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One-pot synthesis of 5,5′-dibromo-2,2′-dipyridylacetylene and its boronic acid derivative

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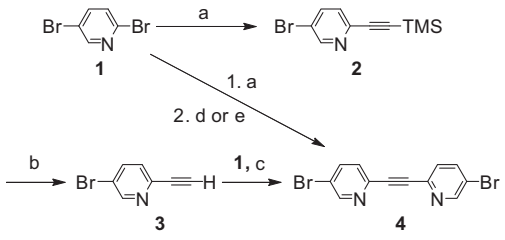
ABSTRACT

5,5′-Dibromo-2,2′-dipyridylacetylene was prepared from 2,5-dibromopyridine and (trimethylsilyl)acetylene via the new one-pot synthesis approach using a regioselective palladium-catalyzed coupling reaction with a 60% yield. Several protocols of lithium–halogen exchange were then attempted to synthesize 6,6′-(1,2-ethynediyl)bis[3-pyridylboronic acid] from 5,5′-dibromo-2,2′-dipyridylacetylene. The former was successfully obtained with a 54% yield by a reverse addition method using toluene and THF and it showed potential as a useful building block for cross-coupling reactions in the formation of carbon–carbon bonds.

Diarylacetylenes are important components in polymers, oligomers, and dendrimers, because their conjugated systems exhibit unique optical and electronic properties, as well as environmental stabilities.[1] Furthermore, compounds such as diarylacetylenes that bear carbon–carbon triple bonds are extensively employed in pharmaceuticals and fine chemicals.[2] Among them, 2,2′-dipyridylacetylene, a linear and rigid molecule with an extended π-conjugation, has won great attention for a proton transfer-mediated electron transfer in organic materials and its molecular complexes with organic proton donors or inorganic compounds showed DA-type intermolecular interactions.[3] In addition, recently, new methods for the preparation of 2,2′-dipyridylacetylene have been reported.[4] However, to our knowledge there have been no report on the synthesis of their derivatives and the further progress in research areas using 2,2′-dipyridylacetylene.

Meanwhile, boronic acids have been used for cross-coupling reactions in formation of carbon–carbon bonds.[5] While arylboronic acids are typically prepared through the lithium–halogen exchange of the corresponding aryl halides,[6] the preparation of a boronic acid of aromatic heterocycle mediated heteroaryllithium has some problems due to the intrinsic instability of heteroaryllithium.[7] Among aromatic heterocyclic compounds, substituted pyridines have a great potential to be used as important components to drug candidates. In particular, 3-bromopyridine has been successfully used to prepare 3-pyridylboronic acid with a good yield.[8] However, so far, the methods for the preparation of a boronic acid of compounds containing two pyridines such as 2,2′-dipyridylacetylene have not been reported. The effective synthesis of a boronic acid derivative could give versatile applications in various fields of chemistry. Therefore, we report the new method for a facile one-pot preparation of 5,5′-dibromo-2,2′-dipyridylacetylene and its boronic acid derivative using the lithium–halogen exchange.

The most commonly employed method for formation of bonds between acetylene and heterocycle is a palladium-catalyzed coupling in the presence of cuprous iodide and an alkylamine solvent.[9] Recently, Tilley and Zawoiski successfully synthesized 5-bromo-2-[2-(trimethylsilyl)ethynyl]pyridine **2** from commercially available 2,5-dibromopyridine **1** and (trimethylsilyl)acetylene by the conventional palladium-catalyzed coupling.[10] In this letter we report that, **1** reacted regioselectively with (trimethylsilyl)acetylene at the 2-position of pyridine, and **2** was obtained with a 74% yield. We focused on the aspect that **1** has the regioselective reactivity in the palladium-catalyzed coupling. For the preparation of



Scheme 1. Synthesis of 5,5′-dibromo-2,2′-dipyridylacetylene **4** and reagents: (a) TMSA, CuI, $Pd(PPh_3)_2Cl_2$, NEt_3; (b) NaOH, MeOH; (c) CuI, $Pd(PPh_3)_2Cl_2$, NEt_3; (d) TBAF; (e) NH_4F, KOH, *i*-PrOH.

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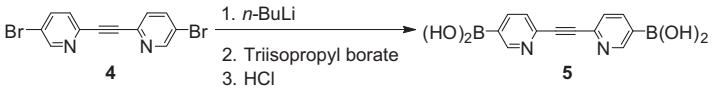


Scheme 2. Synthesis of 6,6′-(1,2-ethynediyl)bis[3-pyridylboronic acid] **5** and reagents.

5,5′-dibromo-2,2′-dipyridylacetylene **4**, we reacted **1** with 5-bromo-2-ethynylpyridine **3** (Scheme 1). As a result of the reaction, we obtained **4** with a 72% yield, which was determined through ^{1}H and ^{13}C NMR, GC–MS, and elemental analyzes for its identification. Although we successfully obtained **4**, this method is not very efficient as it was carried out in stepwise procedures and the expensive catalyst palladium was used in two different steps. Also, the purification of products **2** and **4** from the reaction mixture is not so easy due to the formation of byproducts and residues of catalysts. To overcome these shortcomings, we developed one-pot synthesis methods in which different reagents were used and obtained **4** in 60% yields.[12] The omission of just one reagent from the mixture of NH_4F, KOH, and *i*-PrOH resulted in no formation of products. The one-pot synthesis methods also exploit the characteristic that bromine ion attached at the 2-position of pyridine is only reactive with the palladium catalyst regioselectively. Furthermore, excessive **1** and additional reagents did not disturb the palladium-catalyzed coupling reaction. The yields by two different one-pot synthesis methods (60%) were higher than the overall yield (53%), which is mediated by **2** and **3**, and we could obtain **4** easily in gram quantities in these new methods. Also, these results demonstrate that the important step for one-pot synthesis method of **4** is how much **2** is generated, because the overall yields deviate a little from the yield of **2**.

We next considered the conversion of bromine to boronic acid, 6,6′-(1,2-ethynediyl)bis[3-pyridylboronic acid] **5** (Scheme 2). Currently, there is no report found for the lithiation of chemicals containing two pyridines such as **4**. Magnesium- or lithium-halogen exchanges are generally used for the conversion. However, in the cases of chemicals containing one pyridine, improved lithium–halogen exchange methods are mainly used, because then magnesium–halogen exchange has some problems in yields and operation.[8] Therefore, we also evaluated different reaction conditions for the lithium–halogen exchange (Table 1).

First, we carried out a conventional method known as the 'sequential addition' (entries 1–6). In this method, **4** was treated with *n*-butyllithium followed by the addition of a triisopropyl borate. At entry 6, we used mixed toluene and THF: although *n*-butyllithium generally requires a coordinating solvent to disassociate aggregations of *n*-butyllithium, it has been reported that toluene is suitable for the exchange of some pyridine derivates.[8b] In general, higher yields were obtained when THF was used as a solvent. The reaction time with *n*-butyllithium did not affect the yields and the excessive use of *n*-butyllithium resulted in no product (entries 5, 6). The use of 2.2 equiv of *n*-butyllithium and one hour reaction time were found to be appropriate for this reaction. Therefore, it appears that the primary difference of yields originated from the solubility of **4**. For the lithiation of **4**, the concentration of dissolved **4**, which can react with *n*-butyllithium, is important; a low concentration gives rise to the limited lithiation. While the solubility of **4** was low in THF at −78 °C, **4** shows a very low solubility in toluene and diethyl ether even at room temperature and the lithiation reaction did not occur. Therefore, with the sequential addition, a stabilizing effect of heteroaryllithium by toluene or diethyl ether is not anticipated, because heteroaryllithium is not generated. It is also assumed that the successful lithiation of chemicals containing one pyridine, such as 3-bromopyridine and 2,5-dibromopyridine, in toluene or diethyl ether stemmed from their good solubility and the stabilizing effect of the solvent. In cases where high amounts of THF were used, higher yields were obtained (entry 2). However, further addition of solvent makes this reaction unpractical.

The lithium–halogen exchange of bromopyridine resulting in THF is hindered by de-protonation occurring as a result of the relative acidity of bromopyridines and this problem causes low yields.[11] The order of addition of the reagents is the key to overcoming the de-protonation. In this regard, the 'in situ quench' method, the 'reverse addition' method, and the use of a non-coordinating solvent in conjunction with these methods were carried out and found to give good yields.[8a,b] We also applied these methods to our lithiation procedures with some modifications.

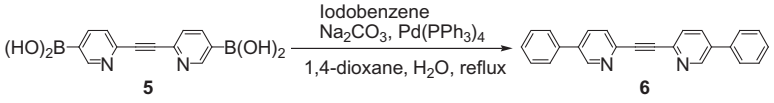
In the 'in situ quench' method, *n*-butyllithium is added to a mixture of pyridyl halide and triisopropyl borate followed by an acid quench.[8a] For the efficient preparation of boronic acid by this method, the lithium–halogen exchange on pyridyl halide should be faster than the reaction between *n*-butyllithium and triisopropyl borate; the generated lithiopyridine intermediate then reacts quickly with the borate to prevent undesired side reactions. However, we obtained **5** with very low yield at −40 °C and significant amounts of **4** were recovered (entry 7). From these results, it was assumed that *n*-butyllithium was relatively more reactive with triisopropyl borate than **4** or the generated pyridyllithium was very labile. In addition, from the result of entry 8, we consider that the dissolved concentration of **4** was very critical, because we could not obtain **5** at −78 °C, a temperature, that is, more appropriate for the prevention of de-protonation at −40 °C, but most of **4** was recovered. Compared with the sequential addition method, the yields were not improved. Therefore, we focused on the reverse addition method.

In the 'reverse addition' method, pyridyl halide solution is added to a solution of *n*-butyllithium followed by the addition of triisopropyl borate.[8b,11,13] In our experiments, THF was used as a solvent for the preparation of the pyridyl halide solution due to the solubility of **4**. THF, diethyl ether, and toluene were used as solvents for *n*-butyllithium and they showed yields of 40%, 21%, and 54%, respectively (entries 9–11). When toluene was used as a solvent in the other methods (entries 6–8), low yields were obtained;

Table 1
Reaction methods and conditions for preparation of 6,6′-(1,2-ethynediyl)bis[3-pyridylboronic acid] **5**

Entry	Method	Solvent	Temperature (°C)	Isolated yield (%)
1	Sequential addition	THF	−78	28
2[a]	Sequential addition	THF	−78	37
3[b]	Sequential addition	THF	−78	30
4[c]	Sequential addition	THF	−78	0
5	Sequential addition	Diethyl ether	−78	10
6[d]	Sequential addition	Toluene + THF	−78	15
7[d]	In situ quench	Toluene + THF	−40	15
8[d]	In situ quench	Toluene + THF	−78	0
9	Reverse addition	THF	−78	40
10[e]	Reverse addition	THF + diethyl ether	−78	21
11[e]	Reverse addition	THF + toluene	−78	54

[a] The volume of THF used here is twofold greater than for entry 1.
[b] Reaction time between *n*-butyllithium and **4** is 2.5 h.
[c] In this entry, 4.4 equiv of *n*-butyllithium was used.
[d] Toluene and THF were in a ratio of 4:1.
[e] Diethyl ether or toluene was used as a solvent for *n*-butyllithium.



Scheme 3. Synthesis of 5,5′-diphenyl-2,2′-dipyridylacetylene **6** and reagents.

however, in the reverse addition method, toluene gave the highest yields. It is thought that the reverse addition method prevented the de-protonation of pyridyllithium and toluene activated the halogen–lithium exchange. Although this method required a large quantity of THF for the preparation of solution of **4**, we could obtain **5** with reproducibility and the best yield. To evaluate its potential as a building block for cross-coupling reactions in formation of carbon–carbon bonds, **5** was reacted with iodobenzene (Scheme 3).[14] As a result of the reaction, we obtained 5,5′-diphenyl-2,2′-dipyridylacetylene **6** in 35% yield and it showed that **5** is useful in cross-coupling reaction.

In conclusion, we synthesized 5,5′-dibromo-2,2′-dipyridylacetylene **4** from 2,5-dibromopyridine **1** with two different one-pot synthesis methods. For the preparation of boronic acid of **4**, we evaluated several reaction conditions and successfully synthesized 6,6′-(1,2-ethynediyl)bis[3-pyridylboronic acid] **5** by a reverse addition method using toluene and THF. The **5** showed potential as a building block for cross-coupling reactions and further researches are in progress in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.062.

References and notes

1. (a) Marsella, M. J.; Piao, G.; Tham, F. S. *Synthesis* **2002**, 1133–1135; (b) Pappenfus, T. M.; Mann, K. R. *Org. Lett.* **2002**, *4*, 3043–3046; (c) Pearson, D. L.; Tour, J. M. *J. Org. Chem.* **1997**, *62*, 1376–1387; (d) Biswas, M.; Nguyen, P.; Marder, T. B.; Khundkar, L. R. *J. Phys. Chem. A* **1997**, *101*, 1689–1695; (e) Stiegman, A. E.; Graham, E.; Perry, K. J.; Khundbar, L. R.; Cheng, L.-T.; Perry, J. W. *J. Am. Chem. Soc.* **1991**, *113*, 7658–7666; (f) Wu, M.; Wei, L.; Lin, C.; Leou, S.; Wei, L. *Tetrahedron* **2001**, *57*, 7839–7844.
2. (a) Blaser, H.-U.; Indolese, A.; Schnyder, A. *Curr. Sci.* **2000**, *78*, 1336–1344; (b) Zapf, A.; Beller, M. *Top. Catal.* **2002**, *19*, 101–109.
3. (a) Zaman, M. B.; Tomura, M.; Yamashita, Y. *Org. Lett.* **2000**, *2*, 273–275; (b) Teitei, T.; Collin, P. J.; Sasse, W. H. F. *Aust. J. Chem.* **1972**, *25*, 171–182; (c) Zaman, M. B.; Tomura, M.; Yamashita, Y. *J. Org. Chem.* **2001**, *66*, 5987–5995; (d) Zaman, M. B.; Smith, M. D.; Ciurtin, D. M.; Loye, H. Z. *Inorg. Chem.* **2002**, *41*, 4895–4903.
4. (a) Abele, E.; Abele, R.; Arsenyan, P.; Lukevics, E. *Tetrahedron Lett.* **2003**, *44*, 3911–3913; (b) Negishi, E.; Xu, C.; Tan, Z.; Kotora, M. *Heterocycles* **1997**, *46*, 209–214; (c) Fleckenstein, C. A.; Plenio, H. *Green Chem.* **2008**, *10*, 563–570.
5. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
6. Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631–2634.
7. Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485–1494.
8. (a) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394–5397; (b) Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 4285–4287; (c) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron Lett.* **2002**, *58*, 2885–2890; (d) Parry, P. R.; Wang, C.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. *J. Org. Chem.* **2002**, *67*, 7541–7543; (e) Bouillon, A.; Lancelot, J.-C.; Santos, J. S. O.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043–10049; (f) Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388–390; (g) Alessi, M.; Larkin, A. L.; Ogilvie, K. A.; Green, L. A.; Lai, S.; Lopez, S.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 1588–1594; (h) Smith, A. E.; Clapham, K. M.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. *Eur. J. Org. Chem.* **2008**, 1458–1463.
9. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467–4470.
10. Tilley, J. W.; Zawoiski, S. *J. Org. Chem.* **1988**, *53*, 386–390.
11. Cai, D.; Hughes, D. L.; Verhoeven, T. R. *Tetrahedron Lett.* **1996**, *37*, 2537–2540.
12. Preparation of 5,5′-dibromo-2,2′-dipyridylacetylene (**4**). (Trimethylsilyl)acetylene (1.47 g, 15 mmol) was added to a solution of 2,5-dibromopyridine (7 g, 29.7 mmol) in triethylamine (80 mL), cooled to 0 °C in an ice bath. The solution was purged using argon gas for 10 min and cuprous iodide (126 mg, 653 μmol) and bis(triphenylphosphinyl)palladium dichloride (466 mg, 653 μmol) were added. The mixture was stirred for 1 h at 0 °C and then removed from the ice bath. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2.5 h. Tetrabutylammonium fluoride (1 M in THF, 15 mL, 15 mmol) or a mixture of ammonium fluoride (560 mg, 15 mmol), KOH (841 mg, 15 mmol), and isopropyl alcohol (30 mL) was then added to the mixture, which was left under stirring at room temperature for 24 h. The mixture was diluted with water (60 mL), extracted with dichloromethane (75 mL × 4), washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. This material was passed through a silica gel column, eluted with 2:1 dichloromethane–ether, and crystallized from chloroform to give a pale gray solid of **4** (2.99 g, 60%); mp: 240–242 °C; MS (EI): *m*/*z* 338 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, 2*H*, *J* = 8 Hz), 7.85 (dd, 2*H*, *J* = 8 Hz, *J* = 2 Hz), 8.70 (d, 2*H*, *J* = 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 88.3, 121.3, 128.9, 139.2, 141.0, 151.7; Anal. Calcd for $C_{12}H_6Br_2N_2$: C, 42.64; H, 1.79; N, 8.29. Found: C, 42.51; H, 1.45; N, 8.30.
13. Reverse addition procedure for the preparation of 6,6′-(1,2-ethynediyl)bis[3-pyridylboronic acid] (**5**). A solution of **4** (500 mg, 1.48 mmol) in anhydrous THF (50 mL) was added dropwise to a solution of *n*-butyllithium (2.5 M in hexane, 1.4 mL, 3.5 mmol) in anhydrous toluene (30 mL), cooled to −78 °C. The mixture was stirred for an additional 1 h while the temperature was held at −78 °C, and triisopropylborate (1 mL, 4.3 mmol) was added. The mixture was kept to reach room temperature for an additional hour. Then, the mixture was quenched by the slow addition of 2 N HCl solution (15 mL) and concentrated under reduced pressure. The residue was dissolved with an aqueous NaOH solution and washed with diethyl ether (30 mL × 3). The resulting aqueous layer was collected and acidified to pH 4 by the dropwise addition of HCl solution to precipitate a yellow solid of **5** (212 mg, 54%); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (d, 2*H*, *J* = 8 Hz), 8.17 (d, 2*H*, *J* = 8 Hz), 8.50 (s, 4*H*), 8.93 (s, 2*H*); ^{13}C NMR (125 MHz, DMSO-d_6) δ 88.4, 126.7, 142.1, 142.6, 155.2; Anal. Calcd for $C_{12}H_{10}B_2N_2O_4$: C, 53.81; H, 3.76; N, 10.46. Found: C, 53.53; H, 3.80; N, 9.91.
14. Preparation of 5,5′-diphenyl-2,2′-dipyridylacetylene (**6**). Compound **5** (100 mg, 0.37 mmol) and iodobenzene (160 mg, 0.78 mmol) were added to a mixture of sodium carbonate (198 mg, 1.86 mmol) and tetrakis(triphenylphosphine)-palladium(0) (43 mg, 0.037 mmol) in 1,4-dioxane (10 mL) and distilled water (4 mL). The mixture was refluxed for 24 h and concentrated under the reduced pressure. The residue was diluted with water (10 mL), extracted with dichloromethane (15 mL × 3), washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. This material was passed through a silica gel column, eluted with 9:1 dichloromethane–ether, and crystallized from a mixture of chloroform and hexane to give a sheeny white solid of **6** (43 mg, 35%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (m, 2*H*), 7.48 (m, 4*H*), 7.60 (m, 4*H*), 7.70 (d, 2*H*, *J* = 8 Hz), 7.89 (dd, 2*H*, *J* = 8 Hz, *J* = 2 Hz), 8.88 (d, 2*H*, *J* = 2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 88.8, 127.3, 127.9, 128.7, 129.4, 134.6, 136.4, 137.4, 141.6, 148.9.