 869, 794, 766 (benzimidazole). ^1H NMR spectrum, δ, ppm: 6.50-7.87 (14 H, m, H_{arom}); 3.50-4.50 (16H, m, OCH_2). Mass spectrum, *m/z* (I_{rel}, %): 5.92 [M^+] (6.4), 340 [M^+ - $C_{15}H_{12}O_2N_2$] (6.4), 296 [M^+ - $C_{17}H_{16}O_3N_2$] (12.8), 252 [M^+ - $C_{19}H_{20}O_4N_2$] (11.6), 237 [M^+ - $C_{19}H_{20}O_4N_2$ -CH_3] (38.6), 212 [M^+ - $C_{15}H_{12}O_2N_2$ - $C_8H_5N_2$] (52), 167 [M^+ - $C_{17}H_{16}O_3N_2$ - $C_8H_5N_2$] (28.0), 129 [M^+ - $C_{18}H_{22}O_6$] (100).

By the same method product **3** (0.13 g, 43%) mp 138-150°C was obtained from the dipropionyl derivative **2b** (0.24 g, 0.5 mmol) and diamine **1** (0.16 g, 0.15 mmol). The IR spectrum coincided with that cited above.

Analogously product **3** (0.07 g, 25%), mp 135-142°C was obtained from the dibutyryl derivative **2c** (0.25 g, 0.5 mmol) and diamine **1** (0.16 g, 0.15 mmol). The IR spectrum and R_f were identical with the previous product.

Analogously product **3** (0.17 g) was obtained, contaminated with the diketone starting material, from the divaleryl derivative **2d** (0.26 g, 0.5 mmol) and diamine **1** (0.16 g, 0.15 mmol). After purification by column chromatography on alumina with 1:4:1 hexane–chloroform–acetone as eluent, compound **3** (0.01 g, 3%) was obtained; mp 138-150°C. The IR spectrum was identical with the previous product.

Product **3** (0.02 g, 12.5%), mp 130-135°C, R_f 0.31, was obtained after 3 h from diamide **2e** (0.13 g, 0.03 mmol) and diamine **1** (0.073 g, 0.08 mmol). IR spectrum, ν, cm^{-1}: 3630-3380 (NH-assoc), 1670-1630 (C=N), 860, 780, 770, 750 (benzimidazole).

Elemental analysis of compound **3** did not give positive results, probably because crown ethers are known to readily sequester molecules of solvent and to form stable solvates.

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