JOC Note

An Improved Protocol for the Preparation of 3-Pyridyl- and Some Arylboronic Acids

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Abstract: 3-Pyridylboronic acid was prepared in high yield and bulk quantity from 3-bromopyridine via a protocol of lithium−halogen exchange and "in situ quench". This technique was further studied and evaluated on other aryl halides in the preparation of arylboronic acids.

Boronic acids have been widely used for cross-coupling reactions in carbon−carbon bond formation.[1,2] A typical preparation of arylboronic acids involves a reaction between an organoborate and an organometal (Li or Mg) species, usually prepared by magnesium insertion or lithium−halogen exchange of the corresponding aryl halides.[3] This method has its limitations, however. First, it is difficult to apply this method to substrates bearing functional groups not compatible with organolithium reagents such as esters and nitriles. Second, some aryllithium intermediates are intrinsically unstable, as in the case of many aromatic heterocycles.[4] Alternately, arylboronic esters can be prepared from aryl halides or aryl triflates via a palladium-catalyzed cross-coupling reaction with tetraalkoxydiboron or dialkoxyhydroborane.[5,6] These methods tolerate a wide range of functional groups. However, they are not suitable for large-scale synthesis because tetraalkoxydiboron and dialkoxyhydroborane are expensive. In this note we report a revised procedure for a high-yielding, reproducible, and scalable preparation of 3-pyridylboronic acid (**3**) via lithium−halogen exchange and in situ quench with triisopropyl borate. A brief study on the generality of this procedure for converting aryl halides to arylboronic acids is also reported.

In our ongoing efforts to synthesize biologically active compounds as potential therapeutic agents, we needed to introduce a 3-pyridyl moiety onto our target. 3-Pyridylboronic acid (**3**) was the choice of reagent for this transformation, since it is nontoxic and thermally and air-stable.[7] Although there are commercial sources for this compound, it is available in only small quantities, and the cost is very high. The existing literature protocol for preparing 3-pyridylboronic acid afforded a poor yield and required conditions not suitable for scale-up.[8] In our studies on preparing 3-pyridylboronic acid from 3-bromopyridine (**1**), we learned that the order of addition of the reagents was the key to a successful preparation. When 3-bromopyridine was treated with *n*-butyllithium at −78 °C followed by triisopropyl borate (**2**), the product was isolated in poor yield (20−30%). The "reverse" addition procedure, in which 3-bromopyridine was added to a solution of *n*-butyllithium followed by addition of triisopropyl borate, gave better yields, but the reaction must be run at low temperatures (below −70 °C) in order to get consistent results, making it inconvenient for large-scale preparation.

Our next approach was to add *n*-butyllithium to a solution of 3-bromopyridine and triisopropyl borate followed by an acid quench (Scheme 1). This protocol has been mentioned before, primarily in patents.[9] However, very little study and discussion about this technique has been described. As it turned out, this sequence of addition was superior to those previously described. Not only did it consistently afford good yields but it also proved to be temperature tolerant, giving the best yields (90−95%) at −40 °C and a respectable 80% yield even at 0 °C. This was probably because the lithium−halogen exchange on 3-bromopyridine is much faster than the reaction between *n*-butyllithium and triisopropyl borate. The 3-lithiopyridine intermediate thus generated reacts rapidly with the borate in the reaction mixture, thereby mini-

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(2) For recent developments of the Suzuki reaction and its industrial application, see: (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (b) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guran, A. S.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 6797−6803. (c) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2416. (d) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804−3805. (e) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388. (f) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (g) Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151−8156.

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(5) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508−7510. (b) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447−3450.

(6) (a) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458−6459. (b) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164−168. (c) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268−9271.

(7) For application of 3-pyridylboronic acid in cross-coupling reactions, see: (a) Enguehard, C.; Hervet, M.; Allouchi, H.; Debouzy, J.-C.; Leger, J.-M.; Gueiffier, A. *Synthesis* **2001**, *4*, 595−600. (b) Li, J. J.; Yue, W. S. *Tetrahedron Lett.* **1999**, *40*, 4507−4510. (c) Bower, J. F.; Guillaneux, D.; Nguyen, T.; Wong, P. L.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 1514−1518. (d) Thompson, W. J.; Jones, J. H.; Lyle, P. A.; Thies, J. E. *J. Org. Chem.* **1988**, *53*, 2052−2055. (e) Juneja, R. K.; Robinson, K. D.; Johnson, C. P.; Atwood, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 3818−3819.

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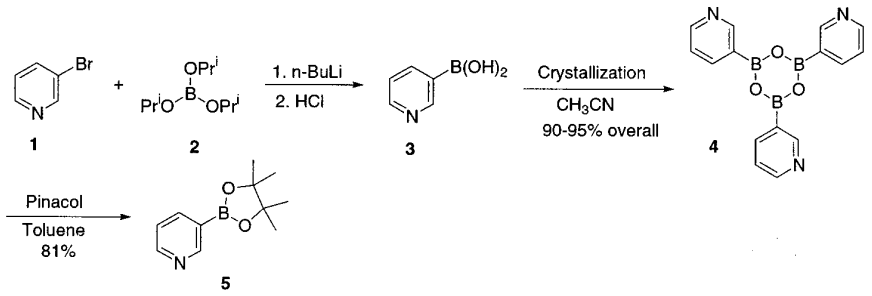
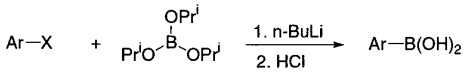
(9) (a) DeCamp, A. E.; Grabowski, E. J. J.; Huffman, M. A.; Xavier, L. C.; Ho, G.-J.; Mathre, D. J.; Yasuda, N. Preparation of 2-Aryl Carbapenems. PCT Int. Appl. WO 9531461, 1995. (b) DeCamp, A.; Dolling, U. H.; Li, Y.; Rieger, D. L.; Yasuda, N.; Xavier, L. C. *Boron Containing Intermediates Useful in the Preparation of Carbapenems.* U.S. Patent 5338875, 1994. (c) Yasuda, N.; Huffman, M. A.; Ho, G.-J.; Xavier, L. C.; Yang, C.; Emerson, K. M.; Tsay, F.-R.; Li, Y.; Kress, M. H.; Rieger, D. L.; Karady, S.; Sohar, P.; Abramson, N. L.; DeCamp, A. E.; Mathre, D. J.; Douglas, A. W.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 5438−5446. (d) Singh, A.; Chen, C.-K.; Grosso, J. A.; Delaney, E. J.; Wang, X.; Polniaszek, R. P.; Thottathil, J. K. Preparation of Isoxazolyl Biphenylsulfonamides from Arylsulfonylboronic Acids, Haloarenes, and Aminoisoxazoles. PCT Int. Appl. WO 0056685, 2000.

10.1021/jo025792p CCC: $22.00

SCHEME 1



SCHEME 2



mizing the chance for 3-lithiopyridine to undergo undesired side reactions. The product was isolated by crystallization from acetonitrile in the form of boroxin **4**.[10] The optimized procedure was easily scaled up to produce 1 kg of crystalline boroxin **4**, which functioned very well in a palladium-catalyzed cross-coupling reaction with aryl halides. The characterization of boroxin **4** was difficult, however, due to the presence of varying amounts of hydrates. Therefore, boroxin **4** was converted to its pinacol ester **5**, which was fully characterized.[11]

To study the general scope of this "in situ quench" protocol, we applied it to several other aryl halides in the preparation of arylboronic acids (Scheme 2). The yields were compared to those observed using the traditional sequential addition method in which aryl halides were treated with *n*-butyllithium followed by addition of the borate.[12] As shown in Table 1, the in situ quench procedure gave better yields in several heterocyclic systems (entries 1−4). This method also worked better in the presence of functional groups that are sensitive to organolithium species (entries 7−9). It could be assumed that the aryllithium species generated from these substrates either were labile or might undergo side reactions. In the in situ quench procedure, the aryllithium species would be quenched by borate immediately after they were formed and, therefore, gave boronic acids in good yields. In contrast, the sequential addition method gave better yield in entries 10−13. This may indicate that these aryllithium species were relatively stable, so the sequential addition of borate had no adverse effect. In fact, in entries 10−13 significant amounts of unreacted aryl bromides were observed in the in situ quench method, whereas the sequential addition method consumed all the aryl bromides. This suggests that the generation of the aryllithium with these substrates was relatively slow, therefore allowing *n*-butyllithium to react competitively with triisopropyl borate.

In conclusion, the revised procedure for lithium−halogen exchange with in situ quench with borate offers an efficient alternative for preparing some arylboronic acids from corresponding aryl halides, especially in substrates that are sensitive to organolithium species.

Experimental Section

General. All reactions were performed under nitrogen. THF and toluene were dried using 4 Å molecular sieves overnight. Commercially available reagents were used without further purification.

3-Pyridylboroxin (4). A 1 L, three-necked flask equipped with a temperature probe, an overhead stirrer, and a septum was charged with toluene (320 mL) and THF (80 mL) and put under a nitrogen atmosphere. The flask was charged with triisopropyl borate (55.4 mL, 240 mmol) and 3-bromopyridine (19.3 mL, 200 mmol). The mixture was cooled to −40 °C using a dry ice/acetone bath. *n*-Butyllithium (2.5 M in hexanes, 96 mL, 240 mmol) was added dropwise via a syringe pump over 1 h, and the mixture was stirred for an additional 0.5 h while the temperature was held at −40 °C. The acetone/dry ice bath was removed, and the reaction mixture was then allowed to warm to −20 °C before a 2 N HCl solution (200 mL) was added. When the mixture reached room temperature, it was transferred to a 1 L separatory funnel and the aqueous layer (pH ≈ 1) was cut into a 500 mL Erlenmeyer flask. While the aqueous layer was stirred, its pH was adjusted to 7 using a 5 N NaOH solution (≈ 30 mL). A white solid product precipitated as the pH approached 7. This mixture was then saturated with 50 g of NaCl, transferred to a 1 L separatory funnel, and extracted three times with THF (250 mL portions). The combined THF extracts were evaporated in vacuo to provide a solid. The solid was taken up in acetonitrile (80 mL) for crystallization. The resulting slurry was heated to 70 °C, stirred for 30 min, and allowed to cool slowly to room temperature before it was cooled to 0 °C using an ice bath. After the slurry was stirred at 0 °C for 30 min, the solid was collected on a fritted glass funnel. The solid was washed with cold acetonitrile (5 °C, 15 mL) and dried under vacuum to afford 19.61 g of white solid. A satisfactory melting point for this solid could not be obtained. ^{1}H NMR (400 MHz, CD_3OD) δ 8.62 (br, 1 H), 8.56−8.54 (m, 1 H), 8.45 (d, 1 H, J = 7.2 Hz), 7.74 (t, 1 H, J = 6.6 Hz). Anal. Calcd for $C_{15}H_{12}B_3O_3N_3$·

(10) (a) Hoye, T. R.; Mi, L. *Tetrahedron Lett.* **1996**, *37*, 3097−3098. (b) Mohri, S.-I.; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072−7073.

(11) During the preparation of this manuscript, a nonaqueous workup procedure for the preparation of arylboronic esters was reported: Wong, K.-T.; Chien, Y.-Y.; Liao, Y.-L.; Lin, C.-C.; Chou, M.-Y.; Leung, M.-K. *J. Org. Chem.* **2001**, *67*, 1041−1044.

(12) **General Procedure for the Sequential Addition Method.** A 50 mL round-bottomed flask equipped with a temperature probe, a magnetic stirrer, and a septum was charged with toluene (16 mL) and THF (4 mL) and put under a nitrogen atmosphere. The flask was charged with aryl halide (10 mmol). The solution was cooled to −70 °C using a dry ice/acetone bath. *n*-Butyllithium (2.5 M in hexanes, 4.8 mL, 12 mmol) was added dropwise via a syringe pump over 1 h. After the mixture was stirred for an additional 0.5 h, triisopropyl borate (2.8 mL, 12 mmol) was added while the temperature was held at −70 °C. The acetone/dry ice bath was then removed, and the reaction mixture was allowed to warm to −20 °C before a 2 N HCl solution (10 mL) was added. When the mixture reached room temperature, it was transferred to a 100 mL separatory funnel and the layers were separated. The organic layer was assayed by HPLC and the yield was determined by comparison with a standard solution of authentic product.

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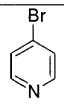
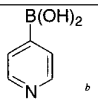
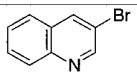
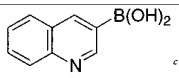
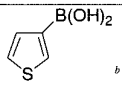
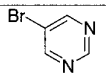
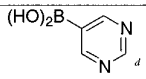
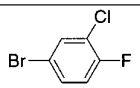
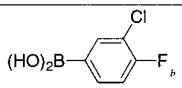
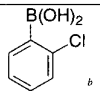
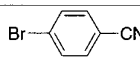
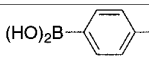
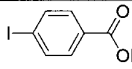
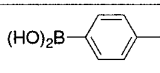
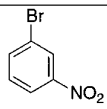
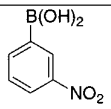
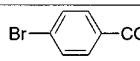
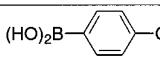
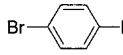
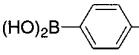
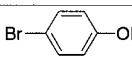
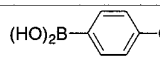
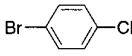
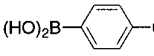
TABLE 1. Preparation of Arylboronic Acids from Aryl Halides

Entry	Aryl halide	Product	Yield with "in situ quench" procedure [a]	Yield with sequential addition procedure [a]
1		 [b]	60%	9%
2		 [c]	79%	31%
3		 [b]	91%	55%
4		 [d]	76%	28%
5		 [b]	86%	58%
6		 [b]	100%	92%
7		 [b]	91%	56%
8		 [b]	22%	0%
9		 [b]	13%	0%
10[e]		 [b]	22%	41%
11		 [b]	66%	91%
12		 [b]	26%	96%
13		 [b]	61%	75%

[a] Yields were determined by HPLC assay. [b] Products show ^{1}H NMR data and HPLC retention times consistent with commercial authentic samples (entries 1, 3, and 5−13). [c] Product shows ^{1}H NMR data consistent with the literature (ref 13a). [d] Product shows ^{1}H NMR data consistent with the literature (ref 13b). [e] In this entry, 2 equiv of *n*-butyllithium was used.

$0.5H_2O$: C, 55.65; H, 4.05; N, 12.98. Found: C, 55.51; H, 4.10; N, 12.88. The yield based on this formula was 91%.

3-Pyridylboronic Acid Pinacol Ester (5). A 1 L three-necked flask equipped with a stir bar, a nitrogen inlet adapter, and a Dean−Stark trap with a condenser was charged with 3-pyridylboroxin **4**·$0.5H_2O$ (10.0 g, 30.8 mmol), pinacol (13.5 g, 114 mmol), and toluene (400 mL). The solution was heated with a 120 °C oil bath and refluxed using a Dean−Stark apparatus for 2.5 h. The reaction was finished when the solution went from cloudy white to clear. The solution was then concentrated in vacuo to provide a solid. This solid was taken up in cyclohexane (50 mL) and crystallized by holding the suspension at 85 °C for 30 min and then allowing the temperature to slowly return to room temperature. The slurry was filtered, and the solid was washed with cyclohexane (10 mL) and dried under vacuum to afford 15.39 g of **5** as a white solid (81% from **4**, 72% from 3-bromopyridine). Mp: 103−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (br, 1 H), 8.67 (dd, 1 H, J = 1.8, 4.9 Hz), 8.06 (dt, 1 H, J = 1.8, 7.5 Hz), 7.29−7.26 (m, 1 H), 1.36 (s, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 151.9, 142.3, 124.0, 123.1, 84.2, 24.9. Anal. Calcd for $C_{11}H_{16}BO_2N$: C, 64.43; H, 7.86; N, 6.83; B, 5.27. Found: C, 64.16; H, 7.72; N, 6.62; B, 5.35.

General In Situ Quench Procedure for the Preparation of Arylboronic Acids. A 50 mL round-bottomed flask equipped with a temperature probe, a magnetic stirrer, and a septum was charged with toluene (16 mL) and THF (4 mL) and put under a nitrogen atmosphere. The flask was charged with triisopropyl borate (2.8 mL, 12 mmol) and aryl halide (10 mmol). The mixture was cooled to −70 °C using a dry ice/acetone bath. *n*-Butyllithium (2.5 M in hexanes, 4.8 mL, 12 mmol) was added dropwise via a syringe pump over 1 h, and the mixture was stirred for an additional 0.5 h while the temperature was held at −70 °C. The acetone/dry ice bath was removed, and the reaction mixture was then allowed to warm to −20 °C before a 2 N HCl solution (10 mL) was added. When the mixture reached room temperature, it was transferred to a 100 mL separatory funnel and the layers were separated. Both the organic and aqueous layers were assayed by HPLC, and the yield was determined by comparison with a standard solution of authentic product.

Isolation for Entries 1, 2, and 4. The aqueous layers were neutralized to pH ≈ 7 using a 5 N NaOH solution followed by extraction with THF (×3). The combined THF extracts were evaporated in vacuo to provide solids, which were recrystallized

from acetonitrile. The recrystallized products gave satisfactory ^{1}H NMR spectra.

Isolation for Entries 3 and 5−13. The organic layers were evaporated in vacuo to provide solids, which were recrystallized from acetonitrile. The recrystallized products gave satisfactory ^{1}H NMR spectra.

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