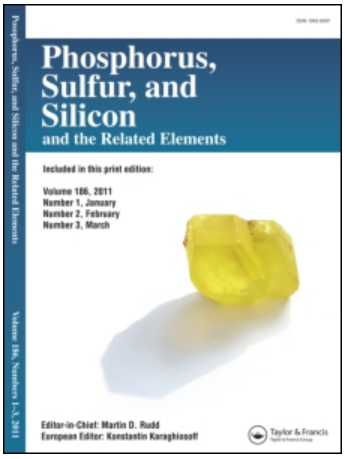

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SYNTHESIS OF NOVEL AMINOPHOSPHONIC DERIVATIVES OF BENZO-15-CROWN-5 ETHER

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Synthesis of new aminomethylphosphonic acids containing benzo-15-crown-5 ether, is described. These compounds were obtained from the 4′-formylbenzo-15-crown-5 by a sequence of reactions, which afforded 4′-(aminomethylphosphono)-benzo-15-crown-5 and its N*-benzyl derivative in high yields.*

Keywords: 4′-Formylbenzo-15-crown-5; addition reaction; aminodiphenylmethane; benzo-15-crown-5; trimethyl phosphite

Chemistry of crown ethers has been considerably developed due to their important properties and applications in many areas of organic and inorganic chemistry. One can find over two hundred publications concerning only the benzo-crown ethers in the chemical literature of the past three years. Application of the benzo-crown ethers as complexing agents, ion carriers, and phase-transfer catalysts is well documented in some monographs[1–3] and in a large number of articles.[4–8]

There is a need to search for new derivatives of crown ethers possessing prospective metal-binding capabilities for specific metal ions. Aminophosphonic acids, as phosphorous analogs of natural amino acids, are well recognized as strong metal-binding donors[9] due to the acid-base characters of the aminophosphonic acids. It seems to be advisable to combine the excellent complexation abilities of the crown ethers together with similar properties of the aminophosphonic acids in one molecule. Existence of a proton-dissociable group in the crown ether

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compound might give additional advantages in various applications. Especially, for biologically important transition metal ions (e.g., Zn^{+2}), a bidentate (N, O) chelation[10] of metal cations by an aminophosphonate-crown ether compound is of great importance.

In this article, we report a synthesis of some aminomethylphosphonic acid derivatives of the benzo-15-crown-5 that could fulfill such expectations. The aminophosphonic residue is attached in a side arm of the crown ether. To the best of our knowledge, crown ethers with inherent aminophosphonic acids are not yet known.

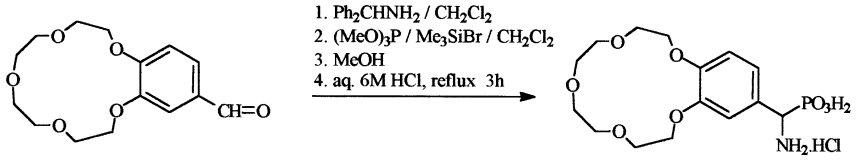
RESULTS AND DISCUSSION

Commercial crown ethers possessing aldehyde groups could be convenient starting materials for synthesis of the postulated crown-aminophosphonic compounds. Availability of the useful formylbenzo-crowns gives a simple ability of obtaining the proper aminophosphonic derivatives. Therefore, the 4′-formylbenzo-15-crown-5 (**1**)[11,12] was used as a key reagent in our synthetic work.

Synthesis was performed by addition of phosphorous acid trimethyl ester (trimethyl phosphite) to a diphenylmethylimine-crown ether compound, which was obtained in situ from the 4-formylbenzo-15-crown-5 (**1**) and aminodiphenylmethane. The addition of a phosphorous nucleophile to a double bond of an imine is known as the Kabachnik-Fields reaction,[13,14] and this way was used in our case. An additional compound (i.e., the crown ether with attached aminophosphonate ester) was converted to the silyl phosphonate ester by means of bromotrimethylsilane and then transformed to the corresponding crown ether-aminophosphonic acid compound by treatment with methanol. At the end, the benzhydryl group was removed from the final product by a hydrolytic cleavage. It is known that the diphenylmethyl-alkylimines are versatile compounds that allow to receive the desired aminophosphonic acids with unsubstituted amino groups,[15] by the removal of the diphenylmethyl fragments in acidic conditions.

A course of the reactions carried out is illustrated in Scheme 1. All of these reactions were done in a one-pot procedure to give the desired product, i.e., the 4′-(aminomethylphosphono)-benzo-15-crown-5 (**2**). The product **2** was isolated as the hydrochloride because of acidic hydrolysis of the reaction mixture (Scheme 1).

Further aminophosphonic derivatives can be easily obtained from the 4′-formylbenzo-15-crown-5 (**1**), primary amines, and diethyl phosphite by exploitation of the known methods of synthesis of *N*-substituted aminophosphonic acids.[13–16] Here we report

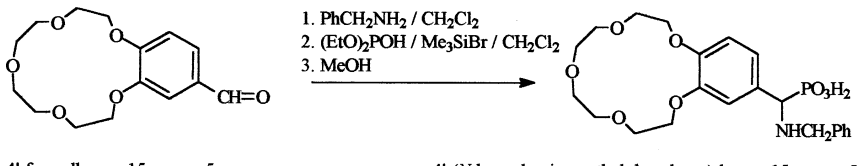


4'-formylbenzo-15-crown-5 — 4'-(aminomethylphosphono)-benzo-15-crown-5

1 **2**

SCHEME 1

the synthesis of one example of such a derivative, that is, 4′-(*N*-benzylaminomethylphosphono)-benzo-15-crown-5 (**3**), which was obtained in high yield by the sequence of reactions detailed in Scheme 2.



4'-formylbenzo-15-crown-5 — 4'-(*N*-benzylaminomethylphosphono)-benzo-15-crown-5

1 **3**

SCHEME 2

The aminophosphonic acid **3** was obtained as a free base by using bromotrimethylsilane as a deprotecting agent of phosphonic esters,[16] like it was done in the preceding synthesis of the 4′-(aminomethylphosphono)-benzo-15-crown-5 (**2**).

The obtained phosphono-crown ethers **2** and **3** are stable, crystalline solids that are soluble in water, and therefore they are suitable for testing as metal-binding agents. Some complexing properties of the obtained compounds will be reported in the near future.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz in D_2O, using 300.13 MHz for ^1H NMR and 121.51 MHz for ^{31}P NMR spectra. Melting points were measured on a digital melting point apparatus electrothermal 9200. Elemental analyses were done in the Laboratory of Instrumental Analysis in the Institute. 4′-Formylbenzo-15-crown-5 and other reagents were obtained from the Aldrich Company.

Procedure for Preparation of the 4′-(Aminomethylphosphono)-benzo-15-crown-5 (2)

4′-Formylbenzo-15-crown-5 (**1**) (280 mg, 0.94 mmol) was dissolved in dry methylene chloride (25 ml), aminodiphenylmethane (183 mg, 1.0 mmol) was added, and the mixture was kept at room temperature for three weeks. After this, the solvent was evaporated to dryness and the residue dissolved again in dry methylene chloride (25 ml); trimethyl phosphite (228 mg, 2.0 mmol) was added followed by bromotrimethylsilane (1.07 g, 7.0 mmol), and the mixture was left for three days, protected against moisture. The solvent was then evaporated, the remaining oily residue was warmed up at 60°C for 1 h, cooled, dissolved in methanol (5 ml), and left for 24 h. The mixture was then evaporated to dryness, treated with anhydrous diethyl ether (50 ml) and refrigerated for several days, until the oily product became crystalline. The crystals were filtered, washed with diethyl ether, and dried. (440 mg). The isolated product was presumably the *N*-benzhydryl derivative of the 4′-(aminomethylphosphono)-benzo-15-crown-5, and it was not additionally analyzed but used directly in the next step. The product (440 mg) was dissolved in 20% HCl (20 ml) and refluxed for 3 h. After cooling, the mixture was extracted with benzene (50 ml), the extract was discarded and the remaining aqueous layer evaporated to dryness to give a crystalline product, i.e., 4′-(aminomethylphosphono)-benzo-15-crown-5 (**2**), yield 285 mg, 0.69 mmol, 73%.

The product **2** was recrystallized from anhydrous ethanol (5 ml) to give fine, white crystals (120 mg), m.p. 166–170°C. ^{1}H NMR(D_2O), δ, ppm: 7.04 (s, 1H, arom.), 6.98 (bs, 2H, arom.), 4.35–4.30 (d, 1H, J = 15.94 Hz, C**H**—P), 4.14 (m., 4H, C$\mathbf{H}_2$). 3.85 (m., 4H, C$\mathbf{H}_2$), 3.71–3.64 (m., 8H, C$\mathbf{H}_2$). ^{31}P NMR(D_2O), δ, ppm: 12.51(s). Elemental Anal. for **2**, Calcd.: N, 3.39; P, 7.49. Found: N, 3.31; P, 7.55.

Procedure for Preparation of the 4′-(*N*-Benzylaminomethylphosphono)-benzo-15-crown-5(3)

4′-Formylbenzo-15-crown-5 (**1**) (300 mg, 1.0 mmol) and benzylamine (118 mg, 1.1 mmol) were dissolved in dry methylene chloride (25 ml), and the solution was kept at room temperature for three weeks. After this, the solvent was evaporated to dryness and the residue dissolved again in dry methylene chloride (25 ml). Diethyl phosphite (166 mg, 1.2 mmol) and bromotrimethylsilane (760 mg, 5.0 mmol) were added and it was protected against moisture. The mixture was left at room temperature for 24 h and evaporated to dryness. The oil obtained was dissolved in methanol (5 ml) and refrigerated. The

next day the solvent was evaporated and the remaining residue was treated with anhydrous diethyl ether (50 ml) and refrigerated for several days, until the oily semisolid became crystalline. The crystals were filtered, washed with diethyl ether, and dried. A product, i.e., 4′-(*N*-benzylaminomethylphosphono)-benzo-15-crown-5 (**3**), was obtained, yield 405 mg, 0.86 mmol, (86%), m.p. 155–162°C. ^{1}H NMR(D_2O), δ, ppm: 7.36 (bs, 5H, Ph), 7.19–6.91 (m, 3H, arom.), 4.15–3.94 (m, 7H, C**H**—P, C$\mathbf{H}_2$N, C$\mathbf{H}_2$O), 3.78–3.76 (m., 4H, C$\mathbf{H}_2$). 3.62–3.55 (m., 8H, C$\mathbf{H}_2$). ^{31}P NMR(D_2O), δ, ppm: 11.30(s). Elemental Anal. for **3**, calcd.: N, 3.00; P, 6.63. Found: N, 3.11; P, 6.54.

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