Synthesis of Sulfonyl Chlorides of Phenylboronic Acids

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Abstract: Sulfonyl chlorides of phenylboronic esters have been made available by selective lithiation of bromo *N*-methyl-diethanolamine phenylboronates to give lithium sulfinyl phenylboronates as intermediates. Oxidations with *N*-chlorosuccinimide give the target sulfonyl chlorides, which may be isolated or used in situ for further reactions. The novel reagents are useful in preparation of among other sulfonamides of phenylboronic acids for use in Pd(0) catalysed cross-couplings. They also hold potential as carbohydrate binders with physiological pK_a.

Key words: boronic acid, pK_a, sulfonamides, lithiation, cross-coupling

Aryl boronic acids have become a very important functional class, with synthetic applications in the popular Suzuki–Miyaura cross-coupling reaction,[1] and recently also in several novel Pd(0) catalysed reactions with formation of C-O, C-N or C-S bonds.[2–4] Additionally, the anionic form of boronic acids, boronates, are known for their reversible binding to various carbohydrates. This feature has been exploited in preparation of among other glucose sensors.[5] However, since the pK_a of simple arylboronic acid is 8.5, glucose binding is usually strong only under alkaline conditions. For use under neutral and/or physiogical conditions, the boronate pK_a can be corrected by derivatising the aromatic nucleus with strongly electron-withdrawing groups. The electron-withdrawing effect of the carboxy group is relatively weak, and pK_a of 4-carboxy-phenylboronic acid is approximately 8.[6] The nitro group is more effective,[7] but this group is usually less attractive from a pharmacological point of view. With these aspects in mind, we recently took interest in sulfonyl arene boronic acids, in particular sulfonamides, which may simultaneously function as strongly electron-withdrawing groups and as handles for attachment of the carbohydrate binders to drugs or reporter groups (fluorophores etc.). Sulfonamides of aryl boronic acids have previously been made for Suzuki–Miyaura application by among other *ortho*-directed metalation, followed by borylation with trialkyl borate.[8,9] An alternative method relies on Pd(0) catalysed coupling of aryl halides with tetraalkoxydiboron[10] or dialkoxyborane.[11] Unfortunately, the Pd(0) catalysed boronation often yields debrominated side product (C-H). Furthermore, neither of the mentioned methods is particularly tolerant with respect to other functionalities, e.g. alcohols and carboxylic acids must usually be used in protected form.

Obviously, sulfonyl halides of aryl boronic acids would be attractive building blocks for the formation of the desired sulfonamides, but such sulfonyl halides are hitherto unknown according to CAS. We report here a method for the preparation of sulfonyl chlorides of phenylboronic acids via selective bromo–lithium exchange of bromo *N*-methyl-diethanolamine phenylboronates, followed by reaction with sulfur dioxide and *N*-chlorosuccinimide oxidation of the resulting lithium sulfinates. The sulfonyl chlorides may be isolated by aqueous workup, but are somewhat unstable, and are therefore preferably applied as in situ reagents. The usefulness of the novel building blocks has been demonstrated by preparation of a set of sulfonamides and a Suzuki–Miyaura coupling.

We initially investigated the bromine–lithium exchange with pinacol, neopentylglycol, and *N*-methyl-diethanolamine protected esters of 3-bromo and 4-bromo phenylboronic acid. Treatment of pinacol or neopentylglycol boronic esters with *n*-butyl lithium at –100 °C for 15 minutes and subsequent quench with sulfur dioxide[12] did not produce the desired lithium sulfinates. Instead, complicated mixtures were formed. In contrast to these results we found that similar treatment of the corresponding *N*-methyldiethanolamine boronates protected esters **1** resulted in clean bromine–lithium exchange,[13] and subsequent quench with sulfur dioxide resulted in immediate precipitation of the lithium sulfinates (**2a**,**b**) which could be isolated in yields of 94% and 99%, respectively (Scheme 1). Possibly the nitrogen atom in the *N*-methyldiethanolamine protection group brings the boron atom in a tetrahedral and more protected state via B-N interaction, thereby making it less susceptible for attack of the butyl lithium. The protocols are straightforward and could easily be performed on a 20 g scale. Notably, the use of 0.9 equivalents of *n*-BuLi in the lithiation step was found to be advantageous, since contamination with lithium butyl sulfinate was otherwise observed. Attempts to selectively lithiate and sulfinate *ortho*-bromo *N*-methyl-diethanolamine phenylboronate were unsuccessful as only complex mixtures were obtained. The lithium sulfinates **2a**,**b** undergoes mild oxidation to the corresponding sulfonyl chlorides **3a**,**b** upon treatment with *N*-chlorosuccinimide. The sulfonyl chlorides are slightly unstable but could be isolated in 50–55% yield after aqueous work up. Alternatively, in situ reaction of **3a**,**b** with primary or secondary amines followed by hydrolysis of the *N*-methyl-diethanolamine boron ester by dilute HCl or Dowex cation exchange resin

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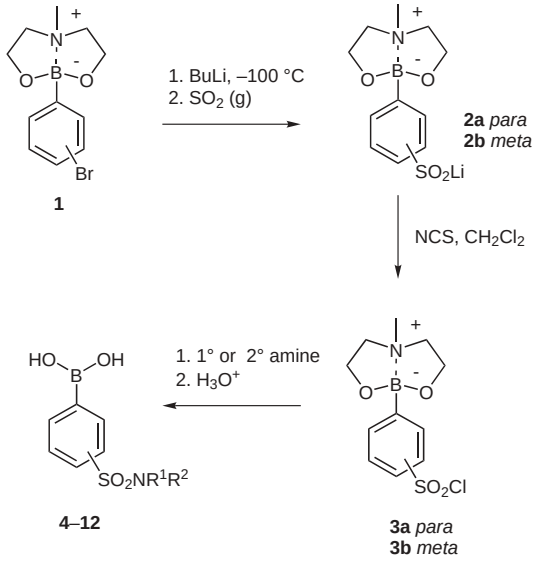


Scheme 1

and simple aqueous workup, gave the corresponsing sulfonamide phenylboronic acids in moderate to high yields and good purities (>90%), see Table 1.

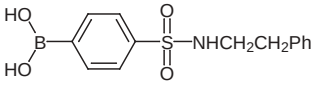
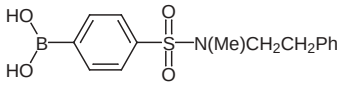
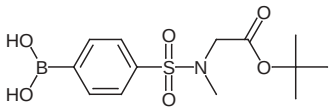
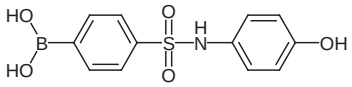
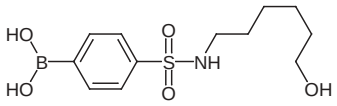
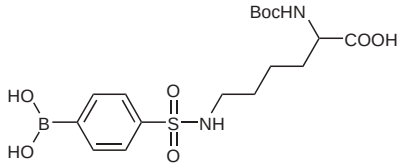
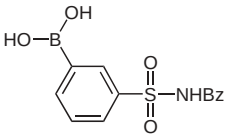
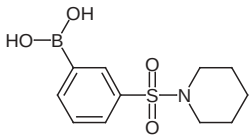
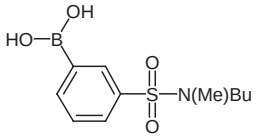
As mentioned, the method of Pd(0) catalysed borylation from diboron usually requires protection of alcohols and carboxylic acids. On the contrary, use of the novel sulfonyl chlorides for formation of sulfonamides allows the employment of alcohol and carboxy functions in unprotected form (*N*-selective sulfonylation), as exemplified by the reaction of in situ generated **3a** with 4-aminophenol, 6-aminohexanol and N^{α}-Boc-L-lysine (**7**, **8** and **9**, Table 1).

Suzuki–Miyaura reaction[14] of the novel sulfonamide-phenylboronic acids was exemplified by reaction of compound **5** with 4-bromo-anisole under Pd(0) catalysis[15] to isolate 4-(*N*-methyl-*N*-phenethyl-sulfonamide)-4′-methoxy-biphenyl **13** in 88% yield (Scheme 2) upon flash chromatography (the amounts of Pd catalysts were adjusted to give Pd/phosphine stochiometry of 1:1).

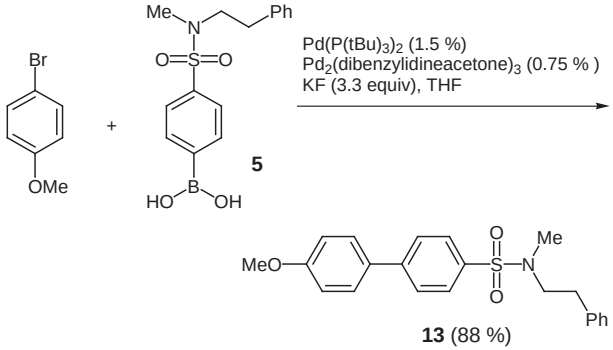
The pK_a of 4-(*N*-methyl-sulfonamide) phenylboronic acid was evaluated by titration with 0.01 M NaOH (Figure 1) and the value was 7.4. Accordingly, sulfonamide phenylboronic acids can be expected to bind carbohydrates strongly at physiological conditions. Additionally, the polar nature of the sulfonamide function seems to generally improve the aqueous solubility of the compounds. Solubility in water has been problematic with many other boronate-based carbohydrate sensors,[16] and they have usually been tested in 50% methanol.[17]

Utilisation of the novel sulfonamide phenylboronic acid building blocks in construction of novel carbohydrate sensors will be reported in due course.

Table 1 Sulfonamide Phenylboronic Acid Products[a]

Compound number	Structure	Yield (%)
4		50
5		61
6		72
7		37
8		54
9		55
10		37
11		76
12		68

[a] Compound identities and purities were evaluated by NMR and LCMS.



Scheme 2

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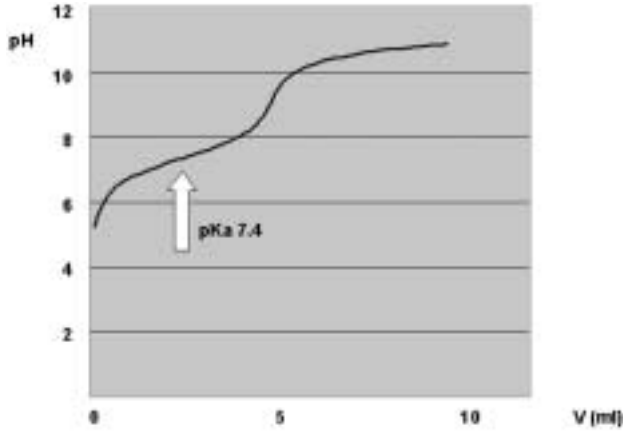

Figure 1 Titration of 4-(*N*-methyl-sulfonamide) phenylboronic acid

Lithium 4-Sulfinyl *N*-Methyl-diethanolamine Phenylboronate (2a)

4-Bromo *N*-methyl-diethanolamine phenylboronate (26.5 g, 94 mmol) in THF (800 mL) at –100 °C was treated dropwise with *n*-BuLi/hexane (1.43 M, 59 mL, 70 mmol) over 10 min. After 15 min, gaseous SO_2 (28 g, 0.43 mol) was added and the mixture was stirred at r.t. for 1 h. The precipitate was collected by filtration, providing 23.0 g (99%) of compound **2a**.

^{1}H NMR (DMSO-d_6): δ = 7.43 (d, 2 H), 7.35 (d, 2 H), 3.97–3.83 (m, 4 H), 3.26–3.19 (m, 2 H), 2.98–2.89 (m, 2 H), 2.17 (s, 3 H).

4-(*N*-Methyl-*N*-ethylphenyl-sulfonamide) Phenylboronic Acid (5)

Suspended sulfinyl **2a** (275 mg, 1.0 mmol) and NCS (147 mg, 1.10 mmol) in CH_2Cl_2 (2 mL) were stirred for 1 h, and treated with *N*-methyl-*N*-phenethylamine (0.305 mL, 2.1 mmol). After 1 h, Dowex 50WX2-400 resin (1 g) was added and the mixture was stirred for 1 h. The mixture was filtered, extracted with 1 M NaOH, washed with CH_2Cl_2 and acidified with 1 M HCl to precipitate 5 (196 mg, 61%).

^{1}H NMR (DMSO-d_6 + DCl): δ = 7.99 (d, 2 H), 7.71 (d, 2 H), 7.32–7.19 (m, 5 H), 3.19 (t, 2 H), 2.77 (t, 2 H), 2.69 (s, 3 H).

References

(1) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.
(2) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.
(3) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933.
(4) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019.
(5) James, T. D.; Shinkai, S. *Guest-Host Chemistry* **2002**, *218*, 159.
(6) Gardiner, S. J.; Smith, B. D.; Duggan, P. J.; Karpa, M. J.; Griffin, G. J. *Tetrahedron* **1999**, *55*, 2857.
(7) Singhal, R. P.; Ramamurthy, B.; Govindraj, N.; Sarwar, Y. *J. Chromatogr., A* **1991**, *543*, 17.
(8) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763.
(9) Fevig, J. M.; Cacciola, J.; Alexander, R. S.; Knabb, R. M.; Lam, G. L.; Wong, P. C.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3143.
(10) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.
(11) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458.
(12) Hamada, T.; Yonemitsu, O. *Synthesis* **1986**, 852.
(13) Brown, G. R.; Clarke, D. S.; Foubister, A. J.; Freeman, S.; Harrison, P. J.; Johnson, M. C.; Mallion, K. B.; McCormick, J.; McTaggart, F.; Reid, A. C.; Smith, G. J.; Taylor, M. J. *J. Med. Chem.* **1996**, *39*, 2971.
(14) McNeil, S. L.; Familoni, O. B.; Snieckus, V. *J. Org. Chem.* **2001**, *66*, 3662.
(15) Littke, A. F.; Dai, C.; Fu, G. F. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
(16) Eggert, H.; Frederiksen, J.; Morin, C.; Norrild, J. C. *J. Org. Chem.* **1999**, *64*, 3846.
(17) Arimori, S.; Ushiroda, S.; Peter, L. M.; Jenkins, T. A.; James, T. D. *Chem. Commun.* **2002**, 2368.

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