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Efficient Pd-catalyzed synthesis of 2-arylaminopyrimidines via microwave irradiation

Henry Q. Zhang,* Zhiren Xia, Anil Vasudevan and Stevan W. Djuric

Enabling Chemistry Technologies, Global Pharmaceutical Research and Development, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, Illinois 60064, USA

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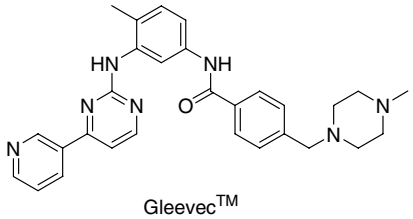
Abstract—An efficient method for the synthesis of 2-arylaminopyrimidines via microwave assisted, Pd-mediated amination of 2-chloropyrimidine is reported. This method is superior to the classical heating process, particularly when one of starting materials is a heteroarylamine.

Compounds containing a 2-arylaminopyrimidine moiety have diverse biological activities, and have been developed as angiogenesis inhibitors for the treatment of cancer,[1] reverse transcriptase inhibitors for HIV disease,[2] and gastric (H+/K+)-ATPase inhibitors for antiulcer therapy.[3] They are also Src kinase inhibitors,[4] retinoid X receptor antagonists for the potential treatment of diabetes and obesity,[5] and corticotropin-releasing hormone (or factor, CRH or CRF) antagonists for clinical application in the fields of depression and anxiety.[6] Gleevec™,[7] a 2-arylaminopyrimidine derivative, was launched in 2001 for the treatment of chronic myelogenous leukemia (CML) and gastrointestinal tumor (Fig. 1).



Gleevec™

Figure 1. Example of 2-arylaminopyrimidine as a drug.

2-Arylaminopyrimidine derivatives are generally synthesized by direct nucleophilic substitution of pyrimidyl halides, sulfone, sulfoxide or sulfide with anilines via the classical heating processes,[8] which often require prolonged heating at high temperatures or large excess of anilines and result in low to moderate yields. Microwave-assisted synthesis of aminopyrimidines has been explored recently.[9] However, the use of heteroarylamines as nucleophiles has not been fully investigated. In this letter, we report an efficient Pd-catalyzed synthesis of 2-heteroaryl and 2-aryl substituted aminopyrimidines under microwave irradiation (Table 1).

The reactions were carried out with equimolar amounts of 2-chloropyrimidines and heteroaryl or arylamines in the presence of 2% $Pd(OAc)_2$ and Xantphos as the ligand. Cs_2CO_3 was used as the base in these studies.[10] All reactions were heated in a single-mode microwave instrument.[11] Compared to the typical reaction conditions of Pd-catalyzed formation of C–N bonds,[12] degassed solvents and multiple cycles of evacuation–backfilling with nitrogen or argon were found not to be essential in our studies.

Initially, we investigated the reactions of diversely substituted 2-chloropyrimidines with electron-rich and electron-deficient substituted anilines under classical heating, microwave,[9] and Pd-catalyzed microwave conditions (Table 1, entries 1–4). All three reaction conditions gave the desired products in good yields (65–86%). However, when we changed the substrate to

* Corresponding author. Tel.: +1 847 935 5250; fax: +1 847 935 0310; e-mail: henry.zhang@abbott.com

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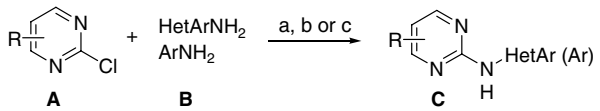
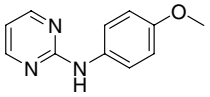
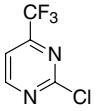
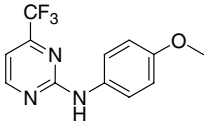
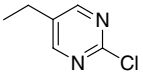
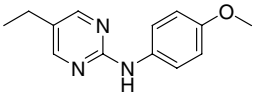
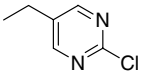
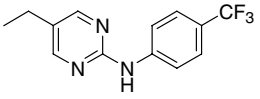
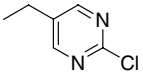
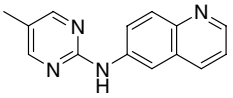
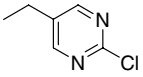
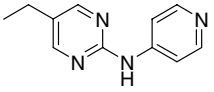
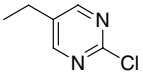
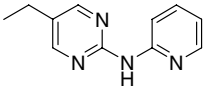
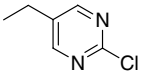
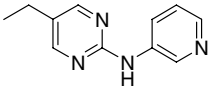
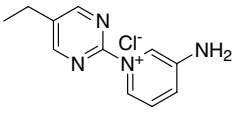
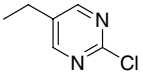
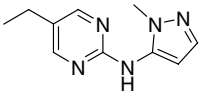
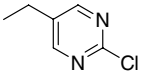
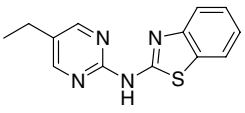
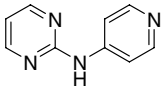
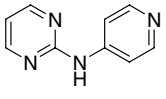
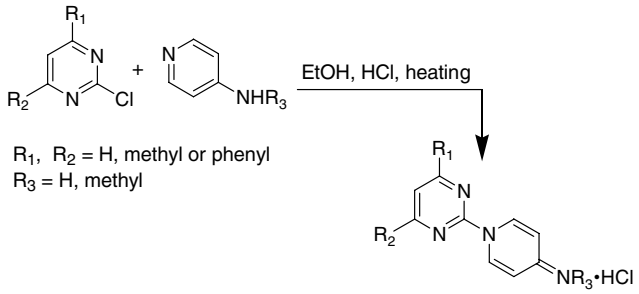
Table 1. Reactions of 2-chloropyrimidines with aryl and heteroarylamines



Entry	A	B	C	Reaction conditions	Yield[a] (%)
1		4-Methoxyaniline		**a** **b** **c**	83 84 80
2		4-Methoxyaniline		**a** **b** **c**	72 65 70
3		4-Methoxyaniline		**a** **b** **c**	78 86 85
4		4-Trifluoromethylaniline		**a** **b** **c**	81 83 80
5		6-Aminoquinoline		**a** **b** **c**	76 0 15
6		4-Aminopyridine		**a** **b** **c**	81 0 0
7		2-Aminopyridine		**a** **b** **c**	83 0 0
8		3-Aminopyridine	 	**a** **b** **c**	85 80 76
9		5-Amino-1-methylpyrazole		**a** **b** **c**	67 0 0
10		2-Aminobenzothiazole		**a** **b** **c**	52 0 0
11		4-Aminopyridine		**a**	51
12		4-Aminopyridine		**a** **b** **c**	50 0 0

Reaction conditions: **a**: 2 mol % $Pd(OAc)_2$, 3 mol % Xantphos, 2 equiv Cs_2CO_3, dioxane (1.5 mL), microwave 160 °C, 40 min; **b**: *n*-BuOH (1.5 mL), 0.4 equiv 4 N HCl/dioxane, microwave 160 °C, 40 min; **c**: *n*-BuOH, 0.4 equiv 4 N HCl/dioxane, oil bath 100 °C, 18 h.

[a] Isolated yield.



Scheme 1.

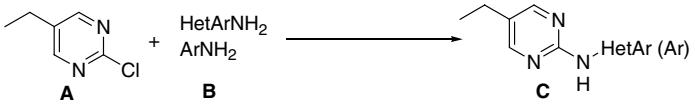
heteroarylamines (Table 1, entries 5–10), only Pd-catalyzed microwave conditions afforded the desired products in moderate to good yields (52–85%). Reaction of 2-chloro-5-ethyl-pyrimidine with 6-aminoquinoline gave only 15% of product when heated in an oil bath for 18 h. The same reaction gave no product under microwave irradiation for 40 min at 160 °C. When 4-aminopyridine and 2-aminopyridine were used as the substrates (Table 1, entries 6–7), both classical or microwave heating did not produce the desired product. Of note, more than three decades ago, there was a report of thermal nucleophilic aromatic substitution reactions of 4-aminopyridine with 2-chloropyrimidines to provide 1-(2-pyrimidinyl)-4-imino-1,4-dihydropyridinium chloride (Scheme 1).[13] Similarly, we isolated the 1-pyrimidin-2-yl-pyridinium chloride in good yield under thermal or microwave heating without Pd catalyst when 3-aminopyridine was employed (Table 1, entry 8, reaction condition **b**, **c**). Gratifyingly, using the Pd-catalyzed microwave conditions identified in this study, all three aminopyridines and other heteroarylamines afforded the desired aminated products in good to moderate yield.

In order to confirm that Pd plays an important role in the C–N bond formation under these microwave irradiation conditions, a control reaction excluding $Pd(OAc)_2$ was carried out (Table 2, entry 13, reaction condition **e**), and no product was observed. Using the classical Pd-catalyzed conditions[12c] in an oil bath at 100 °C for 18 h gave only 32% of the product and some recovery of aniline (Table 2, entry 13, reaction condition **d**). Replacement of Xantphos with BINAP as a ligand did not improve the yield (Table 2, entry 14, reaction condition **f**). However, the typical $Pd_2(dba)_3$ /BINAP/NaO-*t*-Bu conditions[12d] decreased the yield dramatically (Table 2, entry 14, reaction condition **g**). We also evaluated reaction conditions with respect to temperature, or percent of Pd used (Table 2, entry 14, reaction condition **h**, **i**). The results showed that 2% $Pd(OAc)_2$ at 160 °C for 40 min was the optimal reaction condition under microwave irradiation.[10]

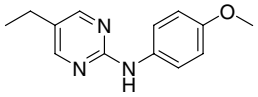
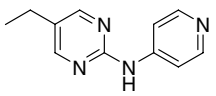
Finally, 2-bromopyrimidine was chosen as a substrate to further investigate the scope and limitation of our method, since it has been reported that attempts to couple 2-bromopyrimidine with various amines failed to yield any of the desired product under Pd-catalyzed amination.[12a] Coupling of 2-bromopyrimidine with 4-aminopyridine gave 51% of the desired product with the conditions reported within (Table 1, entry 11). Using 2-chloropyrimidine as a substrate gave similar yield (Table 1, entry 12).

In conclusion, we report herein, an efficient Pd-catalyzed synthesis of 2-heteroaryl and 2-aryl substituted aminopyrimidines under microwave irradiation. This method is superior to the classical heating process when heteroarylamines are used as substrates. Application of this method for drug lead discovery and lead optimization programs is currently in progress.

Table 2. Reactions of 2-chloro-5-ethyl-pyrimidines with aryl and heteroarylamines



A **B** **C**

Entry	B	C	Reaction conditions	Yield[a] (%)
13	4-Methoxyaniline		**e**	32
			d	0 + **A** and **B**
14	4-Aminopyridine		**f**	79
			g	12–14
			h	31–50
			i	60

Reaction conditions: **d**: 2 mol % $Pd(OAc)_2$, 3 mol % Xantphos, 2 equiv Cs_2CO_3, dioxane (1.5 mL), oil bath 100 °C, 18 h; **e**: 3 mol % Xantphos, 2 equiv Cs_2CO_3, dioxane (1.5 mL), microwave 160 °C, 40 min; **f**: 2 mol % $Pd(OAc)_2$, 3 mol % BINAP, 2 equiv Cs_2CO_3, dioxane (1.5 mL), microwave 160 °C, 40 min; **g**: 2–4 mol % $Pd_2(dba)_3$, 3–6 mol % BINAP, 2 equiv NaO-*t*-Bu, dioxane (1.5 mL), microwave 160 °C, 40 min; **h**: 2 mol % $Pd(OAc)_2$, 3 mol % Xantphos, 2 equiv Cs_2CO_3, dioxane (1.5 mL), microwave 120–140 °C, 40 min; **i**: 1 mol % $Pd(OAc)_2$, 1.5 mol % Xantphos, 2 equiv Cs_2CO_3, dioxane (1.5 mL), microwave 160 °C, 40 min.

[a] Isolated yield.

References and notes

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10. Vasudevan, A., unpublished results.
11. The microwave instrument used in these experiments was the Discover® from CEM Corporation. The reactions were carried out in their proprietary 10 mL sealed tubes. *Typical procedure for Pd-catalyzed microwave irradiation*: To a mixture of 4-aminopyridine (47 mg, 0.5 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Cs_2CO_3 (325 mg, 1.0 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 8.7 mg, 0.015 mmol) was added 2-chloro-5-ethylpyrimidine (71 mg, 0.5 mmol) in anhydrous 1,4-dioxane (1.5 mL). The tube was sealed and irradiated at 160 °C for 40 min. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2, filtered and concentrated. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH 20:1) on silica gel to give 81 mg (81%) of the desired product (Table 1, entry 6, reaction condition **a**) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) 1.20 (t, $J = 8$ Hz, 3H), 2.55 (q, $J = 8$ Hz, 2H), 7.75 (d, $J = 6$ Hz, 2H), 8.34 (d, $J = 6$ Hz, 2H), 8.48 (s, 2H), 10.00 (br s, 1H). ^{13}C NMR 158.09, 157.18 (2C), 149.76 (2C), 147.20, 128.34, 112.13 (2C), 22.06, 15.15. MS (ESI APCI+) m/z 201 $(M+H)^+$.
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