A Practical Preparation of 2-Carboxyphenylboronic Acid and its Application for the Preparation of Biaryl-2-carboxylic Acids using Suzuki Coupling Reactions

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Abstract: A practical synthesis of 2-carboxyphenylboronic from 2-tolylboronic acid and aqueous potassium permanganate under mild conditions is reported. The title compound couples with aryl bromides containing electron-withdrawing groups to give biaryl-2-carboxylic acids.

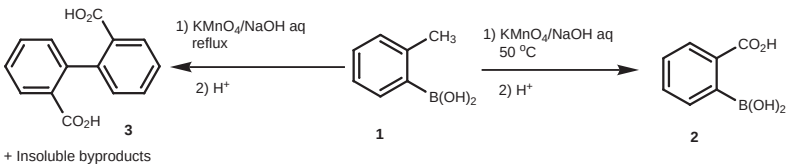
Key words: 2-carboxyphenylboronic acid, 2-tolylboronic acid, biaryl-2-carboxylic acids, Suzuki coupling, palladium catalyst

The Suzuki reaction has become a very important and powerful tool in the construction of C–C bonds in organic chemistry.[1,2] As a result of the tremendous developments in this area in recent years, there are increasing demands for boronic acid products. In the process of preparing a variety of boronic acids, we needed a method to prepare 2-carboxyphenylboronic acid.

Carboxyphenylboronic acids are typically prepared from oxidation of tolylboronic acids,[3] which, in turn, are synthesized from commercially available chloro- or bromotoluenes. 3- and 4-Carboxyphenylboronic acids are readily prepared from 3- and 4-tolylboronic acids, respectively. However, it was reported more than 60 years ago that the attempts to synthesize 2-carboxyphenylboronic acid from 2-tolylboronic acid did not yield the desired product.[3] Up to now, there have been no reported synthetic methods for 2-carboxyphenylboronic acid.[4] We describe here a practical method for the preparation of 2-carboxyphenylboronic acid under mild conditions and its Suzuki coupling reactions with aryl bromides under various conditions to prepare biaryl-2-carboxylic acids.

The title compound was prepared from 2-tolylboronic acid by reacting with potassium permanganate in aqueous NaOH solution, followed by removal of the manganese dioxide precipitate and workup of the acidified aqueous solution. Strict temperature control is essential to the success of the preparation of 2-carboxyphenylbronic acid. The optimal reaction temperature was found to be between 40−50 °C. At room temperature, the reaction did not proceed after 12 hours with most of the starting material being recovered; at 60−70 °C, it yielded a mixture of 2-carboxyphenylbronic acid and diphenic acid; at reflux, it afforded diphenic acid and insoluble byproducts. Diphenic acid is probably generated by homocoupling of 2-carboxyphenylboronic acid under the oxidative reaction conditions. This type of the reaction is known under Suzuki coupling conditions.[5] Neither diphenic acid nor insoluble byproduct(s) could be isolated as a single compound by changing the reaction time, temperature and the amount of the oxidant. Thus, 2-carboxyphenylboronic acid was prepared in 76% yield by oxidation of 2-tolylboronic acid with potassium permanganate by controlling the reaction temperature at 40−50 °C (Scheme). The mild reaction conditions, easy operations and economical starting materials make this method potentially useful for large scale synthesis of 2-carboxyphenylboronic acid.

With 2-carboxylphenylboronic acid in hand, several Suzuki coupling reactions were carried out. First, the coupling reaction with 4-bromobenzotrifluoride was examined, mainly because the coupling reaction would provide a one-step method to synthesize xenalipin, a compound which lowers cholesterol and triglyceride levels in plasma.[6] The reaction indeed gave xenalipin in 72% yield using 5% $Pd(PPh_3)_4$, and 61% yield using 1% $Pd(PPh_3)_4$ (Table, entries 1 and 2, respectively). In order to examine



Scheme Preparation of 2-Carboxyphenylboronic acid

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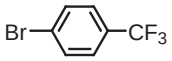
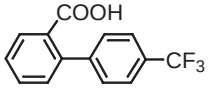
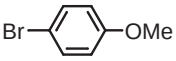
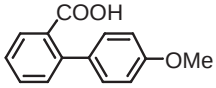
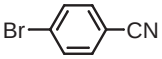
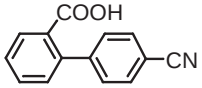
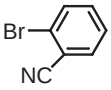
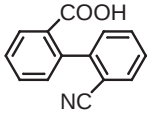
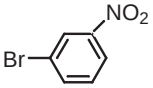
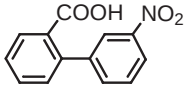
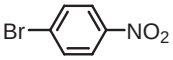
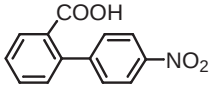
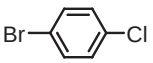
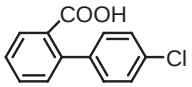
the scope of the reaction, 2-carboxyphenylboronic acid was subjected to similar conditions with 4-bromoanisole, which bears an electron-donating methoxyl group. The reaction yielded the desired product in about 20%. The low yield is probably due to the electron-donating nature of the methoxyl group. In an effort to improve the coupling yield of the reaction, we tried several different catalytic systems. Buchwald et al[7] reported a catalytic system in which sterically hindered boronic acids coupled with different aryl bromides, even chlorides, in high yields. Under their conditions, 2-carboxylphenylboronic acid did not react with 4-bromoanisole in toluene after 24 hours with most of the starting material being recovered (Method C, entry 3). We reasoned that aqueous conditions might be beneficial to the reaction due to the presence of the polar carboxyl group. Substituting toluene with DMF–H_2O gave the product in 18% yield (Method D, entry 4); switching the solvent to MeCN–H_2O afforded the product in 30% yield (Method E, entry 4). We then examined a non-phosphine system, namely palladium/imidazol-2-ylidene system which is very effective in coupling aryl chlorides with arylboronic acids.[8] Unfortunately, neither the original (in dioxane) nor the modified aqueous condition (in MeCN–H_2O) afforded any detectable amounts of the coupling product (results not shown). Other coupling systems in aqueous media, such as Pd/C/DMA–H_2O,[9] Pd/C/K_2CO_3/*i*-PrOH–H_2O,[10] were also examined and yields of these reactions were no better than 30% (results not shown). Subsequently, the modified Buchwald's method was chosen for further study of the coupling reactions.

Under modified Buchwald's conditions, the reactions of 2-carboxyphenylboronic acid were examined with other aryl bromides. They generally gave the desired products in moderate to good yields. For example, both 2- and 4-bromobenzonitrile coupled with 2-carboxyphenylboronic acid in 49 and 70% yield, respectively (entries 6 and 5). The low yield with the former is likely a result of steric effects.[11,12] It is worth noting that the coupling reaction with 3- and 4-bromonitrobenzene gave good yields of the desired products, with the nitro group intact. Finally, the re-

Table The Coupling Reactions of 2-Carboxyphenylboronic Acid with Aromatic Bromides

Entry	Aromatic Bromide	Product	Conditions[a]	Yield (%)
1			A	72
2			B	61
3			A,C	20, 0
4			D,E	18,30
5			E	70
6			E	49
7			E	50
8			E	74
9			E	82

[a] Method A: Compd **2**/bromide/K_2CO_3 = 1:1.5:2.0 mmol, 5% $Pd(PPh_3)_4$ in MeCN–H_2O, 90 °C, 12 h; Method B: 1% $Pd(PPh_3)_4$ used instead of 5% as in Method A; Method C: **2**/bromide/K_3PO_4 = 1:1.5:2.0 mmol, 3% $Pd(OAc)_2$/6% Cy_2P(bi-Ph) in toluene, 100 °C, 24 h; Method D: **2**/bromide/K_2CO_3 = 1.1.5:3.0 mmol, 3% $Pd(OAc)_2$/6% Cy_2P(bi-Ph) in DMF–H_2O, 90 °C, 20 h; Method E: MeCN–H_2O used instead of DMF–H_2O in Method D.

action with 4-bromochlorobenzene gave the expected coupling product in 82% yield.

In conclusion, we have developed a practical method, from readily available starting materials, for preparation of 2-carboxyphenylboronic acid by oxidation of 2-tolylboronic acid under mild conditions. The title compound reacts with the electron-rich 4-bromoanisole to afford the corresponding biaryl-2-carboxylic acid in modest yields under several different conditions, and with a variety of aryl bromides with electron-withdrawing groups to provide biaryl-2-carboxylic acids in fair to good yields.

All reactions were carried out in oven-dried glassware under N_2. 2-Tolylboronic acid was manufactured by Optima Chemical Group. $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd_2(dba)_3$, 2-(dicyclohexylphosphino)biphenyl [Cy_2P(bi-Ph)] and 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride were purchased from Strem Chemical Co. All other reagents used in the reactions were purchased from Aldrich and used as received. Melting points were determined in an open capillary tube on a MEL-TEMP 3.0 instrument and are uncorrected. ^{1}H and ^{13}C NMR data were recorded at 300 MHz spectrometer (75 MHz for ^{13}C), and DMSO-d_6 was used as the solvent and chemical shifts reported in ppm with reference to TMS. Karl-Fisher tests were conducted on a Mettler DL 70ES titrator.

2-Carboxyphenylboronic Acid (2)

2-Tolylboronic acid (13.6 g, 0.1 mol) was dissolved in a solution of 50% aq NaOH (50 mL) and H_2O (100 mL) at r.t. and the solution was heated to 50 °C. A solution of $KMnO_4$ (36.0 g, 0.23 mol) in H_2O (400 mL) was added in six portions over 1 h. The green-colored solution was kept at 50 °C for an additional 3 h. It was cooled to 0 °C and treated with concd HCl to pH 8, and then filtered through a Celite pad to remove the precipitated MnO_2. The filtrate was further acidified dropwise with concd HCl to pH 2 at 0 °C. The lightly brown solution was evaporated under reduced pressure to nearly dryness and acetone (500 mL) was added. The salt was filtered off and the solution was evaporated to give the crude product, which was washed with a minimum amount of cold H_2O to yield a white solid. It was dried overnight in vacuum at 50 °C to give the final product as a white solid (12.6 g, 76%); mp 159−162 °C.

^{1}H NMR: δ = 7.70 (m, 4 H), 5.13 (br s, 3 H).

^{1}H NMR (DMSO-d_6–D_2O): δ = 7.69 (d, *J* = 7.5 Hz, 1 H), 7.28 (dd, *J* = 7.2, 7.2 Hz, 1 H), 7.41 (d, *J* = 7.2 Hz, 1 H), 7.35 (dd, *J* = 7.2, 7.5 Hz, 1 H).

^{13}C NMR (DMSO-d_6–D_2O): δ = 170.3, 134.1, 132.1, 130.7, 129.4(d, $^1J_{CB}$ = 45 Hz), 128.0, 127.3.

Anal. KF Test: found 21.8% (cacld 21.7%).

Diphenic Acid (3)

2-Tolylboronic acid (0.68 g, 5.0 mmol) was dissolved in a solution of 50% aq NaOH solution (5 mL) and H_2O (10 mL) at r.t. The solution was heated to ~60 °C and treated with three portions of a solution of $KMnO_4$ (2.0 g) in H_2O (30 mL) over 30 min and then heated at reflux for 20 h. It was cooled down to r.t. and filtered through a Celite pad. The filtrate was cooled to 0 °C and acidified with conc. HCl to pH 2 to give a white precipitate, which was filtered and washed with cold H_2O to give a white solid (0.51 g). It was then dissolved in MeOH and filtered. Evaporation of the solvent afforded the title compound (0.26 g) as a white solid; mp 222−224 °C (Lit.[13] mp 220−221 °C).

^{1}H NMR: δ = 12.47 (br s, 2 H), 7.86 (d, *J* = 7.5 Hz, 2 H), 7.53 (dd, *J* = 7.5, 7.5 Hz, 2 H), 7.41 (dd, *J* = 7.5, 7.5 Hz, 2 H), 7.14 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR: δ = 167.8, 143.0, 131.0, 130.3, 129.5, 126.9.

Coupling Reactions of 2-Carboxyphenylboronic Acids with Aromatic Bromides; General Procedure

Under N_2, $Pd(PPh_3)_4$ (60 or 10 mg, 0.05 or 1.0 mmol), or $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and Cy_2P(bi-Ph) (21.0 mg, 0.06 mmol), was (were) added to a solution of a bromide (1.0 mmol), 2-carboxyphenylboronic acid (0.23 g, 1.4 mmol) and K_2CO_3 (0.42 g, 3.0 mmol) in MeCN–H_2O (10 mL, 3:1) at r.t. The mixture was heated to 90 °C for 12−24 h, and then the hot mixture was filtered. Bulk of the solvent was removed by rotatory evaporation. The residue was added to aq 10% NaOH solution (10 mL) at 0 °C and extracted with CH_2Cl_2 (3 × 10 mL). The aqueous layer was then washed with brine and cooled down to 0 °C and acidified with conc. HCl to pH 2. The white precipitate was filtered out and washed with cold H_2O and dried to give the product (Table).

4′-(Trifluoromethyl)[1,1′-biphenyl]-2-carboxylic Acid

Mp 168–170 °C.

^{1}H NMR: δ = 12.88 (s, 1 H), 7.83–7.81 (m, 1 H), 7.76 (d, *J* = 8.1 Hz, 2 H), 7.65−7.59 (m, 1 H), 7.54−7.49 (m, 3 H), 7.40 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR: δ = 160.9, 145.3, 140.0, 131.8, 131.3, 130.6, 129.6, 129.2, 128.1, 127.6 (q, $^2J_{CF}$ = 31 Hz), 124.9 (q, $^3J_{CF}$ = 3.4 Hz), 124.4 (q, $^1J_{CF}$ = 270 Hz).

4′-Methoxy[1,1′-biphenyl]-2-carboxylic Acid

Mp 140–142 °C (Lit.[14] 142–143 °C).

^{1}H NMR: δ = 12.78 (br s, 1 H), 7.67 (d, *J* = 7.5 Hz, 1 H), 7.54 (dd, *J* = 7.8, 7.5 Hz, 1 H), 7.43−7.34 (m, 2 H), 7.26 (d, *J* = 8.1 Hz, 2 H), 6.97 (d, *J* = 7.8 Hz, 2 H), 3.79 (s, 3 H).

^{13}C NMR: δ = 169.9, 158.6, 140.4, 133.0, 132.3, 130.7, 130.3, 129.4, 128.9, 126.8, 113.6, 55.1.

4′-Cyano[1,1′-biphenyl]-2-carboxylic Acid

Mp 216–218 °C (Lit.[15] 215–218 °C).

^{1}H NMR: δ = 12.93 (br s, 1 H), 7.86 (m, 3 H), 7.63 (dd, *J* = 7.5, 7.2 Hz, 1 H), 7.56−7.51 (m, 3 H), 7.40 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR: δ = 168.7, 146.1, 139.9, 131.9, 131.5, 131.4, 130.5, 129.7, 129.4, 128.3, 118.9, 109.9.

2′-Cyano[1,1′-biphenyl]-2-carboxylic Acid

Mp 168–170 °C (Lit.[16] 170–172 °C).

^{1}H NMR: δ = 12.94 (br s, 1 H), 8.01 (d, *J* = 7.2 Hz, 1 H), 7.87 (d, *J* = 7.8 Hz, 1 H), 7.76−7.67 (m, 2 H), 7.66−7.60 (m, 1 H), 7.57−7.52 (m, 1 H), 7.43 (d, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR: δ = 167.4, 145.3, 139.0, 133.1, 132.2, 132.1, 131.1, 130.3, 129.5, 128.9, 127.9, 118.2, 111.2.

3′-Nitro[1,1′-biphenyl]-2-carboxylic Acid

Mp 154–156 °C (Lit.[17] 155–157 °C).

^{1}H NMR: δ = 12.99 (br s, 1 H), 8.22 (d, *J* = 7.8 Hz, 1 H), 8.11 (s, 1 H), 7.86 (d, *J* = 7.5 Hz, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 7.72−7.61 (m, 2 H), 7.54 (dd, *J* = 7.5, 7.5 Hz, 1 H), 7.45 (d, *J* = 6.9 Hz, 1 H).

^{13}C NMR: δ = 168.7, 147.5, 142.7, 139.2, 135.2, 131.6, 131.5, 130.8, 129.9, 129.6, 128.4, 122.9, 122.1.

4′-Nitro[1,1′-biphenyl]-2-carboxylic Acid

Mp 232–235 °C (Lit.[18] 231 °C).

^{1}H NMR: δ = 13.02 (br s, 1 H), 8.26 (d, *J* = 7.8 Hz, 2 H), 7.88 (d, *J* = 7.5 Hz, 1 H), 7.68−7.53 (m, 4 H), 7.43 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR: δ = 168.6, 148.2, 146.6, 139.6, 131.5, 130.5, 129.9, 129.8, 128.5, 123.1.

4′-Chloro[1,1′-biphenyl]-2-carboxylic Acid
Mp 164–165 °C (Lit.[15] 162–164 °C).

^{1}H NMR: δ = 12.99 (br s, 1 H), 8.27 (d, *J* = 8.7 Hz, 2 H), 7.87 (d, *J* = 7.5 Hz, 1 H), 7.69−7.53 (m, 4 H), 7.43 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR: δ = 168.6, 148.2, 146.6, 139.6, 131.5, 130.5, 129.9, 129.8, 128.5, 123.1.

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