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Convenient synthesis of heteroaryl-linked benzimidazoles via microwave-assisted boronate ester formation

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ABSTRACT

N-Substituted 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazoles were conveniently accessed via microwave-assisted synthesis. Subsequent Suzuki–Miyaura cross-coupling with heteroaryl halides proceeded to give a wide variety of heteroaryl-substituted benzimidazoles.

Benzimidazole ring systems are found in a number of biologically active molecules including kinase inhibitors,[1] gastric secretion inhibitors,[2] and RNA polymerase inhibitors.[3] As such, functionalization of benzimidazoles is generally an important component for evaluating structure–activity relationships (SARs) in lead optimization efforts for improving biological activity or pharmacokinetic properties of the series. Therefore, convenient methods for functionalization of benzimidazole rings that allow rapid analog synthesis are highly desirable.

As part of an ongoing effort to develop inhibitors of Polo-like kinase 1 (PLK1)[4] based on the thiophene amide template shown in Figure 1, we became interested in exploring SAR around 5-heteroaryl-linked benzimidazoles. The presence of primary amide and *2H*-benzimidazole functional groups in the template necessitated a mild synthetic route, such as transition-metal-catalyzed Suzuki–Miyaura reaction, for installation of the desired heteroaryl unit. An examination of the literature revealed only a few reports of Suzuki–Miyaura cross-coupling reaction of benzimidazoles with heteroaryl coupling partners.[5,6] Since heteroaryl boronate ester or acid coupling partners have limited commercial availability and are generally expensive, it was desirable to develop a new methodology in order to fully investigate heteroaryl-substitution on the benzimidazole ring.

Our efforts were initially focused on the preparation of boronate esters **2** starting from **1**, where X was either a bromide or a triflate (X = Br or OTf). Standard conditions for the transformation of **1** using 1,1′ bisdiphenylphosphinoferrocene dichloropalladium(II) as a palladium source and potassium acetate as a base, and heating the reaction mixture to 80 °C in DMF on the benchtop[7] (Table 1, entry 1) led to minimal conversion to the desired boronate ester product (**2**) after 14 h of reaction time. Interestingly, heating the reaction mixture in a microwave reactor at 150 °C for only 20 min significantly increased the amount of boronate observed (Table 1, entry 2).[8,9] Raising the reaction temperature to 170 °C further improved the boronate formation to 59%. However, heating the reaction at 150 °C for 40 min did not increase the amount of boronate observed (Table 1, compare entry 4 and entry 5). Changing the palladium catalyst to dichloro(bistriphenylphosphine)palladium(II) resulted in a modest improvement in the formation of desired boronate **2**, but with less recovered starting material **1**[10] (Table 1, compare entry 4 and entry 6). Since it was undesirable to carry unreacted **1** through to the subsequent Suzuki reaction, it was important that our methodology leave minimal unreacted starting material. In addition, the corresponding boronic acid derivative of **2** was routinely observed as a by-product of the reaction conditions (less than 10% by LC–MS). We found that the subsequent coupling reaction would generally proceed with the crude reaction mixture containing both boronate ester and acid after a simple water workup.

With the boronate ester (**2**) formation optimized, we next attempted a series of Suzuki–Miyaura coupling reactions with commercially available heteroaryl halides in order to access a diverse set of 5-heteroaryl-substituted benzimidazole analogs (**3a**–**m**). Microwave and conventional benchtop heating reaction conditions were both evaluated (Table 2, entries 1, 5, and 6). In contrast to the

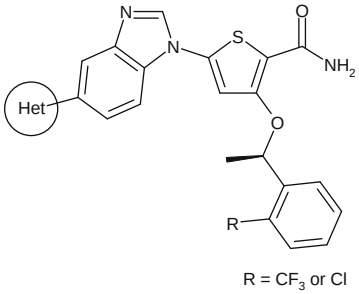

Figure 1. Thiophene amide-based PLK1 inhibitor template.

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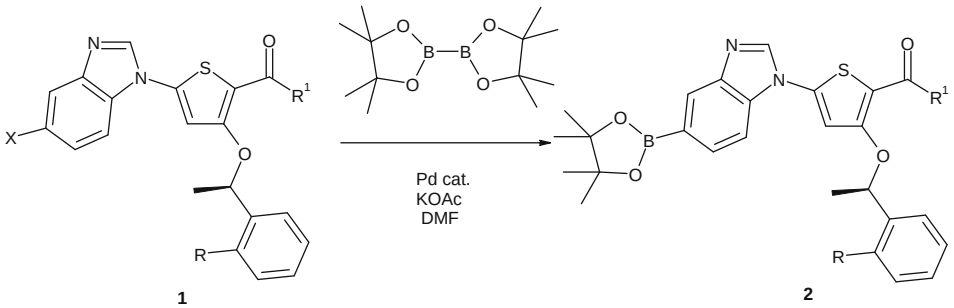
Table 1
Optimization of boronate ester formation[a]



1 **2**

Entry	X	R	R^1	Pd cat.	Temperature °C	Microwave (Y/N)	Time (min)	LC-MS% Formation of **2**	LC-MS% Remaining **1**
1	Br	Cl	OMe	$PdCl_2$(dppf)	80	N	840	20	35
2	Br	Cl	OMe	$PdCl_2$(dppf)	150	Y	20	45	14
3	Br	Cl	OMe	$PdCl_2$(dppf)	170	Y	20	59	13
4	OTf	CF_3	NH_2	$PdCl_2$(dppf)	150	Y	20	53 (52)[c]	17
5	OTf	CF_3	NH_2	$PdCl_2$(dppf)	150	Y	40[b]	48	21
6	OTf	CF_3	NH_2	$PdCl_2(PPh_3)_2$	150	Y	20	64	6
7	Br	CF_3	NH_2	$PdCl_2(PPh_3)_2$	150	Y	20	54 (50)[c]	0
8	Br	Cl	NH_2	$PdCl_2(PPh_3)_2$	150	Y	20	74 (70)[c]	0

[a] General reaction conditions: **1** (1.1 mmol), bis(pinacolato)diboron (1.2 equiv, 1.3 mmol), KOAc (3 equiv, 3.3 mmol), and Pd cat. (10 mol %), 0.16 M, in DMF.
[b] After 20 min of heating, the reaction was stopped and additional 7 mol % $PdCl_2$(dppf) was added, followed by 20 additional minutes of heating.
[c] Isolated yield.

boronate ester formation reaction, we found in this case that heating on the benchtop generally provided a cleaner reaction with reduced formation of side products compared to microwave heating. Coupling reactions with a variety of pyrimidine halides generally proceeded efficiently with isolated yields routinely above 50% (Table 2, entries 2–4, 6, and 7). Chloro-, bromo-, and iodo-pyrimidines were all found to be reasonable coupling partners with the boronate esters **2a** and **2b** (Table 2, entries 1, 2, and 5; and entries 6 and 7). Encouragingly, good isolated yields were also achieved with electron-rich pyrimidines (Table 2, entries 1, 3, and 4). Cross-coupling reactions with halo-pyridine derivatives were also demonstrated and resulted in moderate isolated yields (Table 2, entries 8–11). Even the reaction with sterically hindered, unprotected 5-bromo-6-methyl-2-pyridinamine proceeded reasonably well giving **3i** in 40% isolated yield (Table 2, entry 10). Coupling reactions with 5-membered ring imidazoles and pyrazoles proceeded less efficiently (Table 2, entries 12–14), and this was particularly noted with sterically hindered substrates (Table 2, entry 14). We suspected that the low yields observed with unprotected aminopyridines and aminopyrimidines (Table 2, entries 1, 9–11) and with pyrazole and imidazole substrates (Table 2, entries 12 and 14) may be due to these substrates competing as ligands for the metal catalyst.[11]

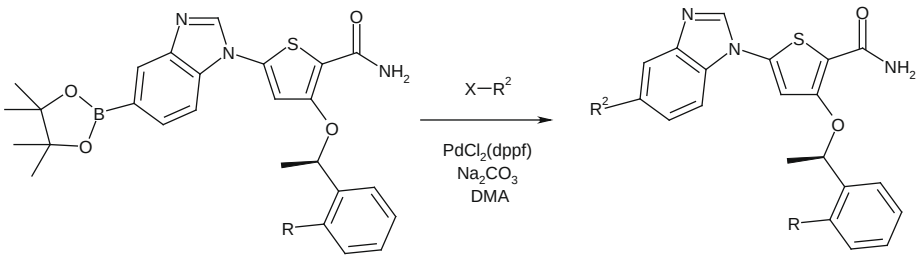
In conclusion, we were able to access a variety of heteroaryl-linked benzimidazole derivatives by developing a convenient and mild microwave-assisted boronate ester methodology. Suzuki–Miyaura cross-coupling reactions of the benzimidazole boronate ester with readily available heteroaryl halides allowed for the rapid synthesis of a diverse set of analogs based on the benzimidazole template shown in Figure 1. The biological evaluation of the analogs synthesized in this Letter will be reported in due course.

Typical procedure: *Microwave-assisted boronate ester formation*[4b]*: 5-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzimidazol-1-yl]-3-({(1R)-1-[2-(trifluoromethyl)phenyl]ethyl}oxy)thiophene-2carboxamide* (***2a***): 5-(5-Bromo-1*H*-benzimidazol-1-yl)-3-({(1*R*)-1-[2-(trifluoromethyl)phenyl]ethyl}oxy)thiophene-2-carboxamide (0.11 g, 0.22 mmol), bis(pinacolato)diboron (0.068 g, 0.27 mmol), potassium acetate (0.055 g, 0.67 mmol), and dichlorobis(triphenylphosphine)palladium(II) (0.016 g, 0.022 mmol) were combined in *N*,*N*-dimethylformamide (1.5 mL). The reaction mixture was heated in a Personal Chemistry microwave reactor at 150 °C for 20 min, after which the mixture was diluted with ethyl acetate and concentrated onto silica gel. Purification by column chromatography (10–100% ethyl acetate–hexanes) provided 0.062 g (50%) of the title compound as an off-white solid. A simple water workup had also been performed: The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over $MgSO_4$, and filtered. The resulting residue was subsequently used crude in the Suzuki–Miyaura cross-coupling reaction. ^{1}H NMR (400 MHz; DMSO-d_6) δ ppm 8.25 (s, 1H), 7.94 (s, 1H), 7.64–7.75 (m, 3H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.20 (br s, 1H), 6.63 (s, 2H), 5.83 (d, *J* = 6.2 Hz, 1H), 1.77 (d, *J* = 6.2 Hz, 3H), 1.34 (s, 12H); MS (ESI): 558.2 $[M+H]^+$.

Suzuki–Miyaura cross-coupling reaction: *5-[5-(2-chloropyrimidin-4-yl)-1H-benzimidazol-1-yl]-3-({(1R)-1-[2-(trifluoromethyl) phenyl] ethyl}oxy)thiophene-2-carboxamide* (***3e***): 5-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-1-yl]-3-({(1*R*)-1-[2-(trifluoromethyl)phenyl]ethyl}oxy)thiophene-2-carboxamide (0.19 g, 0.35 mmol) and 2,4-dichloropyrimidine (0.089 g, 0.60 mmol) were dissolved in *N*,*N*-dimethylacetamide (2.0 mL). Sodium carbonate (1 N in water, 0.70 mL) was added followed by 1,1′-bisdiphenylphosphinoferrocene dichloropalladium(II) (0.029 g, 0.035 mmol). The reaction mixture was stirred under nitrogen while heating at 80 °C for 15 h. The mixture was then cooled and partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organics were dried over $MgSO_4$, concentrated onto silica gel and purified by column chromatography (10–100% ethyl acetate–hexanes) to afford 0.10 g (53%) of the title compound as a white solid. ^{1}H NMR (400 MHz; DMSO-d_6) δ ppm 8.63 (d, *J* = 5.3 Hz, 1H), 8.49 (d, *J* = 1.3 Hz, 1H), 8.17 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.00 (s, 1H), 7.66–7.76 (m, 3H), 7.64 (d, *J* = 7.3 Hz, 1H), 7.43–7.53 (m, 2H), 7.14–7.22 (m, 1H), 6.68 (s, 1H), 5.86 (d, *J* = 6.2 Hz, 2H), 1.80 (d, *J* = 6.2 Hz, 3H); MS (ESI): 544.1 $[M+H]^+$.

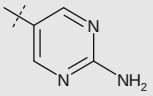
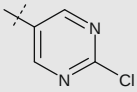
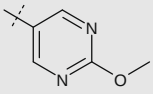
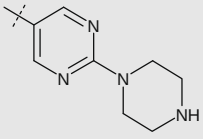
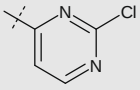
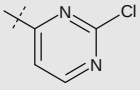
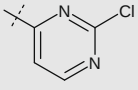
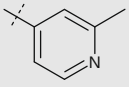
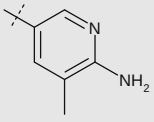
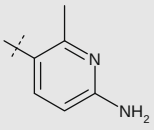
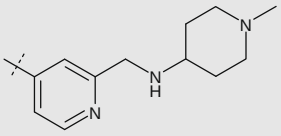
Simplified two-step procedure using crude ***2*** *for Suzuki–Miyaura cross-coupling reaction: 5-[5-(6-amino-2-methyl-3-pyridinyl)-1H-benzimidazol-1-yl]-3-{[(1R)-1-(2-chlorophenyl)ethyl]oxy}-2-thiophenecarboxamide* (***3i***): 3-{[(1*R*)-1-(2-chlorophenyl)ethyl]oxy}-5-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzimidazol-1-yl]-2-thiophenecarboxamide (0.38 g, 0.80 mmol), bis(pinacola-

Table 2
Suzuki–Miyaura cross-coupling of benzimidazole **2** with heteroaryl halides[a,b]



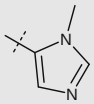
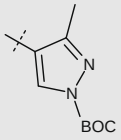
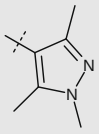
2a R = CF_3
2b R = Cl

3a-m

Entry	Compd	X	R^2	R	Temperature (°C)	Microwave (Y/N)	Time (min)	Isolated yield (%) **2**
1	**3a**	I		CF_3	150	Y	10	37
2	**3b**	Br		Cl	80	N	60	63
3	**3c**	Cl		Cl	80	N	60	64
4	**3d**	Br		Cl	80	N	30	56
5	**3e**	Cl		CF_3	150	Y	10	55[c]
6	**3e**	Cl		CF_3	80	N	900	53
7	**3f**	Cl		Cl	80	N	600	79 (57)[e]
8	**3g**	Cl		Cl	80	N	1080	(31)[e]
9	**3h**	Br		Cl	80	N	600	(44)[e]
10	**3i**	Br		Cl	80	N	600	(40)[e]
11	**3j**	Cl		Cl	80	N	600	20

(*continued on next page*)

Table 2 (*continued*)

Entry	Compd	X	R^2	R	Temperature (°C)	Microwave (Y/N)	Time (min)	Isolated yield (%) **2**
12	**3k**	Br		Cl	80	N	600	30[d]
13	**3l**	Br		Cl	80	N	60	58
14	**3m**	Br		Cl	80	N	600	13

[a] All reactions were carried out using a two-step procedure with purified **2** unless otherwise noted.
[b] General reaction conditions: **2** (0.350 mmol), heteroaryl halide (0.60 mmol), Na_2CO_3 (1 M aq, 0.7 mL) and $PdCl_2$(dppf) (10 mol %), 0.18 M, in DMA.
[c] % Conversion by LC–MS. Attempted reaction with $PdCl_2(PPh_3)_2$ as the catalyst resulted in minimal conversion to **3e**, and multiple side products were noted.
[d] Attempted reaction with 4-bromo-1*H*-imidazole did not provide any desired imidazole-coupled product.
[e] Isolated yield over two steps. Reactions carried out according to simplified two-step procedure using crude **2** for Suzuki–Miyaura coupling reaction.

to)diboron (0.25 g, 0.98 mmol), potassium acetate (0.20 g, 2.4 mmol), and dichlorobis(triphenylphosphine)palladium(II) (0.058 g, 0.083 mmol) were combined in *N*,*N*-dimethylformamide (5.0 mL). The reaction mixture was heated in a Personal Chemistry microwave reactor at 150 °C for 20 min, after which the mixture was diluted with ethyl acetate and washed with water. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The resulting crude residue was diluted with *N*,*N*-dimethylacetamide (10 mL), and 5 mL of this solution was carried into the subsequent Suzuki–Miyaura coupling reaction. To this solution of crude **2b** in *N*,*N*-dimethylacetamide, 5-bromo-6-methyl-2-pyridinamine (0.15 g, 0.8 mmol) and sodium carbonate (1 N in water, 1.5 mL) were added, followed by 1,1′-bisdiphenylphosphinoferrocene dichloropalladium(II) (0.033 g, 0.040 mmol). The reaction mixture was stirred under nitrogen while heating at 80 °C for 15 h. The mixture was then cooled and partitioned between dichloromethane and water. The aqueous layer was extracted twice with dichloromethane. The combined organics were dried over $MgSO_4$, concentrated onto silica gel, and purified by column chromatography (10–40% 1:9:90 NH_4OH–MeOH–DCM in DCM) to afford 0.080 g (40%) of the title compound over two steps. ^{1}H NMR (400 MHz; $CDCl_3$) δ ppm 7.98 (s, 1H) 7.70 (s, 1H) 7.39–7.49 (m, 3H) 7.26–7.37 (m, 3H) 7.22 (d, J = 1.1 Hz, 2H) 6.63 (s, 1H) 6.42 (d, J = 8.2 Hz, 1H) 5.87 (d, J = 6.4 Hz, 2H) 4.51 (br s, 2H) 2.35 (s, 3H) 1.77 (d, J = 6.2 Hz, 3H). MS (ESI): 504.2 $[M+H]^+$.

Acknowledgments

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9. The LC–MS data included in Table 1 were obtained using LC–MS systems calibrated on a daily basis with a system-suitability seven-component test mix to ensure fit for purpose (identity and purity).
10. In addition to unreacted **1**, the following by-products were also routinely observed: X = H, 2–12% by LC–MS; unreacted boronic acid, 7–11% by LC–MS; and dimers formed from homocoupling of **1**, 0–6% by LC–MS.
11. (a) Fleckenstein, C. A.; Plenio, H. *Chem. Eur. J.* **2008**, *14*, 4267. and references cited therein; For examples of pyrazole and imidazole moieties functioning as Pd ligands in Suzuki–Miyaura reactions see: (b) Mukherjee, A.; Sarkar, A. *Tetrahedron Lett.* **2004**, *45*, 9525; (c) Zeng, F.; Yu, Z. *J. Org. Chem.* **2006**, *71*, 5274.