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Selective protodeboronation: synthesis of 4-methyl-2-thiopheneboronic anhydride and demonstration of its utility in Suzuki–Miyaura reactions

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Abstract—An efficient synthesis of 4-methyl-2-thiopheneboronic anhydride is reported. Regioselective lithiation of 3-methylthiophene followed by reaction with triisopropylborate and hydrolysis provides a 92:8 ratio of 4-methyl-2-thiopheneboronic acid (**1**) and regioisomeric 2-methyl-3-thiopheneboronic acid (**3**). The undesired regioisomer is selectively protodeboronated with concentrated acid to provide only the desired 4-methyl-2-thiopheneboronic acid (**1**). The title compound is isolated by dehydration/crystallization and employed in several Suzuki–Miyaura reactions.

1. Introduction

Boronic acids are useful compounds in organic synthesis due to their reactivity in a wide range of reactions,[1] including the carbon–carbon bond forming Suzuki–Miyaura reaction.[2] The corresponding cyclic boronic anhydrides are similarly reactive and, in many cases, more easily isolated as a single species.[3] As part of a recent project, we required an efficient and practical synthesis of 4-methyl-2-thiopheneboronic acid (**1**) (Fig. 1).[4] Substituted thiophenes are common structural moieties in pharmaceuticals;[5] thus a regioselective synthesis of **1** would be a valuable addition to current chemistry.

2. Results and discussion

Two challenges associated with designing a synthesis of **1** were the regioselective metallation of **2** and the isolation and purification of the product boronic acid.

The lithiation of **2** has been the subject of several literature reports.[6] Only recently has a highly regioselective lithiation been developed for this substrate; however, the method reported is inefficient and impractical on scale due to the use of expensive stoichiometric reagents and cryogenic (i.e., −78 °C) reaction conditions.[6a]

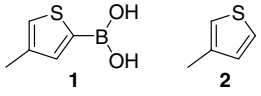

Figure 1. 4-Methyl-2-thiopheneboronic acid (**1**).

Our efforts towards the selective generation of boronic acid **1** are shown in Table 1. A screen of lithiation protocols revealed that the use of in situ generated LDA at 0 °C or −35 °C followed by a boronate quench and hydrolysis gave the best ratio of **1** to **3** (Table 1). Importantly, both lithiation and quench could be carried out at more industrially useful temperatures than reported previously.

Seeking to further upgrade the purity of **1** beyond the 12:1 mixture obtainable via selective lithiation, we considered the possibility of selectively protodeboronating **3** in the presence of **1**. Such a protocol would constitute a valuable control point for controlling the ultimate purity of **1**. In 1961, Kuivila reported that the rate of protodeboronation of substituted phenylboronic acids was impacted by acid strength and substituent effects. In general, protodeboronation was shown to proceed via an A-S_E2 mechanism, where protonation of the aryl

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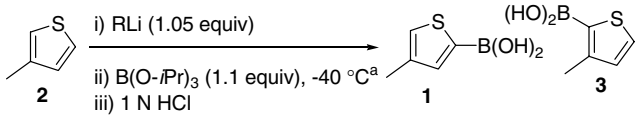
Table 1. Selectivity of lithiation-quench sequence with several lithiating reagents

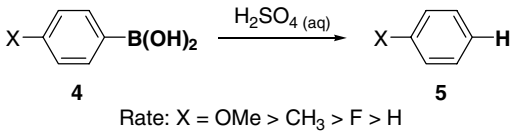


Entry	RLi	T (°C)	1:3[b]
1	*n*-Butyllithium	−35	3:1
2	*n*-Butyllithium/TMEDA	−35	4:1
3	*n*-Butyllithium/diisopropylamine	−35	12:1
4	*n*-Butyllithium/diisopropylamine	0	12:1
5	*n*-Butyllithium/TMP (20%)[c]	0	8:1
6	*n*-Butyllithium/diisopropylamine (20%)[c]	0	7:1

[a] Higher temperatures resulted in bis-addition of thiophene to boron.
[b] Complete lithiation was observed in all cases. The ratio of 1:3 was measured by HPLC.
[c] *n*-Butyllithium (1.05 equiv), amine (0.20 equiv).

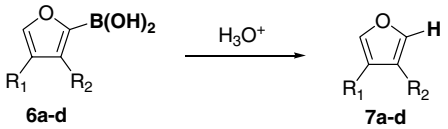
ring was the rate-determining step and was followed by a rapid ionic cleavage of the boron–carbon bond (**4**→**5**, Scheme 1).[7] Stronger acid resulted in more rapid protodeboronation, as did the use of more electron-rich substituents (e.g., *p*-methoxyphenylboronic acid vs *p*-fluorophenylboronic acid).

Subsequent to these reports, Roques studied the impact of substituents on the protodeboronation rates of furanboronic acids.[8] As with phenylboronic acids, electron-withdrawing substituents retarded the rate of protodeboronation (Table 2, cf, entries 2 and 3); however, the rate decrease was greater when such substituents were located at the 3-position (**6c**, entry 3) compared to the 2-position (**6b**, entry 2). The rate of protodeboronation was also shown to be proportional to the pK_a of the boronic acid, with the most acidic furanboronic acids having the slowest rates of protodeboronation. Extrapolating these results to 3-methyl-2-furanboronic acid (**6d**, entry 4), it could be expected that



Scheme 1.

Table 2. Rates of protodeboronation and acidity constants for several substituted furanboronic acids



Entry	Substrate	R_1	R_2	pK_a	k (s^{-1})
1	**6a**	H	H	7.89	4
2	**6b**	CHO	H	2.15	6.0×10^{-4}
3	**6c**	H	CHO	0.95	1.7×10^{-4}
4	**6d**	H	CH_3	8.5	NR[a]

[a] Not reported.

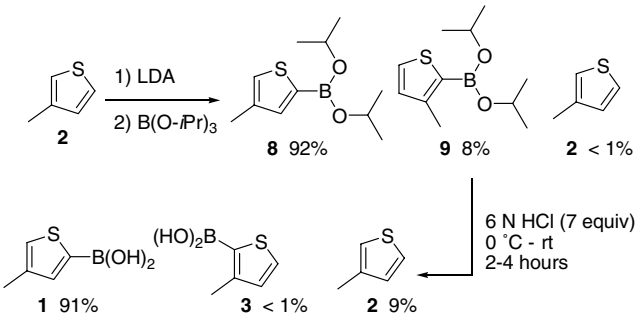
this substrate would protodeboronate more rapidly than its 2-methyl-substituted counterpart. Similar relative reactivities were expected for the thiophene system based upon Roques work.[9]

In the event, treatment of a mixture of boronate esters **8** and **9** in a 92:8 ratio with 6 N HCl resulted in hydrolysis followed by selective protodeboronation of undesired regioisomer **3** (Scheme 2). The final product mixture was enriched to greater than a 91:1 ratio of **1** to **3**, indicating that the rate of protodeboronation of **3** is approximately eight-fold than that of **1**. Using this protocol, the desired boronic acid (**1**) could be generated to the near exclusion of regioisomer **3**.

With a selective protodeboronation protocol established, efforts were focused on developing an efficient isolation of boronic acid **1**. Unfortunately, all attempts to crystallize the free boronic acid resulted in a mixture of **1** and the corresponding boronic anhydride **10** (Fig. 2). Even when isolated from methanol/water, drying of the solid resulted in near complete dehydration of **1** to **10**. Given the apparent ease of dehydration, and cognizant that boronic anhydrides often display reactivity similar to boronic acids, we targeted the isolation of **10**. Under optimized conditions, boronic anhydride **10** was isolated in 84% yield as a crystalline solid from toluene/heptane. Residual boronic acid **3** was present in the product in less than 1%.[10]

The utility of boronic anhydride **10** was demonstrated in several Suzuki–Miyaura reactions (Table 3). These unoptimized reactions utilizing $Pd(OAc)_2$ and XPhos[11] as the precatalyst clearly show that **10** can be used in place of the free boronic acid.[12]

In conclusion, we have developed a practical and efficient synthesis of 4-methyl-2-thiopheneboronic



Scheme 2.

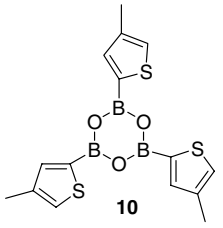
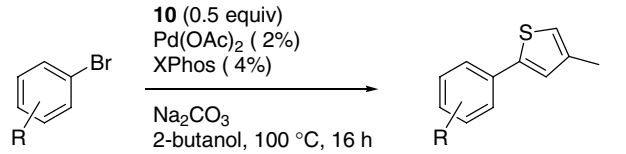
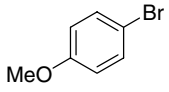
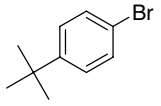
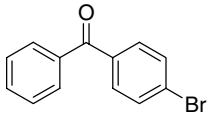


Figure 2. 4-Methyl-2-thiopheneboronic anhydride (boroxine) (**10**).

Table 3. Demonstration of the utility of 4-methyl-2-thiopheneboronic anhydride (**10**) in Suzuki–Miyaura reactions



Entry	ArBr	Product	Isolated yield (%)
1		**11**	93
2		**12**	96
3		**13**	90

anhydride (**10**) utilizing a selective protodeboronation protocol to achieve regioisomeric purity. Controlled dehydration and isolation of the crystalline boronic anhydride has also been developed to deliver the product in excellent yield. In addition, the utility of **10** in Suzuki–Miyaura couplings was successfully demonstrated. We anticipate that this protocol will provide ready access to a range of pharmaceutically important thiophene-containing compounds.

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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.2007.09.060.

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10. *Procedure for the synthesis of 4-methyl-2-thiophenecyclotriboroxane* (**10**): 3-Methylthiophene (**2**, 10.0 g, 0.102 mol, 1.0 equiv), diisopropylamine (15.1 mL, 0.107 mol, 1.05 equiv) and THF (100 mL) were added to a 1 L three-neck round-bottomed-flask equipped with an overhead stirrer and internal temperature probe, which had previously been evacuated/backfilled with N_2(g) three times. The flask was then cooled to 0 °C in an ice bath. When the internal temperature reached 2.0 °C, the dropwise addition of *n*-BuLi (1.58 M) (67.7 mL, 0.107 mol, 1.05 equiv) was initiated. Addition required 1.5 h, and the internal temperature did not exceed 3 °C. The mixture was allowed to stir at 0 °C for 1 h before cooling to −40 °C in an acetonitrile/dry ice bath. After 1 h, the internal temperature was −38.5 °C and the dropwise addition of triisopropylborate (25.8 mL, 0.112 mol, 1.1 equiv) was initiated. Addition required 45 min, and the internal temperature did not exceed −38 °C. The mixture was stirred with warming to rt over a period of 16 h. Analysis of an aliquot (three drops, via syringe, quenched into 1 N HCl (three drops), and then diluted with methanol) by HPLC revealed a product distribution of 92.5:7.2:0.3 (**1**:**3**:**2**). The reaction mixture was cooled to 0 °C in an ice bath and 6 N HCl (119 mL, 0.714 mol, 7.00 equiv) was added dropwise over 2 h such that the internal temperature did not exceed 4 °C. The mixture was again sampled and analyzed by HPLC, revealing a product ratio of 92.6:6.7:0.5 (**1**:**3**:**2**). The mixture was warmed to rt and sampled at intervals until the product ratio reached 91.1:0.3:8.6 (**1**:**3**:**2**) (2 h after the end of acid addition). The mixture was again cooled to 0 °C, and 6 N NaOH (86 mL, 0.516 mol, 5.1 equiv) was added slowly over 1.5 h until pH 4. The internal temperature did not exceed 5 °C. The mixture was warmed to rt, and the phases were separated. The organic layer consisted of a product ratio

of 90.5:0.2:9.2 (**1**:**3**:**2**). The organic phase was washed with 10% $NaHSO_4$ (100 mL), and brine (100 mL). The organic phase was concentrated to 40 mL, toluene (100 mL) was added, and the solution was concentrated to 40 mL total volume. This process was repeated four times, or until all of the THF (0% remaining by NMR) and isopropyl alcohol (0.6% remaining by NMR) were removed. The final 40 mL solution of toluene (containing precipitate) was stirred in a 250 mL round-bottomed-flask, and heptane (70 mL) was added with stirring. The mixture was stirred for 30 min at rt before cooling to 0 °C and stirring for an additional 30 min. The slurry was filtered through a 60 mL medium porosity fritted funnel and the wet cake was rinsed with 2 × 10 mL of cold (0 °C) heptane. The filtrate contained 339 mg (2.2%) of **1**. The solids were dried on the filter frit under vacuum with a sweep of nitrogen for 16 h to yield 10.64 g (84.2%) of **10** as a white solid, mp 203–207 °C. This compound cannot be observed by HPLC due to hydrolysis. ^{1}H NMR (400 MHz, DMSO) δ 7.30 (s, 1H), 7.27 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (400 MHz, DMSO) δ 139.8, 138.0, 136.3, 126.1, 15.0; IR (neat, cm^{-1}) 2920 (m), 2865 (w), 1541 (s), 1420 (s), 1320 (m), 1255 (s), 1194 (s), 1019 (s), 861 (s), 751 (s), 701 (s); Anal. Calcd for $C_{15}H_{15}B_3O_3S_3$: C, 48.44; H, 4.07; S, 25.87. Found: C, 48.55; H, 4.23; S, 25.78.

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