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Communication

Preparation of a novel group of hybrid compounds *N*-benzyl aminoboronbenzylphosphonic and *N*,*N*′-ethylenedi (aminoboronbenzylphosphonic) acids

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ABSTRACT

Two groups of new boronic acids containing aminophosphonate functions were synthesized and characterized by NMR spectroscopy and ESI-MS. Both groups of compounds were obtained by simple reactions of prepared *in situ* tris(trimethylsilyl) phosphite with a corresponding imine. The synthesized compounds may serve as a potential new class of building blocks, BNCT agents and supramolecular host molecules.

1. Introduction

Recently boronic compounds have attracted much attention due to their supramolecular and biomedicinal functions. They are recognized as potent receptors to diols, saccharides, hydroxycarboxylates, dicarboxylates [1,2], also acting as inhibitors of proteases (with BORTEZOMIB being the most spectacular example), glycosidases and agents in Boron Neutron Capture Therapy (BNCT) [3–8]. Boronic acids have been customarily applied in organic chemistry as building blocks in Suzuki-Miyaura and Petasis reactions or as water tolerant Lewis acids, or Brønsted acids catalysts [9–11]. Similar functions are carried out by phosphonic acids and their derivatives, which could be considered as good supramolecular host molecules for carbohydrates, catecholamines, amino acids, peptides and proteins [12]. Furthermore this group of compounds finds many applications as enzyme inhibitors towards proteolytic enzymes and antiosteoporotic drugs [13,14].

Recently we have published the unexpected pathway of formation of a hybrid compound containing both boronic and aminophosphonate units [15]. In this paper we describe the unesterified forms of its analogues starting from benzylamine and ethylenediamine.

2. Results and discussion

For the synthesis of the new boronate compounds the most convenient classical hydrophosphonylation of imines procedure for aminophosphonates was applied [16]. However, during acidic hydrolysis of the phosphonate ester groups the cleavage of boronate entities was observed. Therefore, tris(trimethylsilyl) phosphite generated by application of trimethylphosphite and TMSBr (bromotrimethylsilane) in the ratio 1:3 was used (Fig. 1) [17]. The *in situ* formed tris(trimethylsilyl) phosphite was cooled down to 5 °C and blended with corresponding imine suspended in dry DCM. The reaction mixture was stirred up to 48 h and evaporated. In order to cleave trimethylsilyl esters methanolic solution was added and left stirring overnight. After 24 h the formed yellow precipitate was filtered off, washed with diethyl ether and the desired product was purified by dissolving in 1 M NaOH and reprecipitated by a dropwise addition of 1 M HCl. The formed white precipitate was washed with water and/or methanol and air-dried (**1**–**3**). The same procedure was used for the preparation of the second group of compounds (**4**–**6**) based on ethylenediamine skeleton. However, due to low solubility of the formed Schiff bases the protected forms of 3- and 4-formylphenylboronic acids esterified with diethanolamine were applied. The rest of the synthetic steps were the same as for the compounds **1**–**3** (see Figs. 2 and 3). These molecules were expected to form two pairs of diastereoisomers of SS/RR and/or

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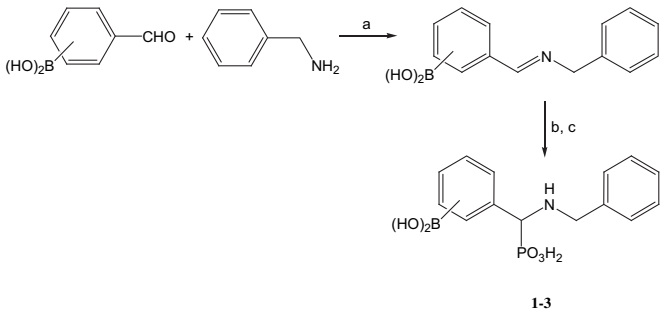

Fig. 1. Synthesis of aminoboronbenzylphosphonates **1**–**3**. a) DCM (using Dean–Stark adapter), b) DCM, $P(OSiCH_3)_3$, c) 10% MeOH in H_2O.

meso SR/RS configurations [18,19]. In fact, this phenomenon is most noticeable at neutral pH in which two phosphorous signals were observed for compounds **4**–**6**. In this environment proton spectra became more complicated most probably due to the presence of stereoisomers and possible formation of intra- and/or intermolecular hydrogen bonds. Therefore the NMR measurements for these structures were performed at pH 11 to simplify the ^1H NMR signals. In such conditions double phosphorous peak remains only for diastereoisomers of molecule **4**. This ^{31}P NMR differentiation might be induced by intramolecular N–B bond formation or steric hindrance of closely located boronic moieties and rigid aminophosphonate entities. The ^{11}B NMR signal is not diagnostic for stereochemical consideration because of large broadening of the signals even over 900 Hz.

The ESI-MS studies were performed in order to resolve the fragmentation pattern of the new group of compounds. All molecules bearing aminobenzyl group exhibited as a main molecular signal at 320 (−) *m*/*z*. The exception was compound **1**, in which most probably immediate dehydration occurs responsible for appearance of signal at 302 (−) *m*/*z*. The same peak was found for the remaining compounds showing that dehydration was standard upon MS conditions. Subsequently, the formation of dimers upon abstraction of two water molecules 605 (−) *m*/*z* was observed. The molecular decomposition was also visible by detachment of the boronate group 276 (−) *m*/*z* and fragmentation of the phosphonate unit 240 (−) *m*/*z*. An interesting fragmentation pattern was found for di(aminoboronbenzylphosphonic) acids **4**–**6**. The molecule **4** substituted in *ortho* position exhibited only traces of molecular signal at 487 (−) *m*/*z*, which were present in the case of compounds **5**–**6**. They showed characteristic stepwise dehydration reaction under ESI-MS conditions. If considering the compound containing a boronic group in the *para* position the observed peak is at 469 (−) *m*/*z* (one molecule of water is released), while for *meta* 469 (−) *m*/*z* and 451 (−) *m*/*z* (two signals: one and two water molecules released). For *ortho* derivative three and four water molecules dissociate at 433 (−) *m*/*z* and 415 (−) *m*/*z*. This phenomenon could be related to structural alignment of amine group or phosphonate moiety, which can prompt dehydration reaction. Additional indication of the essential role of this acidic group is the disappearance of molecular signals for boronic acids being substituted at *ortho* position for **1** and **4**. This may also be explained regarding the direct trigonal boron binding to amine nitrogen B(OH)–N or B(OH)–O–P.

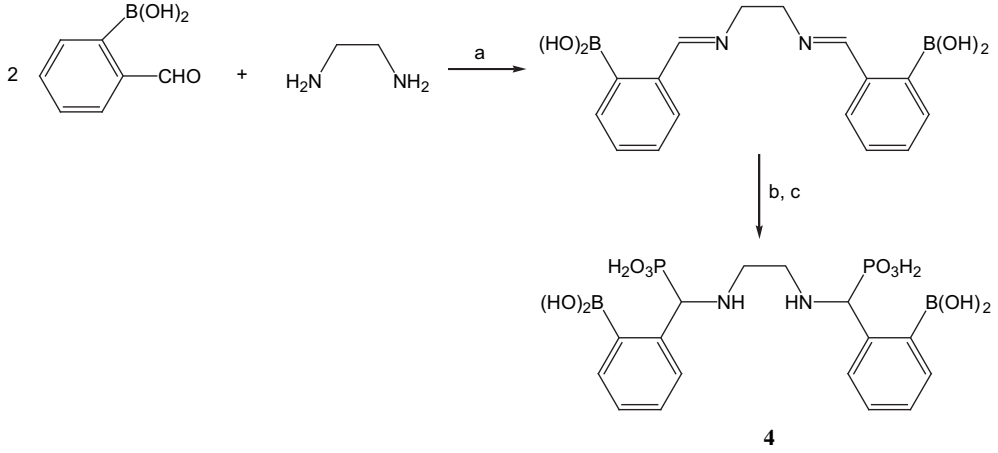

Fig. 2. Synthesis of *N*,*N*-ethyl aminoboronbenzylphosphonate **4**. a) MeOH, b) DCM, $P(OSiCH_3)_3$, c) 10% MeOH in H_2O.

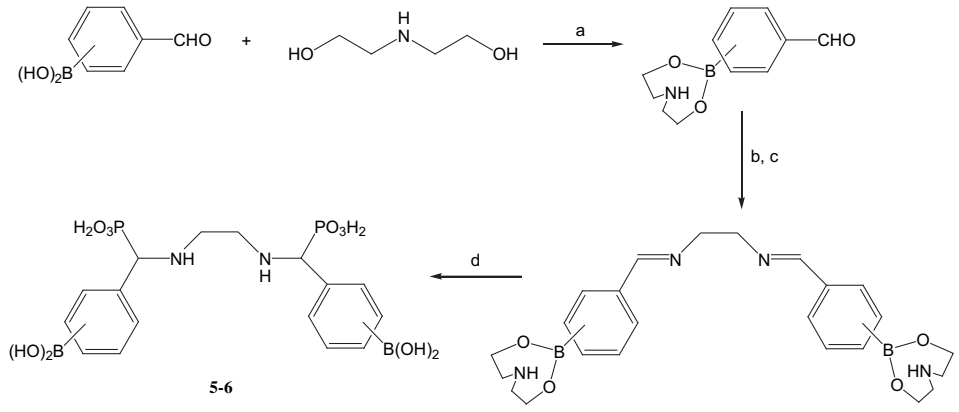

Fig. 3. Synthesis of *N*,*N*-ethyl aminoboronbenzylphosphonates **5**–**6**. a) THF, 2-propanol, b) ethylenediamine, MeOH, c) DCM, $P(OSiCH_3)_3$, d) 10% MeOH in H_2O.

The examination of the ^{11}B NMR data performed with addition of NaOH showed the same differentiation in chemical shifts: for compounds **2**, **3**, **5** and **6** the signal appears at *ca.* 3 ppm, while for **1** and **4** it is close to 10 ppm showing different behaviour of *ortho* substituted compounds, most likely resulting from intramolecular cyclization caused by B–N or B–O–P binding.

3. Conclusions

In this work the simple and convenient synthetic routes for the new compounds bearing aminoboronphosphonic units were developed. The obtained molecules revealed interesting fragmentation pattern under ESI-MS conditions, most likely depending upon position of the boronic unit with respect to aminophosphonate group. These compounds are interesting as potential supramolecular hosts, BNTC agents and building blocks for Suzuki-Miyaura or Petasis reactions.

4. Experimental

4.1. General procedure – preparation of a Schiff base for compounds **1**–**3**

A mixture of adequate formylphenylboronic acid (1.0 g, 6.7 mmol), benzylamine (0.8 g, 7.3 mmol) and 50 cm^3 of dichloromethane (methylene chloride) was refluxed for 7 h. After that time the volatiles were removed under reduced pressure resulting in a yellow residue containing a Schiff base, which was not further purified.

4.2. General procedure – preparation of N-benzyl aminoboronbenzylphosphonic acids **1**–**3**

A mixture of trimethyl phosphite (0.87 cm^3, 0.9 g, 7.3 mmol) and bromotrimethylsilane (4.4 cm^3, 5.1 g, 33.3 mmol) was dissolved in 40 cm^3 of dried methylene chloride, cooled to −5 °C and stirred for 45 min. After this time 1.6 g of a crude Schiff base was suspended in 15 cm^3 of dried methylene chloride and added to the solution of *in situ* generated tris(trimethylsilyl) phosphite. This solution was stirred for 48 h at a room temperature. After that time the reaction mixture was evaporated and the yellow residue was treated with a methanolic solution (5 cm^3 of methanol and 15 cm^3 water) and stirred overnight. Crude product was filtered off and dissolved in 1 M solution of sodium hydroxide. Subsequently, 1 M of hydrochloric acid was added dropwise until a white precipitate was formed which was filtered off and washed with diethyl ether.

4.2.1. N-Benzylamino-2-boronbenzylphosphonic acid **1**

^1H NMR (D_2O + NaOD, 600 MHz, δ (ppm)): 3.26 (d, J = 13.8 Hz, 1H), 3.84 (d, J_{H-P} = 17.2 Hz, 1H), 4.10 (d, J = 13.8 Hz, 1H each), 7.10–7.19 (m, 3H), 7.25–7.38 (m, 6H). ^{13}C NMR (D_2O + NaOD, 150 MHz, δ (ppm)): 51.96 (d, J_{C-P} = 7.7 Hz), 62.63 (d, J_{C-P} = 125.8 Hz), 124.95 (bs), 126.59 (bs), 127.35 (bs), 128.14, 128.96, 129.53 (bs), 135.70, 142.22 (d, J_{C-P} = 5.18 Hz). ^{13}P NMR (D_2O + NaOD, 243 MHz, δ (ppm)): 13.9. ^{11}B NMR (D_2O + NaOD, 192 MHz, δ (ppm)): 9.9. Yield 44.2%, 0.95 g, 3.0 mmol, decomposing at 310 °C.

4.2.2. N-Benzylamino-3-boronbenzylphosphonic acid **2**

^1H NMR (D_2O + NaOD, 600 MHz, δ (ppm)): 3.44 (d, J = 12.9 Hz, 1H), 3.55 (d, J = 13.2 Hz, 1H), 3.60 (d, J_{H-P} = 17.7 Hz, 1H), 7.10–7.36 (m, 8H), 7.42 (bs, 1H). ^{13}C NMR (D_2O + NaOD, 150 MHz, δ (ppm)): 51.45 (d, J_{C-P} = 13.41 Hz), 63.57 (d, J_{C-P} = 134.4 Hz), 126.40 (d, J_{C-P} = 4.7 Hz), 126.81 (bs), 127.13 (bs), 128.59, 128.72, 129.12 (bs), 132.06 (d, J_{C-P} = 5.39 Hz), 138.62 (d, J_{C-P} = 4.37 Hz), 139.66. ^{13}P NMR (D_2O + NaOD, 243 MHz, δ (ppm)): 17.19. ^{11}B NMR (D_2O + NaOD, 192 MHz, δ (ppm)): 3.07. Yield 44.3%, 0.95 g, 3.0 mmol, decomposing at 261 °C.

4.2.3. N-Benzylamino-4-boronbenzylphosphonic acid **3**

^1H NMR (D_2O + NaOD, 600 MHz, δ (ppm)): 3.43 (d, J = 13.2 Hz, 1H), 3.56 (d, J = 12.7 Hz, 1H), 3.58 (d, 1H, J_{H-P} = 17.7 Hz,), 7.10–7.31 (m, 7H), 7.39 (d, J = 7.9 Hz, 2H). ^{13}C NMR (D_2O + NaOD, 150 MHz, δ (ppm)): 51.38 (d, J_{C-P} = 13.38 Hz), 63.11 (d, J_{C-P} = 135.5 Hz), 127.23, 128.00 (d, J_{C-P} = 5.1 Hz), 128.62, 128.77, 130.75 (bs), 137.12 (d, J_{C-P} = 4.8 Hz), 139.36. ^{13}P NMR (D_2O + NaOD, 243 MHz, δ (ppm)): 16.80. ^{11}B NMR (D_2O + NaOD, 192 MHz, δ (ppm)): 3.44. Yield 61%, 1.3 g, 4.0 mmol, decomposing at 308 °C.

4.3. General procedure – preparation of a Schiff base for compound **4**

A mixture of 2-formylphenylboronic acid (1.0 g, 6.7 mmol), ethylenediamine (0.18 g, 3 mmol) and 50 cm^3 of methanol was stirred for 3 days. The solvent was then removed under reduced pressure resulting in a yellow residue containing a Schiff base, which was not further purified.

4.4. Preparation of N,N′-ethylenedi(amino-2-boronbenzylphosphonic) acid **4**

A mixture of trimethyl phosphite (1.5 cm^3, 1.57 g, 12.6 mmol) and bromotrimethylsilane (7.6 cm^3, 8.78 g, 57.4 mmol) was dissolved in 50 cm^3 of dried methylene chloride, cooled to −5 °C and stirred for 1 h. After this time 0.93 g of a crude Schiff base was suspended in 10 cm^3 of dried methylene chloride and added to the solution of *in situ* generated tris(trimethylsilyl) phosphite. This solution was stirred for 48 h at a room temperature. The reaction mixture was evaporated and the obtained yellow residue was treated with methanolic solution (10 cm^3 of methanol and 60 cm^3 water) and stirred overnight. Crude product was filtered off and dissolved in 1 M of sodium hydroxide. 1 M of hydrochloric acid was subsequently added dropwise until a white precipitate was formed. It was filtered off and washed with diethyl ether.

^1H NMR (D_2O + NaOD, 300 MHz, δ (ppm)): 2.86–2.97 (m, 2H), 3.17–3.29 (m, 2H), 3.88 and 3.95 (d, 2H all, J_{H-P} = 14.6 Hz and J_{H-P} = 15.8 Hz), 7.17–7.31 (m, 6H), 7.32–7.41 (m, 2H). ^{13}C NMR (D_2O + NaOD, 75 MHz, δ (ppm)): 46.14 (bs), 64.63 (d, J_{C-P} = 124.3 Hz), 124.72 (bs), 126.51 (bs), 127.31, 129.12 (bs), 142.41 (d, J_{C-P} = 5.0 Hz). ^{13}P NMR (D_2O + NaOD, 121 MHz, δ (ppm)): 12.96 and 13.06. ^{11}B NMR (D_2O + NaOD, 192 MHz, δ (ppm)): 10.3. Yield 29%, 0.425 g, 0.87 mmol, decomposing over 300 °C.

4.5. Formation of formylphenyl boronic acids diethanolamine esters of compounds **5**–**6**

To an adequate formylphenylboronic acid (1.0 g, 6.7 mmol) dissolved in 15 cm^3 of tetrahydrofuran (THF) the solution of diethanolamine (0.77 g, 7.3 mmol) in 5 cm^3 of 2-propanol was added. After that a yellow precipitate was formed. The whole mixture was stirred for 3 h in a room temperature to complete the reaction. Next, the precipitate was filtered off, washed with 5 cm^3 of THF and dried. Yield compound: **5** – 99% (1.45 g, 6.6 mmol); **6** – 46% (6.8 g, 3.1 mmol).

4.6. General procedure – preparation of a Schiff base for compounds **5**–**6**

A mixture of the proper formylphenyl diethanolamine boronic ester (**5** – 1.45 g, 6.6 mmol; **6** – 0.395 g, 1.8 mmol) and ethylenediamine (**5** – 0.2 g, 3.3 mmol; **6** – 0.054 g, 0.9 mmol) in 50 cm^3 of methanol was stirred at a room temperature up to 48 h. The volatiles

were then removed under reduced pressure resulting in a white residue containing a Schiff base, which was not further purified.

4.7. Preparation of N,N′-ethylenedi(aminoboronbenzylphosphonic) acids **5**–**6**

Mixtures of trimethyl phosphite (**5** – 0.76 cm^3, 0.8 g, 6.45 mmol; **6** – 0.16 cm^3, 0.171 g, 1.38 mmol) and bromotrimethylsilane (**5** – 4.3 cm^3, 4.9 g, 32.3 mmol; **6** – 0.9 cm^3, 1.05 g, 6.88 mmol) were dissolved in 50 cm^3 of dried methylene chloride, cooled to −5 °C and stirred for 1 h. After this time a proper amount (1.36 g or 0.29) of a crude Schiff base was suspended in 15 cm^3 of dried methylene chloride and added to the solution of *in situ* generated tris(trimethylsilyl) phosphite. This solution was stirred for 48 h at a room temperature. After that time the reaction mixture was evaporated and the yellow residue was treated with a 20 cm^3 of methanol and stirred, evaporated again, treated with 20 cm^3 of water and left stirring for the next day. After 24 h a pale precipitate was filtered off and washed with water and methanol.

4.7.1. N,N′-Ethylenedi(amino-3-boronbenzylphosphonic) acid **5**

^{1}H NMR (D_2O + NaOD, 300 MHz, δ (ppm)): 2.70–2.91 (m, 4H), 3.76 and 3.79 (d, each 1H, J = 16.12 Hz), 7.13–7.28 (m, 4H), 7.39–7.53 (m, 4H). ^{13}C NMR (D_2O + NaOD, 75 MHz, δ (ppm)): 45.04 (d, J_{C-P} = 9.76 Hz), 45.30 (d, J_{C-P} = 10.0 Hz), 63.29 (d, J_{C-P} = 131.2 Hz), 63.45 (d, J_{C-P} = 131 Hz), 126.67 (bs), 127.29, 130.26, 131.83 (d, J_{C-P} = 3.6 Hz), 135.83 (d, J_{C-P} = 4.1 Hz) 135.90 (d, J_{C-P} = 4.13 Hz). ^{13}P NMR (D_2O + NaOD, 121 MHz, δ (ppm)): 13.37 (bs). ^{11}B NMR (D_2O + NaOD, 192 MHz, δ (ppm)): 4.1. Yield 33%, 0.29 g, 0.6 mmol, decomposing over 300 °C.

4.7.2. N,N′-Ethylenedi(amino-4-boronbenzylphosphonic) acid **6**

^{1}H NMR (D_2O + NaOD, 300 MHz, δ (ppm)): 2.46 (bs, 4H) 3.50 (d, 2H, J_{H-P} = 17.48 Hz), 7.14 (d, 4H, J = 7.64 Hz), 7.35 (d, 4H, J = 7.64 Hz). ^{13}C NMR (D_2O + NaOD, 75 MHz, δ (ppm)): 47.38 (d, J_{C-P} = 11.1 Hz), 63.86 (d, J_{C-P} = 134.4 Hz), 127.78 (d, J_{C-P} = 4.63 Hz), 130.67, 137.52 (d, J_{C-P} = 3.23 Hz), 137.59 (d, J_{C-P} = 3.39 Hz). ^{13}P NMR (D_2O + NaOD, 121 MHz, δ (ppm)): 16.50. ^{11}B NMR (D_2O + NaOD, 192 MHz, δ (ppm)): 3.3. Yield 34%, 1.12 g, 2.3 mmol, decomposing over 300 °C.

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