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Unusual reactivity of *ortho*-carbonylphenylboronic acids with diethanolamine

Tomasz Kliś* and Janusz Serwatowski

Warsaw University of Technology, Faculty of Chemistry, Noakowskiego 3, 00-660 Warsaw, Poland

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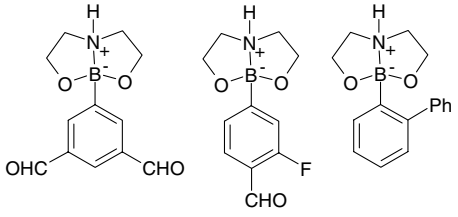
Abstract—The reaction of carbonyl-substituted phenylboronic acids with diethanolamine has been investigated. For compounds containing carbonyl groups at the *meta* or *para* positions the reaction occurs exclusively at the boronic acid. Different reactivities were observed for *ortho*-substituted acetyl- and formylphenylboronic acids where the reaction occurred at both the boronic acid and at the carbonyl group. X-ray studies revealed the presence of a polycyclic structure with tetravalent boron and nitrogen atoms.

1. Introduction

Arylboronic acids are a group of compounds which are employed in a broad range of biological and synthetic applications such as carbohydrate recognition,[1–7] protease enzyme inhibition,[8] neutron capture therapy,[9] or as substrates for the synthesis of biaryls[10] or amino acids.[11,12] These applications have created a demand for functionalized boronic acids. Carbonyl group-containing boronic acids are especially valuable substrates as the carbonyl group can be easily modified to give complex structures. Recent examples include the synthesis of (*N*-alkyl)-aminomethylphenylboronic acids via reductive amination of formylphenylboronic acids[13] and formation of arylboronic acids containing a chalcone moiety in aldol type reactions between 4-acetylphenylboronic acids and aldehydes.[14] However, the Lewis acid character of the boron atom usually requires protection of the dihydroxyboryl group with diethanolamine before modification of the structure.[15,16] The advantage of generating diethanolamine complexes is that they provide stable high melting solids,[17] which can be easily purified and later hydrolyzed back to boronic acids.[18] The protection relies on the extremely low solubility of the diethanolamine complexes in THF and is operationally simple: diethanolamine is added dropwise to a solution of boronic acid in THF to form a complex as a precipitate. According to this procedure we prepared complexes **1** and **2**, in excellent yields (see Scheme 1).

The structures of these types of complex were confirmed by X-ray studies. For example, the B–O bond lengths in known complex **3** are nearly identical (1.464(2) and 1.448(2) Å) and the B–N bond length is 1.658(2) Å.[19] Next we were interested in the synthesis of analogous diethanolamine complexes with *ortho*-acetylphenylboronic acid and *ortho*-formylphenylboronic acid. Unexpectedly, we did not observe any precipitate formation which was characteristic for reactions with other boronic acids. Instead, evaporation of the solvent gave the crystalline, air stable boronic acids **4** and **5** both in 77% yield (Scheme 2).

Their structures were solved by multinuclear NMR spectroscopy. The ^{11}B NMR spectra revealed one signal at 14 ppm attributed to a tetrahedral boron atom connected to one carbon, two oxygen and one nitrogen



1 2 3

Scheme 1.

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* Corresponding author. Tel.: +48 22 2347575; fax: +48 22 6282741; e-mail: ktom@ch.pw.edu.pl

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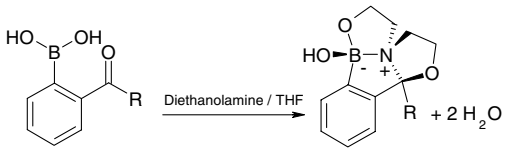

4 R= CH_3, **5** R= H

Scheme 2.

atoms.[20] Contrary to the ^{13}C NMR spectra of **1** and **2**, where two resonances due to diethanolamine carbon atoms were apparent, for **4** and **5**, four resonances were observed. This suggested that the carbon atoms from diethanolamine were not identical. These measurements were supported by X-ray diffraction studies which revealed the presence of three, fused five-membered rings in **4** and **5** (Figs. 1 and 2). This unexpected result

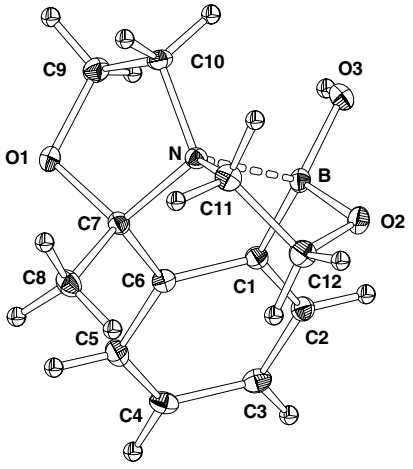

Figure 1. ORTEP drawing of **4** with thermal ellipsoid plot (50% probability). Selected bond lengths (Å): B–N 1.780(5), B–O(2) 1.473(9), B–O(3) 1.402(3), N–C(7) 1.541(4), N–C(11) 1.487(7), N–C(10) 1.492(7), C(7)-O(1) 1.444(8). Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 639871.

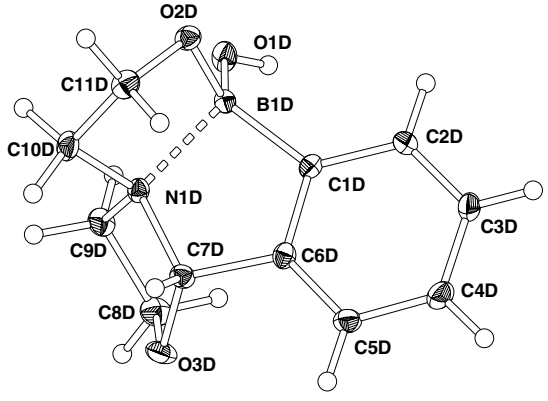

Figure 2. ORTEP drawing of **5** with thermal ellipsoid plot (50% probability). Selected bond lengths (Å): B1D–N1D 1.780(5), B1D–O1D 1.400(3), B1D–O2D 1.460(4), N1D–C7D 1.513(3), N1D–C10D 1.482(4), N1D–C9D 1.491(3). Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 639872.

was possible because of the close proximity of the two Lewis acid centres. The boron and carbonyl carbon atoms act as nitrogen acceptors. The carbonyl group undergoes nucleophilic addition to give the respective *N*,*O*-acetals and the boron atom undergoes complexation with the O and N atoms. It should be noted that for the phenylboronic acid containing the less reactive *ortho*-neopentyloxycarbonyl group, complexation with diethanolamine occurred exclusively at the boron atom.[21]

Analysis of the crystal structure of **4** shows the presence of tetravalent B, N, and C(7) atoms. The B–N bond is much longer than the N–C bonds and is even greater than the range 1.666(3)–1.762(3) reported for other cyclic boron–nitrogen complexes, where B and N atoms are part of five-membered rings.[22–27] The molecule contains three five-membered rings. The B–N–C(7)–C(6)–C(1) ring is essentially coplanar with the benzene ring. The CH_3– and OH– groups as well as the C(7)–O(1)–C(9)–C(10)–N and N–B–O(2)–C(12)–C(11) rings are on the opposite sides of the benzene ring plane. The X-ray studies of **5** revealed the presence of four molecules in the independent part of the unit cell.

The bond lengths in **5** differ only marginally and the geometry is similar to **4**. The obtained complexes contain three chiral centres but they were formed as racemates. Summing up, the diethanolamine protection of carbonylarylboronic acids works well when the carbonyl group is in a *meta* or *para* position with respect to the boron atom. This method, however, is not effective for *ortho* formyl- and *ortho* acetylarylboronic acids because of the simultaneous protection of the boronic acid and carbonyl group. Unfortunately, **4** and **5** do not undergo the typical reaction with amines which is characteristic for other carbonylarylboronic acids. However, **4** and **5** contain an O–C–N moiety which can be reactive when the oxygen atom is bonded to a phenyl ring.[28] This interesting property opens the way to studies on the applications of compounds based on **4** and **5** as chemosensors.

2. Experimental

Compound **1**. Diethanolamine (1.05 g, 0.01 mol) in THF (50 mL) was added dropwise to a solution of 3,5-diformylphenylboronic acid (1.77 g, 0.01 mol) in THF (50 mL) at room temperature. The resulting precipitate was filtered off, washed with THF and dried in air to give **1** as a colourless solid, mp 214–215 °C. Yield: 2.3 g (93%). ^1H NMR (DMSO, 400 MHz) δ 10.11 (s, 2H), 8.26 (d, $J = 1.6$ Hz, 2H), 8.22 (s, 1H), 7.13 (m, 1H), 3.95–3.83 (m, 4H), 3.17–3.10 (m, 2H), 2.96–2.91 (m, 2H). ^{13}C NMR (DMSO, 100 MHz) δ 193.64, 139.36, 135.49, 129.05, 63.32, 50.83. IR (cm^{-1}): 3108, 2868, 1708, 1588. Anal. Calcd for $C_{12}H_{14}BNO_4$: C, 58.35; H, 5.67; N, 5.67. Found: C, 58.23; H, 5.64; N, 5.61.

Compound **2**. Prepared as described for **1** starting from 3-fluoro-4-formylphenylboronic acid (1.67 g, 0.01 mol). The crude precipitate was filtered off, washed with

THF and dried in air to give **2** as a colourless solid, mp 201–202 °C. Yield: 2.2 g (93%). ^{1}H NMR (DMSO, 400 MHz) δ 9.94 (d, $J = 1.2$ Hz, 1H), 7.69–7.66 (t, $J = 7.6$ Hz, 1H), 7.60–7.58 (d, $J = 7.6$ Hz, 1H), 7.43–7.41 (d, $J = 8.8$ Hz, 1H), 7.27 (m, 1H), 3.88–3.82 (m, 2H), 3.74–3.69 (m, 2H), 3.20–3.12 (m, 2H), 2.90–2.85 (m, 2H). ^{13}C NMR (DMSO, 100 MHz) δ 192.45, 167.44–165.03 (d, $J = 240.4$ Hz), 137.40–137.33 (d, $J = 6.8$ Hz), 135.58–135.47 (d, $J = 11.4$ Hz), 124.74–124.73 (d, $J = 1.6$ Hz), 114.01–113.74 (d, $J = 26.6$ Hz), 62.67, 50.84. IR (cm^{-1}): 3140, 2860, 1696, 1560. Anal. Calcd for $C_{11}H_{13}BNO_3F$: C, 55.74; H, 5.49; N, 5.91. Found: C, 55.69; H, 5.43; N, 5.85.

2.1. (*N–B*)-5-Hydroxy-8-methyl-6,7-benzo-4,9-dioxa-1-aza-5-bora[6,3,0]undecane (4)

Diethanolamine (1.05 g, 0.01 mol) in THF (50 mL) was added dropwise to a solution of *ortho*-acetylphenylboronic acid (1.63 g, 0.01 mol) in THF (50 mL) at room temperature. The resulting light yellow solution was left for 1 day to evaporate. The resulting yellow crystalline solid was washed with diethyl ether. Finally, the solid was recrystallized from THF (50 mL) to give **4** as colourless crystals, mp 100–102 °C. Yield: 1.7 g (77%). ^{1}H NMR (DMSO, 400 MHz) δ 7.28–7.21 (m, 4H), 4.52 (s, 1H), 3.82–3.78 (m, 1H), 3.61–3.54 (m, 2H), 3.40–3.31 (m, 2H), 3.06–2.97 (m, 2H), 2.80–2.73 (m, 1H), 1.70 (s, 3H). ^{13}C NMR (DMSO, 100 MHz) δ 145.69, 129.05, 128.13, 127.28, 122.45, 101.29, 62.69, 60.22, 53.54, 52.96, 23.10. IR (cm^{-1}): 3590, 3410, 2860, 1480. Anal. Calcd for $C_{12}H_{16}BNO_3$: C, 61.85; H, 6.87; N, 6.01. Found: C, 61.74; H, 6.86; N, 5.96.

2.2. (*N–B*)-5-Hydroxy-6,7-benzo-4,9-dioxa-1-aza-5-bora[6,3,0]undecane (5)

Prepared as described for **4** starting from *ortho*-formylphenylboronic acid (1.50 g, 0.01 mol). The crude product was washed with diethyl ether and recrystallized from THF (50 mL) to give **5** as colourless crystals, mp 70–72 °C. Yield: 1.6 g (77%). ^{1}H NMR (DMSO, 400 MHz) δ 7.27–7.18 (m, 4H), 5.78 (s, 1H), 4.55 (s, 1H), 4.02–3.99 (m, 1H), 3.64–3.56 (m, 3H), 3.36–3.33 (m, 1H), 3.08–2.87 (m, 3H). ^{13}C NMR (DMSO, 100 MHz) δ 141.52, 129.60, 128.60, 127.22, 123.36, 99.99, 65.37, 60.19, 57.95, 53.36. IR (cm^{-1}): 3436, 3292, 2880, 1460. Anal. Calcd for $C_{11}H_{14}BNO_3$: C, 60.33; H, 6.40; N, 6.40. Found: C, 60.23; H, 6.35; N, 6.31.

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