Notes

Synthesis of Benzene- and Pyridinediboronic Acids via Organotin Compounds

Sandra D. Mandolesi,[†] Santiago E. Vaillard,[‡] Julio C. Podestá,*[,†] and Roberto A. Rossi*[,‡]

Departamento de Química and CONICET (Buenos Aires), Universidad Nacional del Sur, Avenida Alem 1253, 8000 Bahía Blanca, Argentina, and INFIQC (UNC-CONICET), Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, 5000 Córdoba, Argentina

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Summary: 1,4- and 1,3-Bis(trimethylstannyl)benzenes as well as 2,5- and 2,6-bis(trimethylstannyl)pyridines react with borane in THF to give intermediates which on hydrolysis lead to benzene- and pyridinediboronic acids in 79−83% yield. While oxidation of the benzenediboronic acids with alkaline hydrogen peroxide gives the corresponding 1,3- and 1,4-dihydroxybenzenes, the pyridinediboronic acids lead via a double Suzuki reaction with 4-iodoanisole to 2,5- and 2,6-bis(4-methoxyphenyl)-pyridines and react with pinacol to give the corresponding pyridine-2,5-pinacol and pyridine-2,6-pinacol diboronic esters.

Introduction

During the 1970s a series of papers by Thorpe and co-workers showed that it was possible to obtain areneboronic acids as well as other arylboron derivatives from reactions between a variety of aromatic organometallic compounds and borane in tetrahydrofuran (THF).[1] The synthesis of areneboronates has also been reported through palladium-catalyzed borylation of aryl halides or triflates with dialkoxyborane.[2] More recently, we reported a very convenient synthesis of arylboronic acids via transmetalations between aryltrialkylstannanes and borane in THF.[3] Areneboronic and arenediboronic acids are very useful intermediates in organic synthesis[4] and also in polymer chemistry.[5] The first synthesis of 1,4- and 1,3-benzenediboronic acids via reaction between lithium and Grignard reagents of the corresponding benzene dibromides and methyl borate was reported in 1957.[6] Other authors improved this procedure by obtaining 1,4- and 1,3-benzenediboronic acids in 50−60% yield.[7] We now report a convenient synthetic route to 1,4- and 1,3-benzenediboronic acids (**2** and **4**) as well as to new 2,5- and 2,6-pyridinediboronic acids (**6** and **8**).

The easy access to bis(trialkylstannyl)-substituted aryl and heteroaryl compounds via $S_{RN}1$ reactions of trimethylstannyl anions with aryl dichlorides,[8] (chloroaryl)trimethylammonium iodides,[9a] and aryl- and heteroaryl diethyl phosphates[9b] in liquid ammonia prompted us to study the reactions between these diorganotins and borane in THF as a possible route to arenediboronic acids.

Results and Discussion

The bis(trimethylstannyl)-substituted benzenes and pyridines were prepared by photostimulated reactions of the appropriate dichlorobenzenes and dichloropyridines with Me_3Sn^- ions in liquid ammonia. Thus, 1,4-(**1**, 88%) and 1,3-bis(trimethylstannyl)benzenes (**3**, 90%) and 2,5- (**5**, 88%) and 2,6-bis(trimethylstannyl)pyridines (**7**, 86%) were obtained by the $S_{RN}1$ mechanism.[8] In this preliminary study we investigated the reactions of borane with these bis(trimethylstannyl)-substituted compounds according to Scheme 1.

Preliminary experiments were first carried out using compounds **1**, **3**, **5**, and **7** under a variety of reaction conditions to determine whether transmetalation occurred and to find the optimum conditions. The organotin compound was dissolved in dry THF and treated with a solution of borane in the same solvent under dry

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[†] Universidad Nacional del Sur.

[‡] Universidad Nacional de Córdoba.

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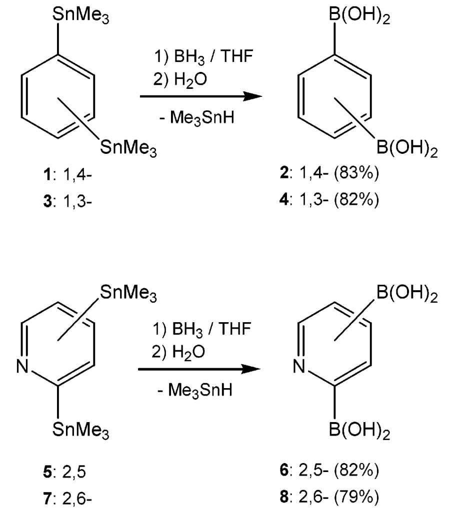
Scheme 1



nitrogen. The solution was stirred at room temperature for 1 h and then heated under reflux for 3 h. After completion of the reaction, water was added to decompose the excess borane and to convert the intermediate aryl- and heteroarylboranes into the corresponding arene- and heteroarenediboronic acids **2**/**4** and **6**/**8**, respectively. The yields shown in Scheme 1 were obtained using the ratio borane/organotin = 3, but we found no differences using higher ratios (4−7). On the other hand, using lower ratios of borane/organotin such as 1 and 1.1, we could not detect the formation of the possible intermediate (trimethylstannyl)benzeneboronic acid and (trimethylstannyl)pyridineboronic acid of types **A** and **B** shown in Figure 1. This would indicate that, if intermediates **A** and **B** were formed, they should react with borane much faster than the starting bis(trimethylstannyl)-substituted aromatic compounds **1**, **3**, **5**, and **7**.

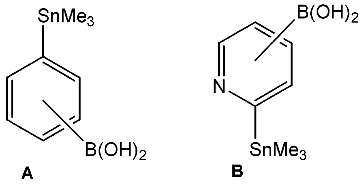
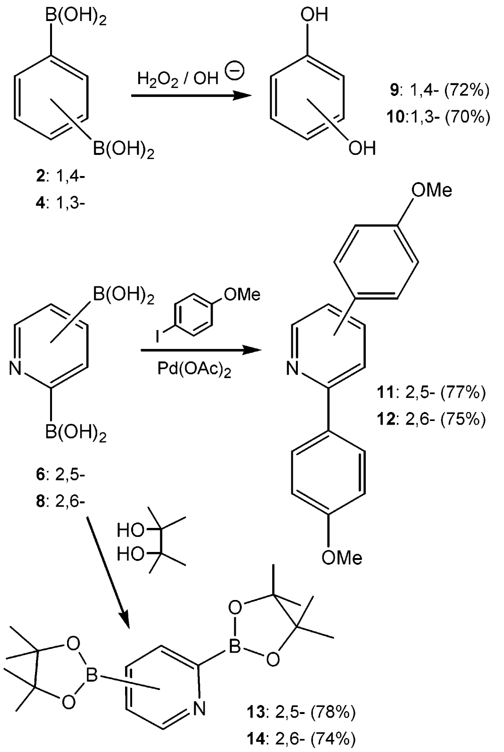


Figure 1. Possible intermediate (trimethylstannyl)benzeneboronic acid and (trimethylstannyl)pyridineboronic acid.

The diboronic acids **2**, **4**, **6**, and **8** were recrystallized from water, and they did not melt below 320 °C. The 1,4- and 1,3-benzenediboronic acids **2** and **4** were easily identified by comparison of their properties with the properties reported for these compounds in the literature.[7,10] The regioselective oxidation of the benzenediboronic acids **2** and **4** with alkaline hydrogen peroxide gave the corresponding 1,4- and 1,3-dihydroxybenzenes **9** and **10**, respectively, in good yields, as shown in Scheme 2.

It should be noted that although it has recently been suggested that this oxidation of areneboronic acids with hydrogen peroxide is a new method for the synthesis of phenols,[11] this reaction was in fact studied by Kuivila et al. during the 1950s[12] and used by Thorpe et al. during the 1970s.[1,13]

Scheme 2



On the other hand, we could not obtain good microanalyses of the new 2,5- and 2,6-pyridinediboronic acids (**6** and **8**). This is not surprising, because it has been reported that boronic acids in general present a host of difficulties with regard to analysis, the principal one being their spontaneous condensation to boroxines to varying degrees.[7] To confirm, at least indirectly, the structure of the pyridinediboronic acids obtained, we first carried out a double Suzuki coupling[14] of compounds **6** and **8** with 4-iodoanisole. These reactions lead to 2,5- and 2,6-bis(4-methoxyphenyl)pyridines (**11** and **12**, respectively) in yields of around 75%, as shown in Scheme 2. The new 2,5-bis(4-methoxyphenyl)pyridine (**11**) was characterized by microanalysis and IR and NMR spectra. The physical characteristics of compound **11** were in agreement with those found in the literature.[15] Then, through the reaction with pinacol (Scheme 2),[16] we obtained the corresponding pyridine-2,5-pinacol (**13**) and pyridine-2,6-pinacol (**14**) diboronic esters, whose ^{1}H NMR spectra confirmed the structure of the starting pyridinediboronic acids **6** and **8**.

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In conclusion, these preliminary studies demonstrate that the transmetalation of bis(trimethylstannyl)benzenes and bis(trimethylstannyl)pyridines with borane in THF is an excellent method for the synthesis of highly pure valuable benzenediboronic acids and new pyridinediboronic acids. The studies also include the first example of a successful double Suzuki reaction that involves the use of pyridinediboronic acids as starting material.

Experimental Section

NMR spectra were obtained in a Bruker ARX 300 instrument. Infrared spectra were recorded with a Nicolet Nexus FT spectrometer. Chemical ionization mass spectra determinations were obtained in a HP 5989 A spectrometer at the Faculty of Pharmacy (Barcelona University, Barcelona, Spain). Microanalyses were performed at Dortmund University (Dortmund, Germany). The refractive indices were measured with a Universal Abbe Zeiss Jena VEB instrument, and the melting points were determined in a Kofler hot stage and are uncorrected. All the solvents and reagents used were analytical reagent grade.

Reactions of Bis(trimethylstannyl)-substituted Benzenes (1/3) and Pyridines (5/7) with Borane in THF. Synthesis of Benzenediboronic acids (2/4) and Pyridinediboronic acids (6/8). The following is a representative procedure.

Synthesis of 2,5-Pyridinediboronic Acid (6). To a stirred solution of **5** (0.5 g, 1.2 mmol) in dry THF (10 mL) was added a solution of borane in THF (3.70 mmol, 3.2 mL of a 1.15 M solution). The preparation was carried out under an atmosphere of nitrogen. The mixture was left at room temperature for 1 h and then refluxed for 3 h. Then the solvent and Me_3SnH (bp 59 °C) thus formed were removed under reduced pressure and a white jellylike residue was obtained. Diethyl ether (10 mL) and water (0.1 mL) were added, the solution was dried with magnesium sulfate, and the solvent was removed under vacuum. The solid 2,5-pyridinediboronic acid was recrystallized from water (0.163 g, 0.98 mmol, 82%). ^1H NMR (DMSO-d_6; δ): 8.30−7.42 (m, 3H), 6.82 (s, 4H). $^{13}C\{^1H\}$ NMR (DMSO-d_6; δ): 141.5, 126.4, 95.8, 80.1, 43.8. IR (KBr, cm^{-1}): ν 3231; 1479.

Under the same reaction conditions 2,6-pyridinediboronic acid (**8**) was obtained in 79% yield. ^1H NMR (DMSO-d_6; δ): 7.55−7.47 (m, 3H), 6.02 (s, 4H). $^{13}C\{^1H\}$ NMR (DMSO-d_6, δ): 122.0, 109.6, 77.6. IR (KBr, cm^{-1}): ν 3320, 1510.

Oxidation of 1,4- and 1,3-Benzenediboronic Acids (2 and 4) to 1,4- and 1,3-Dihydroxybenzenes (9 and 10). The following is a representative procedure.

1,4-Dihydroxybenzene (9). A mixture of a 3 M sodium hydroxide solution (0.6 mL) and 30% hydrogen peroxide (1.9 mL) was added slowly to a solution of **2** (0.2 g, 1.2 mmol) in THF (6 mL) and the resulting mixture stirred for 30 min. Ether (6 mL) was added and the mixture extracted with a 3 M sodium hydroxide solution (3 × 2 mL). The combined aqueous extracts were acidified with dilute hydrochloric acid and extracted with ether (3 × 4 mL). The ether extracts were combined, and the solvent was removed under vacuum. The solid residue was recrystallized from benzene (0.096 g, 0.86 mmol, 72%). Under the same reaction conditions 1,3-dihydroxybenzene (**10**) was obtained in 70% yield.

Double Suzuki Coupling of Pyridinediboronic Acids (6 and 8) with 4-Iodoanisole. Synthesis of 2,5- and 2,6-Bis(4-methoxyphenyl)pyridines (11 and 12). The following is a representative procedure.

2,5-Bis(4-methoxyphenyl)pyridine (11). 4-Iodoanisole (0.33 g, 1.4 mmol), 2,5-pyridinediboronic acid (0.11 g, 0.66 mmol), and triphenylphosphine (0.037 g, 0.14 mmol) were dissolved in 1,2-dimethoxyethane (1.6 mL). Then, K_2CO_3 (2 mL of a 2 M aqueous solution, 3.7 mmol) was added and the mixture was purged with nitrogen. Palladium acetate (0.0082 g, 3×10^{-5} mmol) was added and the mixture refluxed for 20 h. The two phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with water (5 mL) and brine (5 mL) and were dried over magnesium sulfate. After evaporation of the solvent, the oily residue was purified by column chromatography (silica gel 60), **11** being eluted with 9/1 hexane/ethyl acetate (yield 0.15 g, 0.46 mmol, 77%). Mp: 125−126 °C (EtOH). ^1H NMR ($CDCl_3$; δ): 8,2 (d, 1H, $J = 1.5$ Hz), 7.80−7.12 (m, 2H), 6.94−6.82 (m, 8H), 3.77 (s, 3H), 3.75 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$; δ): 159.9, 159.1, 150.0, 141.4, 138.5, 134.8, 132.7, 130.7, 122.3, 128.6, 125.9, 114.1, 113.5, 55.3. Anal. Calcd for $C_{19}H_{17}NO_2$ (291.33): C, 78.32; H, 5.88. Found: C, 78.48; H, 6.04. Under the same reaction conditions 2,6-bis(4-methoxyphenyl)pyridine (**12**) was obtained in 75% yield.

Reaction of Pyridinediboronic Acids (6 and 8) with Pinacol. Synthesis of Pyridine-2,5-pinacol and Pyridine-2,6-pinacol Diboronic Esters (13 and 14). The following is a representative procedure.

Pyridine-2,5-pinacol Ester (13). To a stirred suspension of 2,5-pyridinediboronic acid (**6**; 0.2 g, 1.2 mmol) in benzene (4 mL) were added pinacol (0.285 g, 2.4 mmol) and magnesium sulfate (1.75 g). The mixture was stirred overnight at room temperature and filtered. The filtrate was concentrated in vacuo to afford **13** as an oil. The compound was purified by column chromatography (silica gel 60), **13** being eluted as a colorless oil with 1/1 hexane/ethyl ether (yield 0.31 g, 0.94 mmol, 78%). $\eta_D^{20} = 1.3565$. MS (CI/CH_4): m/z (%) 332.30 (2) $[M^+ + 1]$. ^1H NMR ($CDCl_3$; δ): 8,98 (s, 1H), 7.955 (d, 1H, $^3J(H,H) = 7$ Hz), 7.93 (d, 1H, $^3J(H,H) = 7$ Hz), 1.26 (s, 12H), 1.15 (s, 12H). $^{13}C\{^1H\}$ NMR ($CDCl_3$; δ): 131.87, 124.50, 83.78, 74.06, 29.31, 23.84, 23.79. IR (film, KBr, cm^{-1}): 1472 (ν_{B-C}), 1375 (ν_{B-O}), 1157 (ν_{B-C}), 1091 (ν_{B-C}). Under the same reaction conditions pyridine-2,6-pinacol ester (**14**) was obtained in 75% yield. $\eta_D^{20} = 1.3583$. MS (CI/CH_4): m/z (%) 332.25 (4) $[M^+ + 1]$. ^1H NMR ($CDCl_3$; δ): 7.64 (m, 1H), 7.46 (m, 1H), 7.11 (m, 1H), 1.20 (s, 12H), 1.17 (s, 12H). $^{13}C\{^1H\}$ NMR ($CDCl_3$; δ): 131.46, 129.86, 82.13, 74.06, 23.83, 23.53. IR (film, KBr, cm^{-1}): 1468 (ν_{B-C}), 1367 (ν_{B-O}), 1126 (ν_{B-C}), 1091 (ν_{B-C}).

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