Research &

Development

A Robust Three-Step Telescoped Synthesis of Electron- Deficient Amide Substituted Arylboronic Acids

Jason Zhu, Thomas M. Razler,* Zhongmin Xu, David A. Conlon, Eric W. Sortore, Alan W. Fritz, Roman Demerzhan, and Jason T. Sweeney

Department of Process Research and Development, Bristol-Myers Squibb Co., One Squibb Drive, New Brunswick, New Jersey 08903, United States

Supporting Information

ABSTRACT: A robust three-step telescoped process for the preparation of electron-deficient amide-substituted arylboronic acids from readily available bromobenzoic acids has been developed. An EDC-HOBT-promoted amide formation of a bromobenzoic acid was followed by subjection of the product stream to a palladiummediated cross-coupling with $B_2(pin)_2$. The resultant mixture of the arylboronate ester and arylboronic acid was directly treated with NaIO₄, followed by a heptane— MeTHF crystallization, to cleanly afford the corresponding arylboronic acid in good yield. This general procedure was used to synthesize electron-deficient amide-substituted arylboronic acids with a diverse array of electronwithdrawing substituents.

INTRODUCTION

Arylboronic acids are extremely useful building blocks that have found utility in the synthesis of a broad range of molecules including materials, agrochemicals, pharmaceuticals, and in the synthesis of natural products.^{1,2} The preparation of many aryl and heteroarylboronic acids,³ boronate esters,⁴ and potassium trifluoroborate salts⁵ are described in the literature, and many are commercially available. Amide-substituted arylboronic acids represent a potentially important bidirectional linchpin building block, readily elaborated at both the boronic acid and carboxy functional sites (Figure 1).⁶ There are a limited number of reports on the preparation of amide-substituted arylboronic acids,⁷ and few are available commercially. Moreover, the amide-substituted arylboronic acids that are commercially available are prohibitively expensive for use in largescale applications.

In addition to the amide functionality, other electron-withdrawing substituents such as fluorine, trifluoromethyl, and nitrile create a highly electron-deficient arene ring, making arylboronic acid preparation through palladium-catalyzed or metal—halogen exchange borylation protocols significantly more challenging.⁸ Also, the electron-deficient arene ring increases the Lewis acidity of boron, leading to problems with arylboronic acid isolation. The boronate ester form of boronic acids is stabilized in electrondeficient arylboronic acids, and Lewis basic species, such as water, coordinate to boron, making isolation of a crystalline compound difficult.⁹ Herein, we report a convenient, three-step telescoped



Bi-directional Linchpin

Figure 1. Three-step telescoped synthesis of electron-deficient amidesubstituted arylboronic acids.

procedure to prepare electron-deficient, amide-substituted arylboronic acids from readily available bromo-substituted benzoic acids (Figure 1). An inverse heptane—methyltetrahydrofuran (MeTHF) crystallization was developed to circumvent the substrate hygroscopicity and afford the isolated arylboronic acids in good yields.¹⁰

RESULTS AND DISCUSSION

We recently needed to prepare a variety of electron-deficient amide-sustituted arylboronic acids. During the preparation of these compounds a number of challenges were encountered that are unique to this class of compounds. The details of the design, challenges, and optimization of the three-step telescoped process for the preparation of electron-deficient amide-substituted arylboronic acids are discussed below.

Installation of the amide moiety was deemed the necessary first step to minimize the number of transformations in the presence of the sensitive boronic acid functionality. An EDC-HOBT coupling protocol with pyrrolidine in acetonitrile proved to be optimal and provided the corresponding pyrrolidine amide **5** in high yield and greater than 98% HPLC purity (Scheme 1). Alternative procedures, including a Schotten— Baumann reaction, delivered a lower yield of the amide and up to







Scheme 2. Unproductive o-amide metalation



25% recovery of the benzoic acid through hydrolysis of the intermediate benzoyl chloride. After 2 h, the reaction mixture was concentrated, solvent exchanged to MeTHF, and washed with 1 N NaOH to remove HOBT and the EDC-urea. On the basis of its high purity, bromo-aryl pyrrolidine amide **5** was carried forward as a solution in MeTHF.

With the amide prepared, our attention turned to installation of the boronic acid moiety through the intermediacy of a boronate ester. Initial development for this transformation focused on utilizing a metal-halogen exchange protocol with bromo-aryl pyrrolidine amide 5, followed by quenching with tri-isopropoxyborane.¹¹ However, in addition to forming the desired boronate ester 8 in 45% yield, a side product was observed in 35% yield that was identified as the o-diisopropoxyboronate amide 9. The competitive o-amide-directed deprotonation was a substantial side reaction that persisted with all of the bases evaluated, e.g., *n*-BuLi, LDA, or *i*-PrMgCl. An earlier report by Wang and Senanayake utilized *i*-PrMgCl to effect the metal-halogen exchange of a similar amidesubstituted aryl halide (however, without substitution at the 3-position) and did not observe the ortho-deprotonation.^{3d} Presumably, the 3-fluoro substitution on the arene ring increases the undesired o-metalated side product by increasing the acidity of the o-amide proton (Scheme 2).¹² Furthermore, the mixture of arylboronate esters (8 and 9) was found to be in an inconsistent equilibrium with the corresponding boronic acids (10 and 11).

A palladium-mediated protocol with bis(pinacolato)diboron $[B_2(pin)_2]$ avoided the formation of the *o*-amide side product, but gave rise to a similar mixture of the boronate ester **12** and the targeted boronic acid **10**. PdCl₂(dppf) (1 mol %), B₂(pin)₂, KOAc, and MeTHF at 80 °C proved to be the optimal reaction conditions and delivered a high yield (85–90%) of the arylboronate ester **12** and arylboronic acid **10** as a 1:1 mixture after 10–15 h (Scheme 3).¹³ Upon reaction workup, pinacol exchange from boron resulted in a fluctuating boronate ester—boronic acid ratio with each workup step.¹⁴ To circumvent the pinacol exchange, treatment of the arylboronate ester and arylboronic acid mixture in MeTHF with sodium periodate (NaIO₄) induced an oxidative cleavage of the free pinacol **13** in solution.¹⁵ The conversion of pinacol **13** to 2 equiv of acetone eliminated the potential to regenerate the boronate ester **12** and drove the equilibrium to the arylboronic acid **10**. Nucleophilic oxidants

such as peroxides are known to oxidatively add to boron,¹⁶ however, electrophilic oxidants, such as $NaIO_4$, are unable to donate an electron pair to boron's empty orbital, thus providing chemoselectivity for the pinacol while leaving the boronic acid functionality intact.

Safety evaluation of the three-step telescoped procedure revealed a significant 70 °C adiabatic temperature rise during the NaIO₄ oxidation (Table 1). Advanced Reactive Systems Screening Tool (ARSST) analysis indicated a reaction runaway at an onset temperature of 120 °C with a self-heating rate of 60 °C/min and a corresponding pressurization rate of 20-30 psig/min. Interestingly, use of an inverse addition mode where the reaction mixture was added to a suspension of NaIO₄ in water resulted in a delayed exotherm where the adiabatic temperature rise $(36 \,^{\circ}C)$ occurred after a 20-min delay at 22 °C, compared to an additioncontrolled, instantaneous exothermic 12 °C temperature rise for the normal mode of addition. In order to operate safely, we avoided the potential hazard of the delayed exotherm at ambient temperature by adding NaIO₄ to the boronate ester-boronic acid solution in MeTHF and maintained the reaction temperature between 20 and 25 °C, with active jacket cooling, well below the 120 °C exothermic onset temperature.

Table 1. Safety comparison of the $NaIO_4$ order of addition and reaction profile

NaIO ₄ order of addition	$\Delta T_{ m adiabatic}$ (22 °C)	ΔH (kJ/mol)	$\Delta T_{ m adiabatic}$ (120 °C)	self heat rate (120 °C)
<u>normal</u> NaIO ₄ addn to rxn mixture	+12 °C	-167.3	+70 °C	$+60^{\circ}C/min$
<u>inverse</u> rxn mixture addn to NaIO ₄	+36 °C (20 min delay)	-305.1	+ 80 °C	+ 61 °C/min

Isolation of the amide-substituted arylboronic acid **10** from the MeTHF reaction stream proved to be problematic. Crystallization from MeTHF and nonpolar antisolvents either directly afforded oils or crystals that transformed into oils upon standing. Repeated azeotropic drying of the arylboronic acid solution from either MeTHF or toluene was unable to achieve a solution with a water content below 0.8 wt % (measured by Karl Fischer titration).



Scheme 3. Arylboronate ester-arylboronic acid equilibrium

In an effort to address these issues, we focused on the development of an inverse crystallization protocol, wherein the polar MeTHF-arylboronic acid solution would be added slowly to a nonpolar solvent. The impetus for this potential solution was our hypothesis that water associated with the arylboronic acid would be insoluble in the nonpolar antisolvent, n-heptane (which has 0.01 wt % solubility in heptane), and would partition out as a separate aqueous phase.¹⁷ In effect, this would create an anhydrous local environment for crystallization to occur and allow for arylboronic acid isolation. Experimentally, a solution of the arylboronic acid 10 in MeTHF (KF = 0.86%) was added simultaneously with heptane over 2 h to a stirred solution of heptane at ambient temperature. We were pleased that no oiling was observed and a thick, white crystalline suspension was obtained to afford arylboronic acid 10 as a white, crystalline solid after filtration and drying.¹⁸

With a robust procedure in hand, we explored the substrate scope of the three-step procedure by evaluating the aryl ring electronics, substitution pattern, and amide functionality (Table 2). A variety of electron-deficient functionalities were well tolerated. 3-Fluoro, 2,6-difluoro, 2- and 3-chloro, 3-trifluoromethyl, and 3-nitro functionalized aryl rings all afforded the desired products in good yields. While both 4-bromo- and 3-bromo-substituted benzoic acids produced the corresponding pyrrolidine amide phenylboronic acids in good yields (entries 1-7), the 2-bromo-substituted example did not. Presumably, a stable five-membered palladacycle was formed with the amide in step 2, precluding transmetalation with $B_2(pin)_2$. In addition to pyrrolidine amides, cyclic morpholine amide (entry 8) and monosubstituted *p*-chlorophenyl amide (entry 10) both afforded the corresponding arylboronic acid products in good yield. Commercially available, 4-(N,N-dimethylcarbamoyl)-3-fluorophenylboronic acid (entry 10) was produced in 0.5 kg and 74% yield over the three steps, thus demonstrating the feasibility of our protocol on a multihundred gram scale.

CONCLUSION

A robust three-step telescoped procedure has been developed for the scalable synthesis of synthetically useful, electrondeficient amide-substituted arylboronic acids. Benefits include the use of readily available benzoic acid starting materials, inexpensive reagents, operational convenience, and generality for a variety of functional groups. A safe operating procedure was developed for the conversion of arylboronate esters to arylboronic acids using NaIO₄. The large-scale preparation of these synthetically useful bidirectional linchpins may aid in the discovery of new medicines to address unmet medical needs.

EXPERIMENTAL SECTION

General. The following experimentals are representative examples and illustrate the general method for the execution of each synthetic step.

Preparation of 4-Bromo-3-fluoro-pyrrolidinylbenzamide (5). Pyrrolidine (20.3 g, 0.28 mol) was added to a solution of 1-bromo-2-fluorobenzoic acid (25.0 g, 0.11 mol), 1-hydroxybenzotriazole hydrate (43.7 g, 0.28 mol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (54.7 g, 0.28 mol) in acetonitrile (8 mL/g) at ambient temperature. The reaction mixture was heated to 70 °C for 2 h and concentrated to approximately 2 mL/g. The reaction mixture was cooled to 20 °C, diluted with MeTHF (20 mL/g), washed with 1 N NaOH (2×, 5 mL/g), and 12 wt % aqueous NaCl (5 mL/g). The solution was passed through Darco and azeotropically dried to an end point of <0.05% water by weight (KF measurement) to afford 4-bromo-3-fluoro-pyrrolidinylbenzamide 5 (28.0 g, 90.5% solution yield) as a solution in MeTHF (\sim 10 mL/g).

Preparation of 2-Fluoro-4-(pyrrolidinylcarbamoyl)phenylboronic Acid, Pinacol Ester (12). Bis(pinacolato)diboron [B₂(pin)₂, 28.0 g, 0.11 mol], potassium acetate (27.1 g, 0.28 mol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloridepalladium-(II) (PdCl₂dppf, 0.75 g, 0.0009 mol) were charged to the solution prepared above. The reaction mixture was sparged (subsurface) with nitrogen for 5 min, and the reaction mixture was heated to 80 °C for 15 h. After cooling to 20 °C, the reaction mixture was diluted with water (10 mL/g) and filtered through Celite. The phases were separated, and the organic stream was washed with water (10 mL/g). The organic stream was filtered through Darco, washed with 1 N NaOH (10 mL/g) and discarded. The aqueous layer was then diluted with fresh MeTHF (10 mL/g), cooled to 0 °C, and acidified to pH 1.5 with 3 N HCl. The MeTHF stream was filtered through Celite and used directly in the next step as a 1:1 mixture of the 2-fluoro-4-(pyrrolidinylcarbamoyl)phenylboronic acid, pinacol ester, and 2-fluoro-4-(pyrrolidinylcarbamoyl)phenylboronic acid (28.9 g, 79.7% solution yield over two steps) in MeTHF (10 mL/g).

Preparation of 2-Fluoro-4-(pyrrolidinylcarbamoyl)phenylboronic Acid (10). Water (10 mL/g) was charged to the 1:1 mixture of the boronate ester and boronic acid in MeTHF, followed by sodium periodate (NaIO₄, 28.2 g, 0.13 mol). The jacketed reaction vessel was maintained at 10 °C by a combination of cooling and addition rates. After 1.5 h, 1 N HCl (7 mL/g) was added, the temperature was warmed to 20 °C, and the reaction stirred for an additional 15 h. Upon reaction completion (nondetectable boronate ester), the phases were separated, and the organic stream was washed with 20 wt %

	Br		1. EDAC DIPE/ 2. PdCl ₂ KOAc 3. NaIO MeTH	2, HOBT A, MeCN dppf, B ₂ (pir , MeTHF 4, HCl IF			
Entry	Benzoic acid ^b	Amide-substituted arylboronic acid	3-Step yield ^e	Entry	Benzoic Acid	Amide-substituted arylboronic acid	3-Step yield
1	Br F O O H	(HO) ₂ B	59 %	6	F ₃ C H	F ₃ C 18 0	70 %
2	Br F OH	(HO) ₂ B 14 F O	48 %	7	O ₂ N U	B(OH) ₂ O ₂ N 19 0	52 %
3	F OH		45 %	8	F ₃ C H	$F_{3}C \underbrace{\begin{array}{c} B(OH)_{2} \\ \hline \\ P_{3}C \underbrace{\begin{array}{c} 0 \\ 20 \end{array}} N \\ \hline \\ 0 \end{array}}^{B(OH)_{2}} N \underbrace{\begin{array}{c} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 $	79 %
4 ^b	Br OH CI O		51 %	9 ^d	Br F OH	(HO) ₂ B 21 O Me	74 %
5	CI OH		88 %	10	F ₃ C OH	B(OH) ₂ F ₃ C 22 0 H Cl	81 %

Table 2. Electron-deficient amide-substituted arylboronic acid substrate scope^a

^{*a*} All reactions were conducted with 25 g of the starting bromo-substituted benzoic acid except entry 9. ^{*b*} All bromo-substituted benzoic acids were commercially available. ^{*c*} Isolated yields. ^{*d*} 0.70 kg of 4-bromo-2-fluorobenzoic acid afforded 0.50 kg of 4-(N_rN -dimethylcarbamoyl)-3-fluorophenyl-boronic acid in 74% yield over the three steps.

sodium thiosulfate (5 mL/g), 12 wt % aqueous NaCl (5 mL/g), filtered through Celite, and concentrated to 4 mL/g. Heptane (4 mL/g) was added simultaneously with the reaction stream over 2 h to a lightly stirred flask of heptane (4 mL/g) at rt. The resultant white slurry was stirred for 1 h, filtered, washed with heptane (2×, 3 mL/g), and dried on the filter for 1 h. The white cake was dried in a vacuum oven at 20 °C with 23 mmHg for 24 h to afford 2-fluoro-4-(pyrrolidinylcarbamoyl)phenylboronic acid as a white solid (15.9 g, 59.1% over three steps). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.75 (d, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 7.4 Hz, 1 H), 7.23 (d, *J* = 9.6, 1 H), 3.45 (t, *J* = 6.6 Hz, 2 H), 3.36 (t, *J* = 5.8 Hz, 2 H), 1.85–1.80, (m, 4 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 166.8, 166.0, 163.6, 140.4, 135.3, 122.2, 113.5, 48.7, 45.9, 25.9, 23.8; Exact mass calcd for C₁₁H₁₃BFNO₃ 238.1051, found 238.1052.

Subkilogram-Scale Preparation of 4-(*N*,*N*-Dimethylcarbamoyl)-3-fluorophenylboronic Acid (21). Preparation of 4-Bromo-2-fluoro-*N*,*N*-dimethylbenzamide. *N*,*N*-Dimethylamine hydrochloride (0.655 kg, 8.03 mol) was added to a solution of 1-bromo-3-fluorobenzoic acid (0.704 kg, 3.21 mol), 1-hydroxybenzotriazole hydrate (0.992 kg, 6.48 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) (1.25 kg, 6.53 mol), and diisopropylethylamine (1.04 kg, 8.06 mol) in acetonitrile (4.42 kg, 8 L/kg) at ambient temperature. The reaction mixture was heated to 70 °C for 2 h and concentrated by vacuum distillation (30 °C internal batch temp, 60 mmHg) to 2 L/kg. The reaction mixture was cooled to 20–25 °C, diluted with MeTHF (20 L/kg), and washed with 1 N NaOH $(2\times, 5 \text{ L/kg})$ and 12 wt % aqueous NaCl (5 L/kg). The solution was passed through a carbon pad (R53SP pad, 1.75" diameter) and azeotropically dried (35 °C batch temp, 60 mmHg) to a KF end point of <0.02 wt % water (KF measurement) to afford 4-bromo-2-fluoro-*N*,*N*-dimethylben-zamide (0.776 kg, 98.1% solution yield) as a solution in MeTHF (10 L/kg).

Preparation of 4-(N,N-Dimethylcarbamoyl)-3-fluorophenylboronic Acid, Pinacol Ester. Bis(pinacolato)diboron [B₂(pin)₂, 0.996 kg, 3.92 mol], potassium acetate (0.948 kg, 9.66 mol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloridepalladium(II) (PdCl₂dppf, 0.026 kg, 0.031 mol) were charged to a solution of 4-bromo-2-fluoro-N,N-dimethylbenzamide (0.776 kg, 3.15 mol) in MeTHF (10 L/kg). The reaction mixture was sparged (subsurface) with nitrogen for 15 min and heated to 80 °C for 15 h. The reaction mixture was cooled to 20-25 °C, diluted with water (10 L/kg), and filtered through Celite. The phases were separated, and the organic stream was filtered through a carbon pad (R53SP, 1.75" diameter), washed with 1 N NaOH (10 L/kg), and discarded. MeTHF (10 L/kg) was added to the aqueous solution, the mixture was cooled to 0 °C and acidified to pH 1.5 with 3 N HCl. The aqueous phase was removed, and the MeTHF stream was filtered through Celite and used directly in the next step as a 1:1 mixture of the 4-(N,N-dimethylcarbamoyl)-3-fluorophenylboronic acid,pinacol ester and 4-(N,N-dimethylcarbamoyl)-3-fluorophenylboronic acid (0.806 kg, 85.6% solution yield over two steps) in MeTHF (10 L/kg).

Preparation of 4-(N,N-Dimethylcarbamoyl)-3-fluorophenylboronic Acid (21). Sodium periodate (NaIO₄, 1.03 kg, 4.84 mol) was charged to the 1:1 mixture of 4-(N,N-dimethylcarbamoyl)-3-fluorophenylboronic acid, pinacol ester, and 4-(N,Ndimethylcarbamoyl)-3-fluorophenylboronic acid (0.806 kg, 2.75 mol) in MeTHF (10 L/kg) and water (10 L/kg). The jacketed reaction vessel was maintained at 10 °C (internal temperature). After 1.5 h, 1 N HCl (7 L/kg) was added, the jacket temperature was adjusted to 20 °C, and the reaction stirred for an additional 15 h. Upon reaction completion (boronate ester nondetectable by HPLC analysis), the phases were separated, and the organic stream was washed with 20 wt % sodium thiosulfate (5 L/kg), 12 wt % aqueous NaCl (5 L/kg), filtered through Celite, and concentrated to 4 L/kg. This solution was added simultaneously with heptane (4 L/kg) over 2 h to a stirred flask of heptane (4 L/kg) at ambient temperature. The resultant white slurry was stirred for 1 h, filtered, washed with heptane $(2 \times, 3 \text{ L/kg})$, and dried on the filter for 1 h. The white cake was dried further in a vacuum oven at 20 °C and 23 mmHg for 24 h to afford 4-(N,N-dimethylcarbamoyl)-3fluorophenylboronic acid as a white solid (0.502 kg, 74.1% over three steps). ¹H NMR (400 MHz, DMSO- d_6) δ 8.34 (br s, 2 H), 7.65 (d, J = 7.5 Hz, 1 H), 7.57 (d, J = 10.7 Hz, 1 H), 7.33 (t, J = 7.1Hz, 1 H), 3.08 (s, 3 H), 2.82 (s, 3 H); ¹³C NMR (100 MHz, DMSO- d_6) δ 165.9, 158.7, 156.3, 130.6, 128.2, 126.5, 120.8, 38.1, 34.5; Exact mass calcd for C₉H₁₁BFNO₃ 211.0812, found 211.0810.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Telephone: (732)-227-5513. E-mail: thomas.razler@bms.com.

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(13) When the water content was high (>5 wt % by Karl Fischer titration) an impurity derived from a palladium-mediated dimerization of the bromo-substituted arylamide was found in up to 50% yield. Water most likely hydrolyzed the corresponding arylpinocolboronate ester to the corresponding arylboronic acid, facilitating a Suzuki cross-coupling. Maintaining the water at 0.02% or less, however, minimized the dimer to 1 wt %, enabling removal during the final arylboronic acid crystallization.

(14) HPLC analysis revealed that arylboronate ester **12** readily hydrolyzed to arylboronic acid **10** when treated with 1 N NaOH and partitioned to the basic aqueous phase. Presumably, this is due to the electron-deficient nature of the aryl ring. Surprisingly, adjustment of the pH to 1.5 and extraction with MeTHF regenerated the 1:1 mixture of arylboronate ester **12** and arylboronic acid **10**, albeit in purified form.

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