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Microwave-assisted synthesis of ethynylarylboronates for the construction of boronic acid-based fluorescent sensors for carbohydrates

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Abstract—A reliable and operationally simple procedure for the synthesis of 2,2-dimethylpropane-1,3-diyl ethynylaryl boronates **4** was developed. The key step is microwave-facilitated selective formation of 2,2-dimethylpropane-1,3-diyl trimethylsilylethynylaryl boronates by Sonogashira reaction from the corresponding bromides. The use of microwave was found to significantly improve the reaction yield and shorten the reaction time. The 2,2-dimethylpropane-1,3-diyl ethynylaryl boronates **4** prepared can be used in the construction of diboronic acid libraries through [2+3] Huisgen cycloaddition for carbohydrate fluorescent sensor development.

Boronic acids are known to form tight complexes with compounds containing two adjacent nucleophiles. These compounds include diols, α-hydroxyacids, α-amino-acids, and most likely aminoalcohols.[1] On the basis of this interaction, recently, there is an increasing interest in using boronic acids for the synthesis of sensors of carbohydrates,[2–10] artificial lectins (boronolectins) targeting cell surface carbohydrates,[1,11–15] and selective transporters of nucleosides, saccharides, and nucleotides.[16–19] In addition, arylalkynes are interesting intermediates for the preparation of a variety of scaffolds for various applications. Some recent examples include fluorescent heterocycles,[20] coupling components as fluorescent dyes,[21] fluorogenic probes,[22] ricin sensors,[23] optically active polymers,[24,25] fluorescent materials,[26–31] antimicrobial trizoles,[32] carbonic anhydrase inhibitors,[33] and natural products with antitumor or antimitotic activity.[34,35]

Our lab has a long-standing interest in the design and synthesis of boronic acid-based fluorescent sensors for carbohydrates and boronolectins.[1,11,12,36–45] Along this line, we and others have been working on developing combinatorial approaches to the synthesis of such sensors.[12,14,46–48] However, for this type of work, the field is hindered by a lack of diverse monoboronic acid monomers that are readily 'polymerizable' under mild conditions. We are interested in developing a general methods for the preparation of arylboronic acids with a terminal alkyne group, which can be used in the [2+3] Huisgen cycloaddition[20,49–51] in library synthesis. Herein, we describe an efficient method for the synthesis of ethynylarylboronic acids through microwave-facilitated Sonogashira coupling reaction starting from bromoaryl boronic acids.

For the synthesis of the ethynylarylboronic acids, we envisioned using the Sonogashira coupling reaction starting with bromoarylboronic acids (Scheme 1). For this we needed to have the boronic acids protected for easy purification. Therefore, bromoaryl boronic acids **1** were reacted with neopentyl glycol in refluxing toluene with a Dean–Stark trap to give the protected 2,2-dimethylpropane-1,3-diyl bromoaryl boronates **2** in almost quantitative yields.

Although there are ample precedents showing that Sonogashira coupling reactions give high yields in general,[52,53] their application in the synthesis of boronic acid-containing compounds has not been well studied. To the best of our knowledge, there is only one such example in the synthesis of **3a** reported in the literature,

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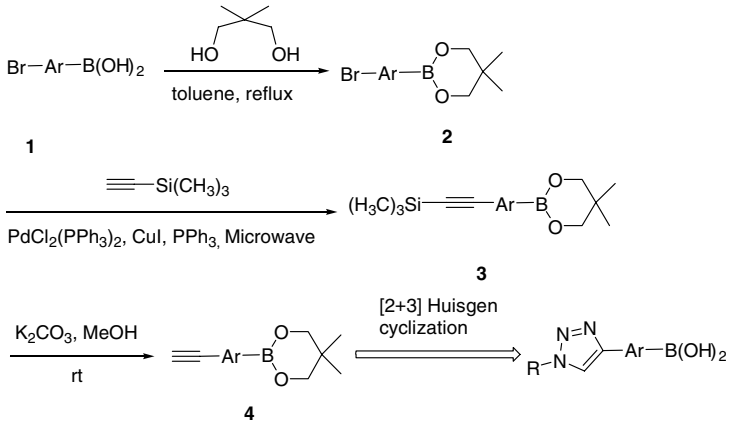


Scheme 1. Synthesis of 2,2-dimethylpropane-1,3-diyl ethynylaryl boronates.

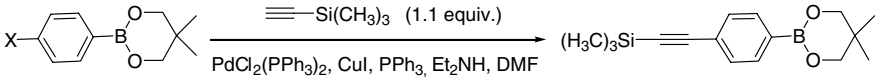
which involved long reaction time and an excess of the expensive reagent trimethylsilylacetylene.[24,25] For our purpose, we need an efficient synthesis, which gives high yield, uses near stoichiometric amount of trimethylsilylacetylene, and allows for the ready synthesis of a large number of such boronic acids. Therefore, we undertook an effort to search for optimal conditions for the Sonogashira reaction. The optimization studies had to take into consideration the presence of a boronic acid group, which is prone to cleavage under acidic, basic, and oxidative conditions. In addition, Suzuki coupling reaction is one possible side reaction in such Sonogashira reactions when a boronic acid is present on one of the starting materials. For this part of the study, we used 2,2-dimethylpropane-1,3-diyl 4-bromophenyl boronate **2a** as the model because it has been used for the synthesis of **3a**.[24]

Our initial optimization efforts focused on reaction temperature. When the reaction was carried out at room temperature, as is the case with most Sonogashira reactions, the product was obtained only in 23% yield after reaction for 48 h (Table 1, entry 1). This was clearly unacceptable to us. When the reaction was conducted in refluxing DMF (entry 2), no desired product was obtained. Therefore, it seems that high temperature did not help the reaction. However, this could also be due to the evaporation of some essential components in the reaction mixture such as diethylamine or trimethylsilylacetylene at elevated temperature. Therefore, we conducted the reaction at 130 °C in a sealed tube. In this case (entry 3), the product was obtained in 60% yield, which is a significant improvement over the existing method. Such results indicate that elevated temperature facilitates the reaction if it does not lead to the escape of reaction components. With this in mind, we became interested in studying the effect of microwave, since its primary function in facilitating organic reactions is to heat up the reaction under very well controlled conditions.

In the microwave reaction[54,55] using a sealed tube, we maintained the reaction temperature at 120 °C. Reaction for 25 min gave 98% isolated yield of the desired product (entry 4). At the same time, the deprotected free boronic acid product was obtained in 1.5% yield. Combined together, these two products gave quantitative conversions of the Sonogashira coupling reaction.

We were interested in examining the scope of application in using microwave to facilitate such reactions. In doing so, we studied the reaction using the less reactive chlorophenylboronic acid instead of the bromo analog (entry 5). In this case, no product was observed. This is understandable since the chloro substitution is less reactive. The results also indicate that chloro substitution can probably be tolerated on the boronic acid moiety because of the reactivity differences with the bromo substitution. Such functional group compatibility information is very important for our future design of new boronic acid analogs.

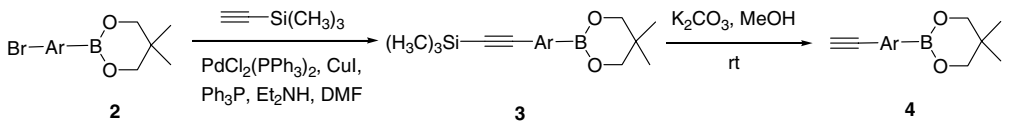
Table 1. Optimization of Sonogashira reaction conditions



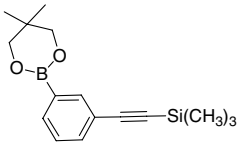
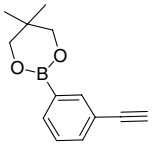
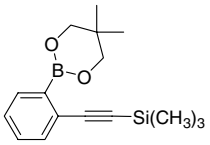
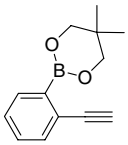
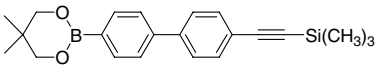
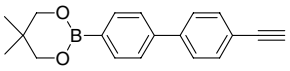
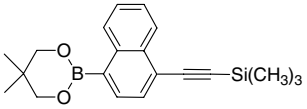
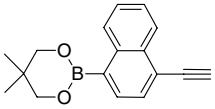
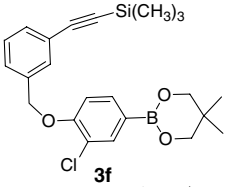
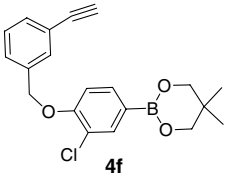
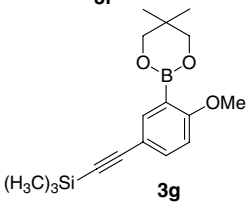
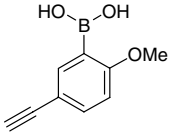
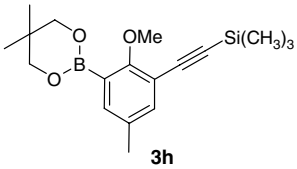
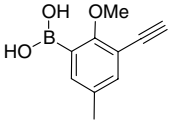
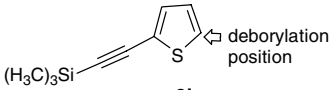
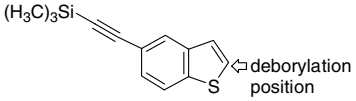
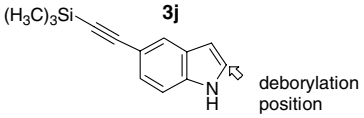
Entry	X	Temperature (°C)	Time	Heating method	Catalyst	Yield[a] (%)
1	Br	rt	48 h	Traditional	5% $PdCl_2(PPh_3)_2$, 5% CuI	23
2	Br	Refluxing	6 h	Traditional	5% $PdCl_2(PPh_3)_2$, 5% CuI	[b]
3	Br	130 (Oil bath)[c]	0.5 h	Traditional	5% $PdCl_2(PPh_3)_2$, 5% CuI	60
4	Br	120	25 min	Microwave	5% $PdCl_2(PPh_3)_2$, 5% CuI	98
5	Cl	120	25 min	Microwave	5% $PdCl_2(PPh_3)_2$, 5% CuI	[b]

[a] Isolated yield.
[b] No product was found by TLC and GC–MS.
[c] The reaction was performed in a sealed vessel.

Table 2. Synthesis of the ethynylaryl boronates



2 **3** **4**

Entry	Product **3**	Yield[a] (%) of **3**	Product **4**	Yield[a] (%) of **4**
1	 **3b**	98	 **4b**	78
2	 **3c**	90	 **4c**	75
3	 **3d**	93	 **4d**	77
4	 **3e**	97	 **4e**	80
5	 **3f**	96	 **4f**	79
6	 **3g**	94	 **4g**	31[c]
7	 **3h**	95	 **4h**	30[c]
8	 **3i**	82[b]	[d]	[d]
9	 **3j**	76[b]	[d]	[d]
10	 **3k**	73[b]	[d]	[d]

[a] Isolated yield.
[b] Yield of the deborylated product.
[c] Yield of boronic acid.
[d] Not available.

The deprotection of the trimethylsilyl group of **3a** was achieved by reaction with potassium carbonate in methanol to give 80% of the desired product **4a**. This compared favorably with the 50% yield obtained in the literature procedures using tetrabutylammonium fluoride in tetrahydrofuran.[24]

With the initial success of the microwave-facilitated reaction, we were interested in examining the scope of application with analogous arylboronic acids. These boronic acids include positional isomers (Table 2, entries 1 and 2), a biphenylboronic acid (entry 3), a naphthaleneboronic acid (entry 4), arylboronic acids that have an additional electron-donating substituent (methoxy) in different positions (entries 6 and 7), and cases where the boronic acid group is on a different aryl group as the alkyne group (entries 3 and 5). In all those cases, the desired Sonogashira coupling product was obtained in over 90% yield. The cleavage of the trimethylsilyl group was accomplished in over 75% isolated yields except with entries 6 and 7, which have an additional electron-donating substituent. In the latter two cases, the deprotection yields were about 30% and the product was the free boronic acids. The more difficult purification of the free boronic acid compared with the protected esters could be part of the reason for the low isolated yields in entries 6 and 7. The results of entry 5 (Table 2) also show that chloro substitution can be tolerated, which is consistent with the relative reactivity (R–Cl < R–Br) of organic halides in palladium-catalyzed reactions[52] and the result obtained is presented in Table 1 (entry 5).

To further examine the scope of applicability, we also studied the Sonogashira reaction with bromoheterocyclic aryl boronates such as thiophene, benzothiophene, and indole with the boronic acid moiety at the 2-position (Table 2, entries 8–10). Such reactions led mostly to the deborylation product **3i**–**k** in 73–82% yields. The desired products (<5%) were the minor component and could only be seen on GC–MS.

In conclusion, we have developed a practical, efficient, and facile method for the synthesis of protected ethynylaryl boronates **4** from bromoarylboronic acids **1** in three steps with good yields. The use of microwave was found to significantly improve the reaction yields and shorten the reaction time of the key step Sonogashira reactions. The reaction is tolerant of the presence of chloro substitution, and can be accomplished with a variety of arylboronic acids. Further work in library construction and screening using the ethynylarylboronic acids synthesized is in progress.

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Supplementary data

Supplementary data (including experimental procedures and spectroscopic data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.012.

References and notes

1. Yan, J.; Fang, H.; Wang, B. *Med. Res. Rev.* **2005**, *25*, 490–520.
2. Wang, W.; Gao, X.; Wang, B. *Curr. Org. Chem.* **2002**, *6*, 1285–1317.
3. Cao, H. S.; Heagy, M. D. *J. Fluorescence* **2004**, *14*, 569–584.
4. Shinkai, S.; Takeuchi, M. *Trend Anal. Chem.* **1996**, *15*, 188–193.
5. James, T. D.; Shinkai, S. *Top. Curr. Chem.* **2002**, *218*, 159–200.
6. Rusin, O.; Alpturk, O.; He, M.; Escobedo, J. O.; Jiang, S.; Dawan, F.; Lian, K.; McCarroll, M. E.; Warner, I. M.; Strongin, R. M. *J. Fluorescence* **2004**, *14*, 611–615.
7. Lavigne, J. J.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1999**, *38*, 3666–3669.
8. Mulla, H. R.; Agard, N. J.; Basu, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 25–27.
9. Secor, K. E.; Glass, T. E. *Org. Lett.* **2004**, *6*, 3727–3730.
10. Badugu, R.; Lakowicz, J. R.; Geddes, C. D. *Bioorgan. Med. Chem.* **2005**, *13*, 113–119.
11. Yang, W.; Gao, S.; Gao, X.; Karnati, V. R.; Ni, W.; Wang, B.; Hooks, W. B.; Carson, J.; Weston, B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2175–2177.
12. Yang, W.; Fan, H.; Gao, S.; Gao, X.; Ni, W.; Karnati, V.; Hooks, W. B.; Carson, J.; Weston, B.; Wang, B. *Chem. Biol.* **2004**, *11*, 439–448.
13. Burnett, T. J.; Peebles, H. C.; Hageman, J. H. *Biochem. Biophy. Res. Commun.* **1980**, *96*, 157–162.
14. Patterson, S.; Smith, B. D.; Taylor, R. E. *Tetrahedron Lett.* **1998**, *39*, 3111–3114.
15. Kramp, K. L.; DeWitt, K.; Flora, J. W.; Muddiman, D. C.; Slunt, K. M.; Houston, T. A. *Tetrahedron Lett.* **2005**, *46*, 695–698.
16. Riggs, J. A.; Hossler, K. A.; Smith, B. D.; Karpa, M. J.; Griffin, G.; Duggan, P. J. *Tetrahedron Lett.* **1996**, *37*, 6303–6306.
17. Draffin, S. P.; Duggan, P. J.; Duggan, S. A. M. *Org. Lett.* **2001**, *3*, 917–920.
18. Smith, B. D.; Gardiner, S. J.; Munro, T. A.; Paugam, M. F.; Riggs, J. A. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1998**, *32*, 121–131.
19. Morin, G. T.; Hughes, M. P.; Paugam, M. F.; Smith, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 8895–8901.
20. Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q. *Org. Lett.* **2004**, *6*, 4603–4606.
21. Schiedel, M.-S.; Briehn, C. A.; Bauerle, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 4677–4680.
22. Yee, D. J.; Balsanek, V.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 2282–2283.
23. Kim, I.-B.; Wilson, J. N.; Bunz, U. H. F. *Chem. Commun.* **2005**, 1273–1275.
24. Yashima, E.; Nimura, T.; Matsushima, T.; Okamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9800–9801.
25. Kawamura, H.; Maeda, K.; Okamoto, Y.; Yashima, E. *Chem. Lett.* **2001**, 58–59.
26. Metivier, R.; Amengual, R.; Leray, I.; Michelet, V.; Genet, J.-P. *Org. Lett.* **2004**, *6*, 739–742.
27. Lavastre, O.; Illitchev, I.; Jegou, G.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2002**, *124*, 5278–5279.

28. Mongin, O.; Porres, L.; Moreaux, L.; Mertz, J.; Blanchard-Desce, M. *Org. Lett.* **2002**, *4*, 719–722.
29. Odom, S. A.; Parkin, S. R.; Anthony, J. E. *Org. Lett.* **2003**, *5*, 4245–4248.
30. Leroy-Lhez, S.; Fages, F. *Eur. J. Org. Chem.* **2005**, 2684–2688.
31. Nakano, Y.; Ishizuka, K.; Muraoka, K.; Ohtani, H.; Takayama, Y.; Sato, F. *Org. Lett.* **2004**, *6*, 2373–2376.
32. Holla, B. S.; Mahalinga, M.; Karthikeyan, M. S.; Poojary, B.; Akberali, P. M.; Kumari, N. S. *Eur. J. Med. Chem.* **2005**, 1173–1178.
33. Mocharla, V. P.; Colasson, B.; Lee, L. V.; Roper, S.; Sharpless, K. B.; Wong, C.-H.; Kolb, H. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 116–120.
34. Hoye, R. C.; Baigorria, A. S.; Danielson, M. E.; Pragman, A. A.; Rajapakse, H. A. *J. Org. Chem.* **1999**, *64*, 2450–2453.
35. Miller, M. W.; Johnson, C. R. *J. Org. Chem.* **1997**, *62*, 1582–1583.
36. Springsteen, G.; Wang, B. *Tetrahedron* **2002**, *58*, 5291–5300.
37. Yang, W.; Springsteen, G.; Yan, J.; Deeter, S.; Wang, B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1019–1022.
38. Yang, W.; Yan, J.; Fang, H.; Wang, B. *Chem. Commun.* **2003**, 792–793.
39. Karnati, V.; Gao, X.; Gao, S.; Yang, W.; Sabapathy, S.; Ni, W.; Wang, B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3373–3377.
40. Gao, X.; Zhang, Y.; Wang, B. *Org. Lett.* **2003**, *5*, 4615–4618.
41. Ni, W.; Fang, H.; Springsteen, G.; Wang, B. *J. Org. Chem.* **2004**, *69*, 1999–2007.
42. Gao, X.; Zhang, Y.; Wang, B. *New J. Chem.* **2005**, *29*, 579–586.
43. Gao, X.; Zhang, Y.; Wang, B. *Tetrahedron* **2005**, *61*, 9111–9117.
44. Wang, J.; Jin, S.; Wang, B. *Tetrahedron Lett.* **2005**, *46*, 7003–7006.
45. Yang, W.; Lin, L.; Wang, B. *Tetrahedron Lett.* **2005**, *46*, 7981–7984.
46. Stones, D.; Manku, S.; Lu, X.; Hall, D. G. *Chem. Eur. J.* **2004**, *10*, 92–100.
47. Hoeg-Jensen, T. *QSAR Comb. Sci.* **2004**, *23*, 344–351.
48. Shinkai, S.; Takeuchi, M. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 40–51.
49. Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686–4687.
50. Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley: New York, 1984; pp 1–176.
51. Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137.
52. Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551–8553.
53. Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729–1731.
54. Erdelyi, M.; Gogoll, A. *J. Org. Chem.* **2001**, *66*, 4165–4169.
55. Erdelyi, M.; Gogoll, A. *J. Org. Chem.* **2003**, *68*, 6431–6434.