Organic Process Research & Development

Communication

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Development of an Efficient Synthesis of (2-Aminopyrimidin-5-yl) Boronic Acid

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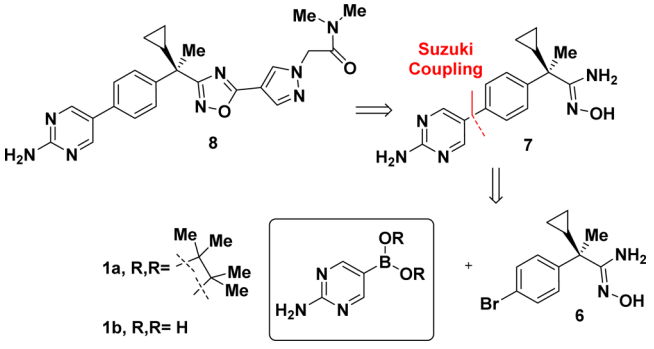
Supporting Information

ABSTRACT: A practical and cost-effective synthesis of (2-aminopyrimidin-5-yl) boronic acid **1b** has been developed. Key features of the synthesis include the inexpensive in situ protection of the amine via bis-silylation using TMSCl followed by metal−halogen exchange using *n*-BuLi and trapping with B(O*i*-Pr)$_3$. The water-soluble boronic acid is isolated by a well-designed acid−base sequence providing the target in 80% yield and high purity for the two-step process. The large-scale (15 kg) implementation of a Suzuki−Miyaura borylation to form the pinacol boronic ester is also described.

INTRODUCTION

Aryl boronic acids and esters[1] have become ubiquitous in synthetic chemistry in both industrial and academic settings due to their straightforward use in a wide range of transition metal-catalyzed coupling reactions.[2,3] However, heterocyclic boronic acids and esters can be difficult to synthesize cost-effectively on large scale. Difficulties with preparation and isolation such as instability to workup conditions, high solubility in water, and residual inorganic salts are often encountered with the synthesis of nondistillable boronic esters or acids. As part of a recent drug development program for a FLAP[4] inhibitor **8**, an effective synthesis of the requisite 2-aminopyrimidine boronic acid was required (Scheme 1). Bryce et al.[5a] have reported a direct synthesis of the corresponding boronic acid **1b** from 2-amino-5-bromopyrimidine **2** employing a metal−halogen exchange (*n*-BuLi in THF/toluene) in the presence of triisopropylborate B(O*i*-Pr)$_3$ to provide the target in moderate yields after purification. An alternative Suzuki−Miyaura borylation of the corresponding bromide **2** by the same investigators employing bis(pinacolato)diboron (KOAc/1,4-dioxane, 80 °C) afforded compound **1a**, which was used directly in cross-coupling reactions without any further purification. Herein, we describe our efforts to develop an efficient, cost-effective and scalable approach to pyrimidine boronate **1**.

Scheme 1. Retrosynthetic Strategy for FLAP Inhibitor 8



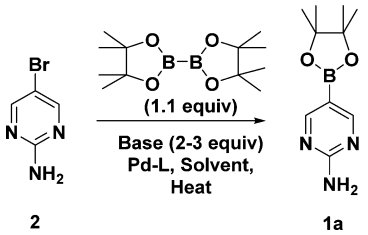
RESULTS AND DISCUSSION

A metal catalyzed Suzuki−Miyaura borylation of compound **2** using bis(pinacolato)diboron (B_2pin_2) provides rapid access to the desired compound **1a**.[5,6b,f] A screening of solvents and catalysts for the metal catalyzed borylation reaction was first conducted (Table 1). It was found that $PdCl_2$(dppf)-DCM adduct at 0.5 mol % catalyst loading in 1,4-dioxane at reflux (∼100 °C) gave complete conversion in 4−6 h. The reaction mixture was filtered through a Celite 545 pad and then rinsed the pad with ethyl acetate. The filtrates were washed with 10 wt % brine solution, and the resulting organic layer was concentrated to obtain oil, which upon trituration from heptane afforded solids in ∼76% yield (1−5 g scale) (Table 1, entry 1). However, the use of the Class 2[7] solvent 1,4-dioxane and high catalyst loading persuaded us to conduct a further screening to render the process efficient for operation at larger scale. In addition, pinacol boronate hydrolysis to the corresponding boronic acid during the aqueous washes was observed, leading to low recoveries (Table 1, entries 1, 2, 3). Hence, a nonaqueous isolation for these reactions was pursued (Table 1, entries 4, 5, 6) by performing a hot filtration of the reaction mixture to remove the inorganic salts, followed by crystallization from ethanol. Replacing 1,4-dioxane with 2-MeTHF allowed for a more efficient removal of the inorganics with the hot filtration and provided **1a** in high purity (>95 wt %) after crystallization (Table 1, entry 6). However, when the process was scaled to 1 kg, the reaction stalled with the lower catalyst loading (0.5 mol %), and an additional charge of catalyst was required to drive the reaction to completion. In order to further align the Pd source for the subsequent cross-

Received: November 3, 2015

DOI: 10.1021/acs.oprd.5b00360
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Table 1. Optimization of Metal Catalyzed Suzuki–Miyaura Borylation of 2



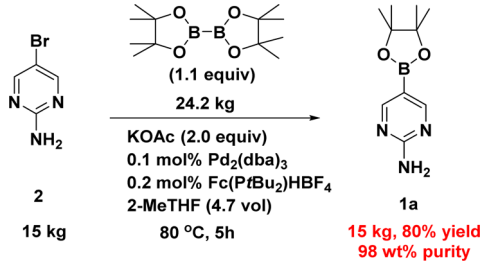
2 1a

entry	solvent	Pd–L source (mol %)	temp. (°C)	conversion (%)	isolated yield (%)
1	1,4-dioxane	$PdCl_2$(dppf)-DCM, 0.5 mol %	100 °C	98%	75.6%[a]
2	DMF	$PdCl_2$(dppf)-DCM, 0.1 mol %	105 °C	97%	62.0%[a]
3	1,4-dioxane	$PdCl_2$(dppf)-DCM, 0.1 mol %	100 °C	98%	76.0%[a]
4	1,4-dioxane	$PdCl_2$(dppf)-DCM, 0.1 mol %	100 °C	98%	86.0%[b,d]
5	1,4-dioxane	$PdCl_2$(dppf)-DCM, 0.1 mol %	100 °C	98%	87.0%[b,c,e]
6	2-MeTHF	$PdCl_2$(dppf)-DCM, 0.5 mol %	80 °C	98%	82%[b,c,f]
7	2-MeTHF	$Pd_2(dba)_3$ (0.1 mol %), $Fc(PtBu_2)$-HBF_4 (0.2 mol %)	80 °C	99.5%	80.1%[b,c,f]

[a]Aqueous work up was performed. [b]No aqueous work up was performed. [c]2 equiv of potassium acetate was used. [d]63 wt % by NMR assay. [e]73 wt % by NMR assay. [f]>95 wt % by NMR assay.

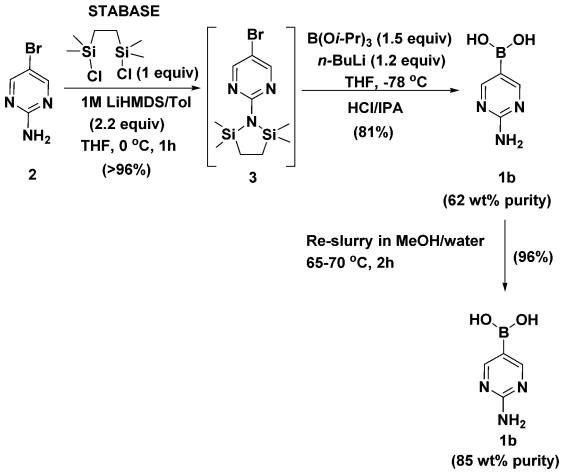
coupling step, the catalyst source was replaced with $Pd_2(dba)_3$ 0.1 mol % /$Fc(PtBu_2)$-HBF_4 (0.2 mol %), which also afforded complete conversion (Table 1, entry 7). The reaction mixture was then diluted with THF and filtered hot (ca. 60 °C) followed by a solvent switch to ethanol, CUNO (type 5) carbon treatment, and crystallization. This optimized process was successfully scaled to provide 15 kg of product **1a** as an off-white crystalline solid in 80% isolated yield and 98 wt % purity (Scheme 2).

Scheme 2. Pilot Plant Synthesis of 1a



The cost and low atom economy associated with B_2pin_2 provided us the impetus to develop a more mature process for the target compound. Initial efforts on the formation of the target boronic acid following a literature procedure,[5a] using 2-amino-5-bromopyrimidine and $B(Oi\text{-}Pr)_3$ with *n*-BuLi/THF/−78 °C gave inconsistent or poor yields (11–40%). It is known that boronic acid **1b** can be prepared from 2-amino-5-bromopyrimidine via an amine protection/metal–halogen exchange process, followed by trapping with trialkylborate.[6] The amine protecting groups that were utilized in the literature methods included the BOC group,[6a,d,e,h,i] imines derived from benzophenone,[6e,j] and a benzyl protecting group;[6g] however, those methods suffered from modest yields and required two or three isolation steps as well as a deprotection step. We sought a procedure where the amine protection group could be installed in situ and also removed without having to perform an additional chemical operation. Our attention thus turned to the potential use of tetramethyldisilylazacyclopentane (STABASE),[8a] a protecting group originally developed by Magnus et al. as a compatible *N*-protecting group for the lithiation chemistry. The desired *N*-protected substrate **3** was readily obtained by treating the solution of 2-amino-5-bromopyrimidine **2** and STABASE (1.0 equiv) in THF with 1 M LiHMDS/Toluene[8b,c] at 0 °C (Scheme 3) in excellent yield (>96%). The *N*-protected

Scheme 3. Synthesis of 1b Using STABASE Group



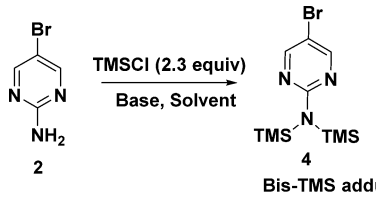
compound **3** was then treated with *n*-BuLi (2.5 M in hexanes, 1.2 equiv) in the presence of $B(Oi\text{-}Pr)_3$ (1.5 equiv) at −78 °C to afford the tetrahedral borate intermediate which upon HCl treatment and pH neutralization provided the desired boronic acid **1b** as a white solid in 81% isolated yield and yet with a low assay (62 wt %). The low assay was determined to be caused by trapped inorganic salts in the boronic acid **1b** solids. Therefore, the crude solids were slurried in hot 4:2 mixture (v/v) of MeOH-water at 70 °C for 2 h followed by cooling and filtration to obtain target **1b** in 96% yield (77% overall yield from **2**) with an improved assay purity of 85 wt %, with the remainder being simply water.[9]

While the STABASE process was suitable for the preparation of kilogram quantities of **1b**, it became apparent that the STABASE reagent was not readily available at low cost on large scale, and thus a final round of process optimization was

DOI: 10.1021/acs.oprd.5b00360
Org. Process Res. Dev. XXXX, XXX, XXX–XXX

undertaken. TMSCl was thus explored as a potential alternative to STABASE. It was previously demonstrated by Asher[10a] that it could be utilized as aniline protecting group[10b] utilizing *lithium*-halogen exchange chemistry. When compound **2** was treated with TMSCl (2 equiv) in THF at 0 °C with 1 M LiHMDS/Toluene as the base (Table 2, entry 1), or MeLi

Table 2. Optimization of Bis-TMS Adduct 4 Formation



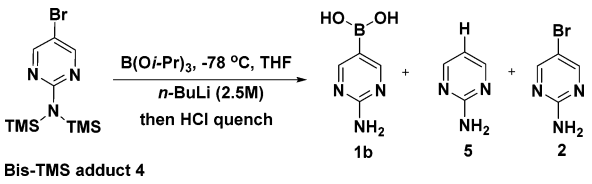
entry	solvent	temp. (°C)	base (2.2 equiv)	conversion (%)[a]
1	THF	0 °C	1 M LiHMDS/Tol	>97%
2	THF	0 °C	1.6 M MeLi/Et_2O	>97%
3	THF	0 °C	NaH	0%
4	THF	22−40 °C	NaH (*i*-PrOH 7 mol %)	>95%

[a]Conversion confirmed by HNMR analysis.

(entry 2) a quantitative formation of the bis-TMS adduct **4** was observed by ^{1}H NMR.[11] When sodium hydride (NaH) was used as the base for silylation no desired bis-TMS adduct **4** was observed (entry 3). However, when bromide **2** was treated with NaH (1.2 equiv) (entry 4) in THF along with catalytic amount of *i*-PrOH (7 mol %) as an additive, the deprotonation reaction initiated with a mild exotherm and concurrent H_2 gas evolution. A process was thus developed whereby sequential addition of NaH and TMSCl (2×) furnished >95% conversion to the desired bis-TMS adduct **4**.

After obtaining the bis-TMS adduct **4** in THF, *n*-BuLi (1.2 equiv of 2.5 M in hexanes) was charged at −78 °C to promote the lithium−bromine exchange in the presence of B(O*i*-Pr)$_3$ (1.3 equiv) (Table 3, entry 1). The reaction mixture was

Table 3. Optimization of Boronic Acid Formation

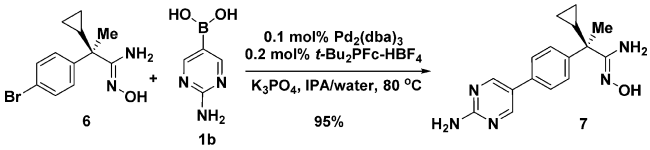


entry	solvent	B(O*i*-Pr)$_3$ (equiv)	*n*-BuLi (equiv)	**1b** (A %)	**5** (A%)	**2** (A %)
1	THF	1.3	1.2	81%	12%	7%
2	THF	1.5	1.45	94%	<0.5%	<2%
3	THF	1.55	1.48	95%	<0.3%	

warmed to 0 °C at which point HPLC analysis indicated the presence of desired boronic acid **1b** (81 area %), ArH **5** (12 area %), and starting material **2** (~7 area %) at 220 nm. By increasing the equivalents of both reagents (B(O*i*-Pr)$_3$ and *n*-BuLi) to 1.5 and 1.45 equiv, respectively, 94 area % conversion was observed to boronic acid **1b** with <2 area % of starting material **2** (entry 2). Complete consumption was observed with additional charge of the reagents (entry 3).

With the optimized reaction conditions in place, we began to streamline the processing procedure. Upon completion of the borylation, the batch was cooled to 0 °C, and the pH was adjusted to ~9 with conc. HCl. Extraction of the boronic acid **1b** with EtOAc failed to provide high recovery due to the high solubility of **1b** in water under basic conditions. A practical purification was found by first removing THF by distillation and then adjusting the pH to 1−1.5 using HCl. Water dilution and organic washes (heptane and ethyl acetate) removed unreacted **2** and nonpolar impurities. Finally, the pH of the aqueous layer was adjusted to 5.5−6 using aq. NaOH, which provided boronic acid **1b** as a precipitate. After filtration, a reslurry in water at 85 °C followed by filtration and drying furnished **1b** in 80% overall yield (from **2**) with 99% (HPLC) and 90 wt % purity. The remaining mass was principally water.[12] The optimized process to boronic acid **1b** is shown in Scheme 4. The boronic acid **1b** obtained from this process was successfully utilized for the Suzuki coupling reaction to synthesize compound **7** for our FLAP Inhibitor program.[4b]

Scheme 5. Suzuki Coupling of Boronic Acid 1b to 7



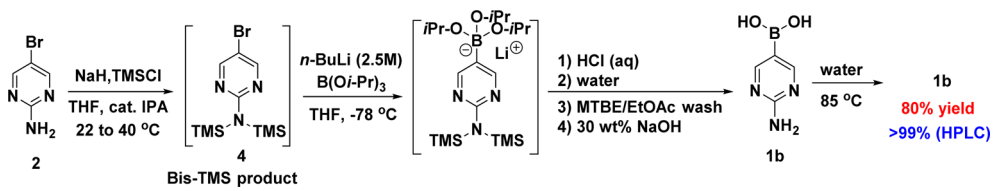
CONCLUSION

In conclusion, we have developed a practical process for the synthesis of (2-aminopyrimidin-5-yl) boronic acid (**1b**) in high yield (80%) and purity (>99% HPLC) from 2-amino-5-bromopyrimidine **2**. Applying inexpensive in situ silyl protection and metal−halogen exchange followed by trapping with borate (B(O*i*-Pr)$_3$ led to an effective process suitable for multikilogram scale production of this heterocyclic boronic acid. Moreover, we have successfully demonstrated the Pd catalyzed Suzuki−Miyaura borylation using bis(pinacolato)-diboron on 15 kg scale.

EXPERIMENTAL SECTION

General Methods. Reaction progress and chemical purity were evaluated by HPLC or ^{1}HNMR analysis (please refer to Supporting Information for ^{1}H NMR information). HPLC conditions were as follows; Agilent Poroshell 120 (EC-C18, 4.6

Scheme 4. Optimized Route to Boronic Acid 1b



DOI: 10.1021/acs.oprd.5b00360
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

× 100 mm) with mobile phases A (0.2% H_3PO_4 and 40 mM NH_4PF_6 in water) and B (acetonitrile). Detection was at 220 nm, flow was set at 1.0 mL/min, and the temperature was 20 °C (Run time: 8.5 min). Gradient: 0 min, A = 98%, B = 2%; 2.5 min, A = 98%, B = 2%; 5.5 min, A = 5%, B = 95%; 8.5 min, A = 5%, B = 95%.

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-pyrimidin-2-amine (1a). To a clean, dry, nitrogen-inerted suitable reactor were charged 2-amino-5-bromopyrimidine **2** (15.0 kg, 100 wt %, 86.2 mol), bis(pinacolato)diboron (24.2 kg, 95.3 mol), di-*tert*-butylphosphinoferrocene tetrafluoroborate (0.072 kg, 0.2 mol %), tris(dibenzylidineacetone)palladium (0.080 kg, 0.1 mol %), and potassium acetate (16.92 kg, 172.4 mol). The reactor was evacuated and purged with nitrogen three times. In a separate vessel, 2-MeTHF (60 kg) was sparged with nitrogen and then transferred to the main reactor. The mixture was heated to 82 °C over 0.5 h and held at 82 °C for 4.5 h (slurry forms). The mixture was cooled to 55 °C, and THF (200 kg) was added and then reheated back to 60 °C. The solution was filtered at 60 °C to remove solids, ensuring both filter and the receiver were heated to 60 °C. THF (67 kg) heated to 60 °C was used to rinse the reactor and filtered solids. The combined filtrates were distilled at ∼55 °C under vacuum (274 Torr) to the minimum stirrable volume. Ethanol (90 kg) was added, and the mixture was again concentrated to minimum volume. Ethanol (240 kg) was added, and the mixture was heated to 65 °C and held for 1 h. The ethanol solution was then filtered through a heated (65 °C) filter containing CUNO type 5 carbon. The reactor and filter were rinsed with preheated (60 °C) ethanol (24 kg). The combined filtrates were placed in a clean reactor and were concentrated at 60 °C under vacuum removing 260 L of distillate. The resulting slurry was cooled to 20 °C over 2 h and then held at 20 °C for 2 h. The solids were collected by filtration and were rinsed with ethanol (36 kg). The solids were dried on the filter for 1 h and then in a vacuum oven at 45 °C for 8 h yielding 15 kg of **1a** as a white crystalline solid (80% yield, 98 wt %, Pd 2 ppm). MP 212 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.59 (s, 1H), 5.69 (s, 2H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 164.87, 164.36, 84.08, 24.99. HRMS: [$C_{10}H_{16}BN_3O_2$ + H^+]: calculated 222.1408, found 222.1399.

5-Bromo-2-(2,2,5,5-tetramethyl-1,2,5-azadisilolidin-1-yl)pyrimidine (3). To a clean, dry, nitrogen-inerted 250 mL three-neck round-bottom flask were charged 2-amino-5-bromopyrimidine **2** (10.0 g, 100 wt %, 57.47 mmol) and 1,2-bis(chlorodimethylsilyl)ethane (12.37 g, 57.47 mmol). The flask was evacuated and purged with nitrogen. THF (50 mL) was charged to the flask, and the resulting mixture was cooled to −10 °C using ice/brine bath. 1 M LiHMDS/toluene (126.44 mL, 126.44 mmol, 2.2 equiv) was charged to above mixture while keeping the internal temperature below 0 °C and stirred the resulting mixture for additional 1 h at 0 °C (0.1 mL reaction aliquot was concentrated using Rotovap, diluted in CD_2Cl_2 and filtered to remove inorganics. ^{1}H-NMR analysis of the filtrate indicated >98% STABASE adduct (**3**). The reaction was quenched with 10 wt % aqueous ammonium chloride (70 mL) while keeping the internal temperature below 15 °C. The top organic layer was washed with water (50 mL), and the resulting organic layer was filtered through a Frit funnel and rinsed with toluene (20 mL). The filtrate was concentrated under vacuum using Rotovap to dryness to afford STABASE adduct **3** as off-white to tan solids (26.0 g, 69.5 wt % purity by ^{1}HNMR assay, quantitative yield), which was used directly in the next step. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ: 8.24 (s, 2H), 0.77 (s, 4H), 0.24 (s, 12H).

Bis-silylation Using TMSCl (5-Bromo-*N*,*N*-bis-(trimethylsilyl)pyrimidin-2-amine) (4). To a clean, dry, nitrogen-interted 2 L multineck jacketed reactor equipped with a reflux condenser and gas bubbler was charged 2-amino-5-bromopyrimidine **2** (50.0 g, 100 wt %, 287.35 mmol). The reactor was evacuated and purged with nitrogen. THF (500 mL) was charged to get beige color suspension followed by *i*-PrOH (1.6 mL, 20.11 mmol, 7 mol %) at 20−23 °C. Sodium hydride (60% dispersed in mineral oil, 13.79 g, 344.83 mmol, 1.2 equiv) was charged to above mixture at once (***Caution!! exotherm to 35−40 °C with gas evolution!***). The resulting suspension was stirred for additional 1 h at 40 °C. Then the slurry was cooled to 20 °C, and TMSCl (37.46 g, 344.83 mmol, 1.2 equiv) was charged slowly over 15 min keeping the internal temperature under 30 °C. The resulting mixture was stirred for additional 1 h after which the batch was cooled to 20 °C. Second portion of sodium hydride (60% dispersed in mineral oil, 12.64 g, 316.09 mmol, 1.1 equiv) was charged to the above mixture at 20 °C (***Caution!! Slow exotherm to 30−35 °C with gas evolution!***) and held at 40 °C for additional 1h before it was recooled back to 20 °C. TMSCl (34.34 g, 316.09 mmol, 1.1 equiv) was charged slowly over 15 min keeping the internal temperature under 30 °C. The final slurry was stirred at 20 °C for additional 2 h after which an aliquot was tested for bis-silylation (0.1 mL aliquot was concentrated using Rotovap, diluted in CD_2Cl_2, and filtered to remove inorganics. ^{1}H NMR analysis of the filtrate indicated >95% bis-silylation intermediate). ^{1}H NMR (CD_2Cl_2, 400 MHz) δ: 8.23 (s, 2H), 0.15 (s, 18H). The crude reaction mixture of bis-silylated adduct **4** was directly used in next borylation step.

(2-Aminopyrimidin-5-yl)boronic Acid (1b). *Borylation.* THF (150 mL) was charged to crude adduct **4** solution, and the batch was cooled to −78 °C. $B(Oi\text{-}Pr)_3$ (81.08 g, 431.12 mmol, 1.5 equiv) was charged to above mixture over 15 min and cooled the mixture to −78 °C. *n*-BuLi (2.5 M in hexanes, 167 mL, 416.74 mmol, 1.45 equiv) was charged to above mixture over 75 min keeping the internal temperature below −65 °C and held at this temperature for additional 1 h after which by HPLC the starting material was consumed (>99% conversion). The batch was warmed up to 0 °C over 1 h and quenched with 12 N HCl solution (20 mL, 240 mmol, 0.84 equiv) to adjust the pH ∼ 9 followed by water (500 mL). The resulting biphasic layers were concentrated under vacuum (temp. 45−50 °C) to distill approximately 700 mL of distillate. Then 12 N HCl solution (45 mL, 540 mmol, 1.88 equiv) was charged to adjust pH ∼ 1−1.5 at 20 °C. Water (600 mL), heptane (175 mL), and ethyl acetate (175 mL) were charged to above cloudy suspension and stirred vigorously for 30 min at 25 °C. The bottom aqueous layer containing product was separated from the top organic layer (Note: The top organic layer contained all nonpolar impurities and remaining bromide **2**). The bottom aqueous layer containing boronic acid was transferred into a clean reactor (Note: Same previous reactor could be utilized after the rinse using ethyl acetate and water). To the aqueous layer was charged 30 wt % aqueous NaOH solution (60 mL) slowly over 90 min to adjust the pH 5.5−6 to afford white slurry. The resulting slurry was stirred at 20 °C for additional 1h after which the solids were collected by suction filtration and rinsed with water (100 mL). The solids were dried on funnel for 1h and then in a vacuum oven at 25 °C for ≥12 h yielding 40.2 g of **1b** (82% yield, 81.6 wt %). Reslurry:

DOI: 10.1021/acs.oprd.5b00360
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Solids of **1b** (40.2) were charged into a suitable 250 mL three-neck RBF equipped with a stir bar, heating mantle, condenser and a temperature probe. Water (100 mL) was charged to RBF and the resulting slurry was heated to 85 °C and stirred for additional 1h. The slurry was cooled to 20 °C and stirred for additional 1−2h before the solids were collected by suction filtration. The solid cake was rinsed with water (80 mL) and then with heptane (100 mL). The air-dried solids were placed in a vacuum oven at 25 °C for ∼12 h yielding 35.51 g of **1b** as an off-white powder (80% overall yield, 90.0 wt %, remaining mass is principally water). MP 200 °C (with decomposition event). ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.52 (s, 2H), 7.99 (s, 2H), 6.76 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 164.1, 163.9. HRMS: $[C_4H_6BN_3O_2 + H^+]$: calculated 140.06258, found 140.0639.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00360.

^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(11) ^{1}H NMR sample was prepared by taking an aliquot (0.1 mL) from the reaction mixture followed by concentration using Rotovap and then dilution with CD_2Cl_2 (1.5 mL).

(12) ICP-MS data of the boronic acid **1b** (see in Supporting Information) indicates no presence of inorganic salts.

DOI: 10.1021/acs.oprd.5b00360
Org. Process Res. Dev. XXXX, XXX, XXX−XXX