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Regioselective synthesis of benzimidazole thiophene inhibitors of polo-like kinase 1

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ABSTRACT

A regioselective synthesis of novel 1-(2-thienyl)-benzimidazole inhibitors of polo-like kinase 1 is described. Amination of substituted 2-iodo or -bromo nitrobenzenes with a 2-aminothiophene derivative catalyzed by Pd_2dba_3 and XANTPHOS in the presence of excess Cs_2CO_3 afforded good yields of the coupled products. Subsequent reduction and cyclization of these intermediates provided the desired benzimidazole compounds.

Polo-like kinase (PLK) belongs to a family of highly conserved serine/threonine kinases that regulate multiple critical processes during mitosis.[1] The unique role of PLK in the cell cycle has prompted the pharmaceutical industry to explore development of small molecule inhibitors of PLK as a therapy for the treatment of cancer.[2,3] Recently, we have discovered a novel class of inhibitors of the polo-like kinase 1 (PLK1) represented by the generic structure **1** (Fig. 1).[4]

A key challenge surrounding these compounds has been their efficient synthesis. Our original synthetic route involved a non-regioselective addition of a substituted benzimidazole **2** to the enone **3** (Scheme 1).[4b,5] In the early stages of our lead optimization program, this methodology offered a facile entry into 1-(2-thienyl)-benzimidazoles necessary for a rapid build-up of structure-activity relationships around the benzimidazole core. As we became interested in specific substitution patterns, however, we required a more efficient route to specific regioisomers. Herein, we report a convenient solution to this regiochemical problem utilizing a palladium-catalyzed amination reaction.

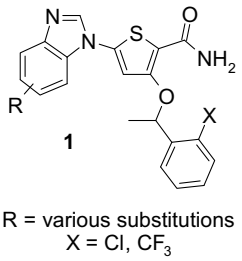
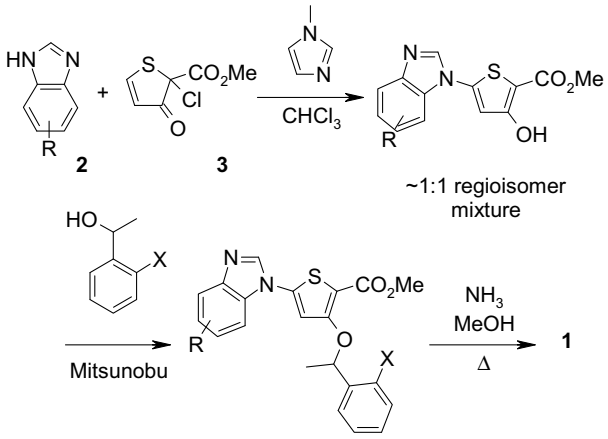


Figure 1. Generic structure of PLK1 inhibitors.



Scheme 1. Non-regioselective route to compounds of structure **1**.

In seeking a solution to this regiochemical impasse, we focused on N-substituted 2-nitroanilines such as **4** as the immediate synthetic precursors to the ultimate benzimidazole targets. In this system, the two nitrogen atoms are differentiated by oxidation state

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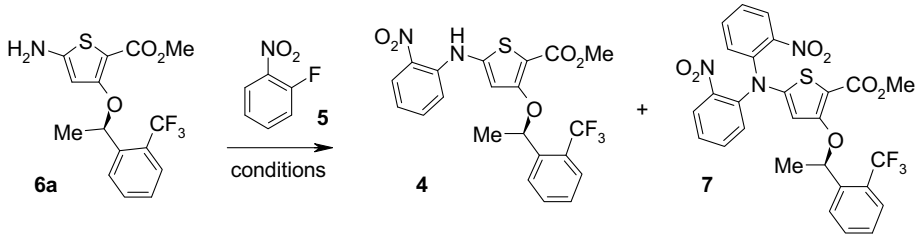
(and thus nucleophilicity), providing a viable solution to the problem of regioselectivity. The subsequent reduction and cyclization of substituted 2-nitroanilines to the corresponding benzimidazoles are well-precedented;[6] these operations may also conveniently be carried out in a one-pot transformation.[7] The most straightforward route to **4** would entail conjugate addition of a nitroaniline to the enone **3**. In practice, however, such reactions gave no products under a variety of conditions (data not shown), presumably due to the poor nucleophilicity of nitroanilines. We then attempted to form the key aniline bond via a nucleophilic aromatic substitution (S_NAr) reaction of 2-fluoronitrobenzene (**5**) with 2-aminothiophene **6a**[8] (Table 1). Unfortunately, this model reaction proceeded inefficiently under a variety of conditions, giving at best only 34% isolated yield of **4** (Entry 7). The frequently observed side product **7** (arising via addtion of **4**–**5**) further complicated the reaction profile.

Reasoning that perhaps the poor nucleophilicity of **6a** was the culprit in this transformation, we next explored a variety of Pd- and Cu-catalyzed aminations between **6a** and 2-iodonitrobenzene **8** (Table 2).[9] The combination of a Pd_2dba_3 catalyst and XANTPHOS ligand, previously utilized in a single instance for an aminothiophene substrate,[10] proved uniquely effective in catalyzing this process. In contrast to many published procedures, it was beneficial to run this particular reaction in the presence of 5 equiv of base (Cs_2CO_3) to obtain optimal yields (Table 2, compare entries 9 and 10). A full equivalent of base is likely consumed in the deprotona-

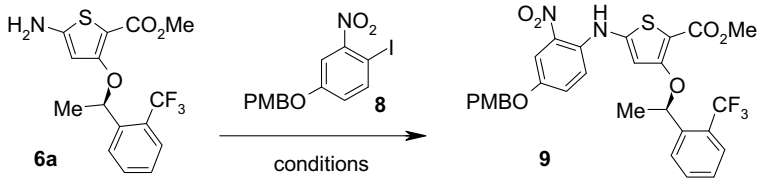
Table 1
S_NAr reaction between **5** and **6a**[a]



Entry	Base (equiv)	Solvent	Temp (°C)	Time (h)	**4** (%)	**7** (%)
1	K_2CO_3 (2.5)	MeCN	60	19	11	0
2	K_2CO_3 (2.0)[b]	DMSO	80	18	0	19
3	KHMDS (3.0)	THF	0 to rt	20	0	0
4	PS-TBD (2.5)	MeCN	60	19	0	0
5	LiOH (2.5)	DMF	60	19	0	20
6	LiOH (2.0)[b]	DMF	60	18	17	43
7	LiOH (5.1)	DMF	rt to 30	72	34[c]	0
8	*i*-Pr_2NEt	DMF	200[d]	10 min	0	0
9	DBU (2.0)[e]	neat	80[d]	1	0	0

[a] All reactions used 1 equiv of **6a**, 2.0 equiv of **5** at a substrate concentration of 0.1 M in the indicated solvent. All yields are isolated yields of the indicated products.
[b] 1.1 equiv. of **5.**
[c] 26% Recovered **6a**.
[d] Microwave heating.
[e] 1.0 equiv. of **5**.

Table 2
Optimization of Pd- or Cu-catalyzed amination of **8** with **6a**



Entry	Cat. (mol %)	L (mol %)	Solvent	Base (equiv)	Temp (°C)	Time (h)	Yield[a]
1	[b] (2)	None	PhMe	NaOMe/Et_3N (2.0/0.5)	60	22	<10
2	Pd_2dba_3 (2.5)	[c] (5)	PhMe	NaO*t*-Bu (2.4)	rt	26	19
3	$PdCl_2dppf$ (5)	dppf (15)	THF	NaO*t*-Bu (2.5)	100	26	0
4	Pd_2dba_3 (0.5)	[d] (2)	DME	K_3PO_4 (2.8)	80	18	0
5	Pd_2dba_3 (0.5)	[e] (2)	DME	K_3PO_4 (2.8)	80	18	0
6	Pd_2dba_3 (1)	X-Phos (8)	*t*-BuOH	K_2CO_3 (5.0)	80	16	19
7	$Pd(OAc)_2$ (3)	BINAP (4.5)	PhMe	Cs_2CO_3 (2.8)	100	17	0
8	$CuBr(PPh_3)_3$ (20)	None	PhMe	Cs_2CO_3 (3.0)	110	24	0
9	Pd_2dba_3 (2)	XANTPHOS (4.4)	1,4-Dioxane	Cs_2CO_3 (1.4)	60	18	59
10	Pd_2dba_3 (2)	XANTPHOS (4.4)	1,4-Dioxane	Cs_2CO_3 (5.0)	60	16.5	78

[a] Isolated yield.
[b] Acetato(2′-di-*t*-butylphosphino-1,1′-biphenyl-2-yl)palladium (II).
[c] 1,1′-Bis(di-*t*-butylphosphino)ferrocene.
[d] 2-(Dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl.
[e] 2-(Dicyclohexylphosphino)biphenyl.

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